

Integrated Science Assessment for Ozone and Related Photochemical Oxidants

(Third External Review Draft)

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ACRONYMS AND ABBREVIATIONS

| | | | |
|----------------------|--|----------|--|
| 129 | mouse strain (129S1/SvImJ) | AOT60 | seasonal sum of the difference between an hourly concentration at the threshold value of 60 ppb, minus the threshold value of 60 ppb |
| α | alpha, ambient exposure factor | | |
| α -ATD | alpha 1-antitrypsin deficiency | | |
| α -SMA | alpha-smooth muscle actin | | |
| α -tocopherol | alpha-tocopherol | AOTx | family of cumulative, cutoff concentration-based exposure indices |
| α -TOH | alpha tocopherol | | |
| a | air exchange rate of the microenvironment | AP | activated protein |
| A2 | climate scenario in IPCC | A2p | climate scenario in IPCC (preliminary version of A2) |
| AADT | annual average daily traffic | APEX | Air Pollutants Exposure (model) |
| A1B | climate scenario in IPCC | APHEA(2) | Air Pollution on Health: a European Approach (study) |
| ABA | abscisic acid | | |
| ABI | abscisic acid insensitive | APHENA | Air Pollution and Health: A European and North American Approach |
| A1c | glycosylated hemoglobin blood test | | |
| Ach | acetylcholine | ApoB | apolipoprotein B |
| ACM | (Harvard University) Atmospheric Chemistry Modeling (Group) | ApoE | apolipoprotein E |
| ACS | American Cancer Society | APX | ascorbate peroxidase |
| ACS-CPSII | ACS Cancer Prevention Study II | aq | aqueous form: (aq)O ₃ |
| ADC | arginine decarboxylase | AQCD | Air Quality Criteria Document |
| ADSP | Adirondack State Park, NY | AQI | Air Quality Index |
| AER | air exchange rate | AQS | (U.S. EPA) Air Quality System (database) |
| AH ₂ | ascorbic acid; ascorbate | AR | acoustic rhinometry |
| AHR | airway(s) hyperresponsiveness, airway(s) hyperreactivity | AR4 | Fourth Assessment Report (AR4) from the IPCC |
| AhR | aryl hydrocarbon receptor | AR5 | Fifth Assessment Report (AR5) from the IPCC |
| AHSMOG | (California Seventh Day) Adventist Heath and Smog (Study) | ARG | arginase variants (ex., ARG1, ARG2, ARG1h4) |
| AI | alveolar interstitial | ARIC | Atherosclerosis Risk in Communities |
| AIC(s) | Akaike's information criterion | ARIES | (Atlanta) Aerosol Research and Inhalation Epidemiology Study |
| AIRS | Aerometric Information Retrieval System; Atmospheric Infrared Sounder (instrument) | atm | atmosphere |
| A/J | mouse strain | ATP | adenosine triphosphate |
| Ala-9Val | genotype associated with Manganese superoxide dismutase (MnSOD) gene | ATPase | adenosine triphosphatase; adenosine triphosphate synthase |
| AM | alveolar macrophage(s) | ATS | American Thoracic Society |
| ANF | atrial natriuretic factor | avg | average |
| AOT20 | seasonal sum of the difference between an hourly concentration at the threshold value of 20 ppb, minus the threshold value of 20 ppb | AVHRR | advanced very high resolution radiometer |
| AOT30 | seasonal sum of the difference between an hourly concentration at the threshold value of 30 ppb, minus the threshold value of 30 ppb | β | beta, beta coefficient; regression coefficient; standardized coefficient; shape parameter; scale parameter |
| AOT40 | seasonal sum of the difference between an hourly concentration at the threshold value of 40 ppb, minus the threshold value of 40 ppb | B | boron |
| | | B1 | climate scenario in IPCC |
| | | B6 | mouse strain (C57BL/6J) |
| | | BAL | bronchoalveolar lavage |
| | | BALB/c | mouse strain |
| | | BALF | bronchoalveolar lavage fluid |
| | | bb | bronchials |

| | | | |
|------------------|---|---|---|
| BB | bronchial airways | CAMP | Childhood Asthma Management Program |
| BC | black carbon | | |
| B cells | bone-marrow-derived lymphocytes; B lymphocytes | CAMx | Comprehensive Air Quality Model, with extensions |
| B6C3F1 | mouse strain | CAN | Canada |
| BDNF | brain-derived neurotrophic factor | CAP(s) | concentrated ambient particles |
| BEAS-2B | human bronchial epithelial cell line | CAR | centriacinar region |
| BEIS | Biogenic Emissions Inventory System | CASAC | Clean Air Scientific Advisory Committee |
| BELD | Biogenic Emissions Landcover Database | CASTNET | Clean Air Status and Trends Network |
| BIPM | International Bureau of Weights and Measures | CAT | catalase |
| BM | basement membrane | CB | carbon black; CMAQ mechanisms (ex., CB04, CB05, CB06) |
| BMI | body mass index | C57BL/6 | mouse strain |
| BNP | β -type natriuretic peptide | C57BL/6J | mouse strain |
| BP | blood pressure | CBSA | core-based statistical area |
| BPD | biparietal diameter | C/C | carbon of total carbon |
| bpm | breaths per minute | CCSP | Clara cell secretory protein |
| Br | bromine | CD | cluster of differentiation (various receptors on T-cells: CD8+, CD44, etc.); criteria document (see AQCD) |
| BRFSS | Behavioral Risk Factor Surveillance System | | |
| BS | black smoke | CD-1 | mouse strain |
| BSA | bovine serum albumin; body surface area | CDC | Centers for Disease Control and Prevention |
| Bsp, BSP | black smoke particles | CF | charcoal-filtered; carbon filtered air |
| Bt, BT, bt | <i>Bacillus thuringiensis</i> ; bacterium proteins used in pesticides (or genetically engineered plants produce Bt toxin) | CF2 | twice-filtered air (particulate filter and activated charcoal filter) |
| | | C-fibers | afferent, slow, unmyelinated nerves innervating the respiratory system |
| BTEX | family of compounds (benzene, toluene, ethylbenzene, and xylene) | CFR | Code of Federal Regulations |
| BW | body weight | CGRP | calcitonin gene-related peptide |
| C | carbon; concentration; (Vitamin C, ascorbate) | CH ₃ | methyl group |
| °C | degrees Celsius | CH ₄ | methane |
| ¹³ C | carbon-13 isotope | C ₂ H ₂ | acetylene |
| C3 | mouse strain (C3H/HEJ) | C ₂ H ₄ | ethylene |
| C3 | plants that use only the Calvin cycle for fixing the carbon dioxide from the air | C3H | mouse strain (C3H/HEJ or C3H/OuJ) |
| C4 | plants that use the Hatch-Slack cycle for fixing the carbon dioxide from the air | C ₃ H ₆ | propylene |
| C16:0 | palmitic acid (saturated fatty acid) | CHAD | Consolidated Human Activity Database |
| C18:1 | unsaturated fatty acid | CH ₃ Br | methyl bromide |
| Ca | calcium | CH ₃ -CHO | acetaldehyde |
| C _a | ambient concentration | CH ₃ Cl | methyl chloride |
| [Ca] | calcium concentration | CH ₃ -CO | acetyl radical(s) |
| Ca ²⁺ | calcium ion | CHD | coronary heart disease |
| CA | Canada (ICD-10-CA) | CHF | congestive heart failure |
| CAA | Clean Air Act | C ₂ H ₅ -H | ethane |
| CALINE4 | California line source dispersion model for predicting air pollutant concentrations near roadways | C3H/HeJ | mouse strain |
| CAM | plants that use crassulacean acid metabolism for fixing the carbon dioxide from the air | CH ₃ I | methyl iodide |
| | | CHIP | Effects of Elevated Carbon Dioxide and Ozone on Potato Tuber Quality in the European Multiple Site Experiment |
| | | CH ₃ O ₂ [*] | methyl peroxy (radical) |
| | | CH ₃ OOH | acetic acid; methyl hydroperoxide |
| | | CHS | Child Health Study |

| | | | |
|-------------------|--|-------------------|---|
| CI | confidence interval(s) | CXC | chemokine family of cytokines, with highly conserved motif:cys-xxx-cys (CXC) amino acid group |
| C _j | airborne O ₃ concentration at microenvironment j | | |
| Cl | chlorine | CXCR2 | CXC chemokine receptor 2 (CXCR2) |
| Cl ⁻ | chlorine ion | CXR | Chest (x-ray) radiograph(s) |
| Cl ₂ | chlorine gas | CyS | protein cysteines |
| CLE | Current Legislation (climate scenario in IPCC) | Cys-LT | cysteinyl leukotrienes (LTC ₄ , LTD ₄ , LTE ₄) |
| CLM | chemiluminescence method | cyt | cytosolic-free |
| CINO ₂ | nitryl chloride | Δ, δ | delta, difference; change |
| cm | centimeter(s) | ΔFEV ₁ | change in FEV ₁ |
| cm ² | square centimeters | ΔV _D | change in dead space volume of the respiratory tract |
| CM | Clinical Modification (ICD-9-CM) | 2-D | two-dimensional |
| CMAQ | Community Multi-scale Air Quality modeling system | 3-D | three-dimensional |
| CN | constant atmospheric nitrogen deposition (in PnET-CN ecosystem model) | DAHPS | 3-deoxy-D-arabino-heptulosonate-7-phosphate synthase |
| CNA | continental North America | DBP | diastolic blood pressure |
| CNS | central nervous system | DC(s) | dendritic cell(s) |
| CO | carbon monoxide; Cardiac output | DDM | direct decoupled method |
| CO ₂ | carbon dioxide | DEP(s) | diesel exhaust particle(s) |
| COD | coefficient of divergence; coefficient of determination | df | degrees of freedom |
| Col-0 | (Arabidopsis ecotype) Columbia-0 | DGGE | denaturing gradient gel electrophoresis |
| COP | Conference of Parties (to the UNFCCC) | DHA | dehydroascorbate |
| COPD | chronic obstructive pulmonary disease | DHAR | dehydroascorbate reductase |
| COX-2 | cyclooxygenase 2 enzyme | DHBA | 2,3-dihydroxybenzoic acid |
| C-R | concentration-response | DLEM | Dynamic Land Ecosystem Model |
| CRA | Centro di ricerca per la cerealicoltura (CRA) [The Centre for Cereal Research] – Unit 5: The Research Unit for Cropping Systems in Dry Environments in Bari, Italy (water-stressed conditions) | dm ³ | cubic decimeter(s) |
| CRP | C-reactive protein | DNA | deoxyribonucleic acid |
| CS | corticosteroid | DOAS | differential optical absorption spectroscopy |
| CSA | cross-sectional area; combined statistical area | DOC | dissolved organic carbon |
| csb, Csb | cockayne syndrome (cb) gene/protein group A | DR | type of human leukocyte antigens (HLA-DR) |
| CSF | colony-stimulating factor | dt | Portion of time-period spent in microenvironment j |
| CST | central standard time | DTH | delayed-type hypersensitivity |
| CSTR | continuous stirred tank reactor | DU | Dobson unit(s) |
| CSV | comma-separated values (a spreadsheet format) | DW | dry weight |
| CT | computer tomography | E | embryonic day (ex., E15, E16, etc); [Vitamin] E |
| CTM(s) | chemical transport model(s) | E _a | exposure to pollutant of ambient origin |
| cum avg | cumulative average | EBC | exhaled breath condensate (fluid) |
| CUOt | The cumulative stomatal uptake of O ₃ , using a constant O ₃ uptake rate threshold (t) of nmol/m ² /sec | EC | elemental carbon |
| CV, C.V. | coefficient of variation | ECE | endothelin converting enzyme(s) [i.e., ECE-1] |
| cv, c.v. | cultivar | ECG | electrocardiogram |
| CVD | cardiovascular disease | ECOPHYS | physiological process modeling to predict the response of aspen forest ecosystems (modeling growth and environmental stress in Populus) |
| | | ED | emergency department; embryonic day (ex., ED5, ED20) |

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|----------------------|---|------------------------------|--|
| EGEA | (The) Epidemiology (study on) Genetics and Environment of Asthma, (adults and children with asthma) | FEM | Federal equivalent method |
| EGEA2 | follow-up study on EGEA (adults with asthma only) | FeNO | exhaled nitric oxide fraction |
| EHC-93 | ambient PM reference sample (urban dust [air particles] collected in Ottawa Canada) | FEV ₁ | forced expiratory volume in 1 second |
| ELF | extracellular lining fluid | FHM | (USDA Forest Service) Forest Health Monitoring Program |
| EMI | (U.S. EPA) Exposure Model for Individuals | FIA | (USDA Forest Service) Forest Inventory and Analysis Program |
| E _{na} | exposure to pollutant of nonambient origin | F _{inf} | infiltration factor |
| ENA-78 | epithelial cell-derived neutrophil-activating peptide 78 | F _{inf,i} | infiltration factor for indoor environment (i) |
| eNO | exhaled nitric oxide | FLAG | Federal land managers' air quality related values workgroup |
| eNOS | endothelial nitric oxide synthase | F _{LRT} | fractional uptake efficiency of the lower respiratory tract (LRT) |
| ENVISAT | (EAS) Earth Observation satellite | F _{nose} | fractional uptake efficiency via nasal absorption |
| EOTCP | European Open Top Chamber Programme | F _o | fraction of time spent in outdoor microenvironments |
| EP | epithelial cells | FPM | Forest Pest Management |
| EPA | U.S. Environmental Protection Agency | FR | Federal Register |
| EPIC | European Prospective Investigation into Cancer and Nutrition | FRAP | ferric reducing ability of plasma |
| ER | emergency room | FRC | functional residual capacity |
| ESA | European Space Agency | FRM | Federal reference method |
| ET | extrathoracic; endothelin (i.e., ET-1) | F _{RT} | fractional uptake efficiency of the respiratory tract (RT) |
| ET ₁ | anterior nasal passages within the extrathoracic (ET) region | F _{st0₁} | flux cut off threshold |
| ET ₂ | oral airway and posterior nasal passages within the extrathoracic (ET) region | F _{URT} | fractional uptake efficiency of the upper respiratory tract (URT) |
| ETS | environmental tobacco smoke | FVC | forced vital capacity |
| EU | European Union | Fv/Fm | a ratio: a measure of the maximum efficiency of Photosystem II |
| EUS | eastern U.S. | FVI | fruits and vegetables index |
| Φ | Phi; calculated efficiency | γ | gamma |
| ΦPSII-max | maximum photochemical effective quantum yield of PSII | γ-TOH | gamma-tocopherol |
| f | Fraction of the relevant time period | g, kg, mg, μg, ng, pg | gram(s), kilogram(s), milligram(s), microgram(s), nanogram(s), picogram(s) |
| F | female | G | granulocyte; guanosine |
| F344 | Fischer 344 (rat strain) | g | gram(s); gaseous form: (g)O ₃ |
| F2a | 8-isoprostane (major F2 prostaglandin [8 iso-PGF2a]) | GAM | generalized additive model(s) |
| FA | filtered air | g _{bs} | conductance through boundary layer and stomata |
| FACE | free-air-CO ₂ enrichment (system) | GCLC | (glutathione genetic variant) glutamate-cysteine ligase catalytic subunit |
| FACES | Fresno Asthmatic Children's Environment Study | GCLM | (glutathione genetic variant) glutamate-cysteine ligase modifier subunit |
| f _B | frequency of breathing | G-CSF | granulocyte colony-stimulating factor (receptor) |
| FC | fibrocartilaginous coat | GD | gestational day |
| FEF | forced expiratory flow | GEE | generalized estimating equations |
| FEF ₂₅₋₇₅ | forced expiratory flow between the times at which 25% and 75% of the vital capacity is reached | GEOS | (NASA) Goddard Earth Observing System model |
| FEFx | forced expiratory flow after (x)% vital capacity (e.g., after 25, 50, or 75% vital capacity) | GEOS5 | GEOS version 5 |
| | | GEOS-Chem | GEOS-Chemistry (tropospheric model) |
| | | GFAP | glial fibrillary acidic protein |

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|---|--|---------------------------------|--|
| GH | growth hormone | HeJ | O ₃ -resistant C3H mouse strain (C3H/HeJ) |
| GHG | greenhouse gas | HEPA | high efficiency particle air (filter) |
| GLM(s) | generalized linear model(s) | HERO | Health and Environmental Research Online, NCEA Database System |
| GMAO | (NASA) Global Modeling and Assimilation Office | | |
| GM-CSF | granulocyte macrophage colony-stimulating factor | 12-HETE | 12-Hydroxyeicosatetraenoic acid |
| GOME | (ESA) Global Ozone Monitoring Experiment (spectrometer) | HF | (HRV signal) high-frequency power |
| GOMOS | Global Ozone Monitoring by Occultation of Stars (ESA ENVISAT spectrometer measuring long-term trends in O ₃) | HFCs | hydrofluorocarbons |
| G6P | glucose-6-phosphate | Hg | mercury |
| G6PD | glucose-6-phosphate dehydrogenase | HHP-C9 | 1-hydroxy-1-hydroperoxynonane |
| GPP | gross primary production | HIST | histamine |
| G-proteins | GTPases | HLA | human leukocyte antigen |
| GPT | gas phase titration | HLA-DR | human leukocyte antigen receptor genes |
| GR | glutathione reductase | HMOX | Heme oxygenase |
| GSH | glutathione; reduced glutathione | HMOX-1 | heme-oxygenase-1 (polymorphism) |
| GSO ₃ ⁻ /GSO ₃ ²⁻ | guanine sulfonates | HNE | 4-hydroxynonenal |
| GSR | glutathione reductase | HNO ₂ | nitrous acid |
| GSS | glutathione synthetase | HNO ₃ | nitric acid |
| GSSG | glutathione disulfide | HNO ₄ | pernitric acid |
| GST | glutathione S-transferase | HO | hydroxyl; heme oxygenase |
| GSTM1 | glutathione S-transferase polymorphism M1 genotypes (GSTM1-null, -GSTM1-sufficient) | HO• | hydroxyl radical |
| GSTP1 | glutathione S-transferase polymorphism P1 genotypes | HO-1 | heme oxygenase 1 |
| GTP | guanosine triphosphate | HO ₂ • | hydroperoxyl; hydroperoxy radical; protonated superoxide |
| GTPases | G-proteins/enzymes | HO ₃ • | protonated ozone radical |
| GWP | global warming potential | H ₂ O | water |
| GxE | gene-environmental interaction | H ₂ O ₂ | hydrogen peroxide |
| h | hour(s) | H ₃ O ⁺ | hydronium ion |
| h/day | hour(s) per day | HOCH ₂ OOH | hydroxymethylhydroperoxide |
| H; H+; H• | atomic hydrogen, hydrogen ion; hydrogen radical | HONO | nitrous acid |
| ³ H | radiolabeled hydrogen; tritium | HO ₂ NO ₂ | peroxynitric acid |
| H ₂ | molecular hydrogen | HOONO | pernitrous acid |
| ha | hectare | HOX | hydrogen radical(s) |
| HA | hyaluronic acid, hospital admission | hPa | hectopascal |
| HA(s) | hospital admission(s) | HPLC | high-pressure liquid chromatography |
| Hb | hemoglobin | HPOT | 13-hydroperoxide linolenic acid |
| HbA1c | glycosylated hemoglobin (blood test) | HR | heart rate, hazard ratio |
| HC(s) | hydrocarbon(s) | HR _{max} | maximum heart rate |
| HCFC(s) | hydrochlorofluorocarbon(s) | HRP | horseradish peroxidase |
| HCHO | formaldehyde | HRV | heart rate variability |
| H ₂ CO | formaldehyde | HSC | Houston Ship Channel (Texas) |
| HCO• | formyl (radical) | hs-CRP | high-sensitivity C-reactive protein |
| HDM | house dust mite | H ₂ SO ₄ | sulfuric acid |
| 2HDM | second-highest daily maximum | HSP | high speed pellet (after centrifuge spin) |
| HDMA | house dust mite allergen | HSP70 | heat shock protein 70 |
| ³ He | non-radioactive isotope of helium | HSS | high speed supernatant (after centrifuge spin) |
| | | 5-HT | 5-hydroxytryptamine |
| | | hv | Energy per photon of electromagnetic energy at frequency v |

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|---------------|---|----------------|---|
| HVAC | heating, ventilation, and air conditioning | INRA | National agronomical research institute (INRA) in Thiverval-Grignon. France (adequately-watered conditions) |
| Hz | hertz | | |
| I | iodine | | |
| IARC | International Agency for Research on Cancer | INTRASTAND | a stand-level model designed for hourly, daily and annual integration of forest carbon and water cycle fluxes |
| IAS | interalveolar septum | | |
| IBM | individual-based model or modeling | I/O | indoor-outdoor ratio |
| IC | inspiratory capacity; intracloud (lightning flash) | IOM | Institute of Medicine |
| ICAM-1 | intercellular adhesion molecule 1 | i.p. | intraperitoneal (route) |
| ICARTT | International Consortium for Atmospheric Research on Transport and Transformation | IPCC | Intergovernmental Panel on Climate Change |
| ICAS | Inner City Asthma Study | IPCC-A2 | Intergovernmental Panel on Climate Change 2nd Assessment Report |
| ICC | intraclass correlation coefficient | IPCC-AR4 | Intergovernmental Panel on Climate Change 4th Assessment Report |
| ICD | implantable cardioverter defibrillator(s); International Classification of Diseases | IPCC-AR5 | Intergovernmental Panel on Climate Change 5th Assessment Report |
| ICD-9 | International Classification of Disease 9th revision | IPCC-TAR | Intergovernmental Panel on Climate Change Third Assessment Report |
| ICD-10 | International Classification of Disease 10th revision | | |
| ICEM | Indoor Chemistry and Exposure Model | IPMMI | International Photolysis Frequency Measurement and Modeling Inter-comparison |
| ICNIRP | International Commission on Non-ionizing Radiation Protection | IQR | interquartile range |
| ICP Forests | International Cooperative Programme on Assessment of Air Pollution Effects on Forests | IR | infrared |
| | | I/R | ischemia-reperfusion |
| ICU | Intensive Care Unit | IRIS | Integrated Risk Information System |
| ICVE | ischemic cerebrovascular events | IRP | Integrated Review Plan for the Ozone National Ambient Air Quality Standards |
| IDW | inverse-distance-weighted | | |
| IFN | interferon (e.g., IFN-()) | ISA | Integrated Science Assessment |
| IFN- γ | interferon-gamma | ISCCP | International Satellite Cloud Climatology Project |
| Ig | immunoglobulin (e.g., IgE) | ISO | International Standards Organization |
| IgA | immunoglobulin A | | |
| IgE | immunoglobulin E | 8-iso-PGF | 8-isoprostane |
| IGF-1 | insulin-like growth factor 1 | IT | intratracheal |
| IgG | immunoglobulin G | IU | International Units |
| IgM | immunoglobulin M | IUGR | intrauterine growth restriction |
| IHD | ischemic heart disease | i.v. | intravenous (route) |
| IL | interleukin (e.g., IL-2, IL-4, IL-6, IL -8, etc.) | IVF | in vitro fertilization |
| IL-1 β | interleukin-1 β | j | Microenvironment |
| Ile | isoleucine | JA | jasmonic acid |
| i.m. | intramuscular (route) | Jmax | maximum rate of electron transport (for regeneration of RuBP) |
| IMPACT | Interactive Modeling Project for Atmospheric Chemistry and Transport | JNK | jun N-terminal kinase |
| IMPROVE | Interagency Monitoring of Protected Visual Environment | JPL | Jet Propulsion Laboratory |
| IN | intranasal | κ | kappa |
| INF | interferon | κ B | kappa B |
| inh | inhalation | k | dissociation rate; root:shoot allometric coefficient; rate of O ₃ loss in the microenvironment |
| iNKT | invariant (type I) natural killer T-cell | K | potassium |
| iNOS | inducible nitric oxide synthase | K ⁺ | potassium ion |

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|------------------|---|-------------------|--|
| K _a | intrinsic mass transfer coefficient/parameter | LOSU | level of scientific understanding |
| KC | keratinocyte-derived chemokine | LOWESS | locally weighted scatter plot smoother |
| kg | kilogram | LOX-1 | Lipoxygenase; lectin-like oxidized low density lipoprotein receptor-1 |
| K _g | mass transfer coefficient for gas phase | LPS | lipopolysaccharide |
| kHz | kilohertz | LRS | lower respiratory symptoms |
| kJ | kilojoules | LRT | lower respiratory tract; lower airways; Long range transport |
| KI | mass transfer coefficient for liquid phase | LST | local standard time |
| km | kilometer | LT | leukotriene (e.g., LTB ₄ , LTC ₄ , LTD ₄ , LTE ₄); local time |
| KM | particle optical reflectance | LT-α | lymphotoxin-α |
| KML | keyhole markup language | LTA | lymphotoxin-alpha |
| KMZ | zipped KML computer language | LUR | land use regression |
| KO | knockout | LVEDD | left ventricular chamber dimensions at end diastole |
| K _r | reaction rate constant | LVEDP | left ventricular end diastolic pressure |
| KROFEX | Krauzberg Ozone Fumigation Experiment | LWC | liquid water content |
| L, dL, mL, μL | Liter, deciLiter, milliLiter, microLiter | μ | mu, micro |
| L0 | Lag (e.x., Lag 0, Lag 1, etc.) | μeq | microequivalent |
| LAI | leaf area index | μg | microgram |
| LBL | Lawrence Berkeley Laboratory | μg/m ³ | micrograms per cubic meter |
| LBLX | Lawrence Berkeley Laboratory model including airflow from natural ventilation | μm | micrometer, micron |
| Lb(s) | pound(s) | m, cm, μm, nm | meter(s), centimeter(s), micrometer/[micron](s), nanometer(s) |
| LBW | low birth weight | M | male |
| LC ₅₀ | median lethal concentration | M, mM, μM, nM, pM | Molar, milliMolar, microMolar, nanoMolar, picoMolar |
| LCL | lower 95th% confidence limit | m ² | square meters |
| LDH | lactate dehydrogenase | m ³ | cubic meters |
| LDL | low-density lipoprotein ; lower detectable level | M# | Month (M1 Month1; M2 Month2; M3 Month3; M4 Month4) |
| LF | (HRV signal) low-frequency power | M2 | type of muscarinic receptor |
| LFHFR | low frequency/high frequency (ratio) | M7 | 7-hour seasonal mean |
| LFT | lower free troposphere | M12 | 12-hour seasonal mean of O ₃ |
| LI | labeling index | ma | moving average |
| LIDAR | Light Detection and Ranging (remote sensing system) | mAOT | modified accumulated exposure over threshold |
| LIF | laser-induced fluorescence | MAP | mitogen-activated protein; mean arterial pressure |
| LINKAGES | individual-based model of forest succession | MAPK | mitogen-activated protein kinase(s), MAP kinase |
| LIS | lateral intercellular space | MAQSIP | Multiscale Air Quality Simulation Platform (model) |
| LLJ | low-level jet | MARAT | Mid-Atlantic Regional Assessment Team |
| L/min | liters per minute | MARCO | Macrophage receptor with collagenous structure |
| Ln | Natural logarithm | max | maximum |
| LnRMSSD | natural log of RMSSD; measure of HRV | MBL | marine boundary layer |
| InSDNN | natural log of the standard deviation of NN intervals in an EKG | MCA | minimum cross-sectional area |
| LOAEL | lowest observed adverse effect level | MCCP | Mountain Cloud Chemistry Program |
| LOD | limit of detection | Mch; MCh | methacholine |
| LOEL | lowest-observed-effect level | MCM | master chemical mechanism |
| LOESS | locally weighted scatterplot smoothing | | |
| LOP | lipid ozonation products | | |

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|--------------------|---|-----------------|--|
| MCP-1 | monocyte chemotactic protein 1 | MOBILE6 | vehicle emissions modeling software version 6; replaced by MOVES |
| MDA | malondialdehyde | | |
| MDAR | monodehydroascorbate reductase | MODNR | Missouri Department of Natural Resources |
| MDI | Mediterranean diet index | | |
| MDL | minimum detection level | MONICA | Monitoring of Trends and Determinants in Cardiovascular Disease |
| MED | minimal erythema dose | | |
| MEF _{50%} | maximal midexpiratory flow at 50% of forced vital capacity | MoOx | molybdenum oxides |
| MEGAN | model of emissions of gases and aerosols from nature | MOSES | Met Office Surface Exchange Scheme |
| MeJA | methyl jasmonate | MOVES | Motor Vehicle Emission Simulator (replaced MOBILE6; for estimating emissions from cars, trucks, and motorcycles) |
| MENTOR | Modeling Environment for Total Risk Studies | | |
| METs | metabolic equivalent unit(s) [of work] | MOZAIC | Measurement of Ozone and Water Vapor by Airbus In-Service Aircraft |
| MFR | Maximum Feasible Reduction | MOZART | Model for Ozone and Related chemical Tracers |
| Mg | magnesium | | |
| MGDG | monogalactosyl diacylglycerol | MPAN | peroxymethacryloyl nitrate; peroxy-methacrylic nitric anhydride |
| mg/m ³ | milligrams per cubic meter | MPO | myeloperoxidase |
| MHC | major histocompatibility complex | MLQ | Minimum quantification limit |
| mi | mile(s) | MRI | magnetic resonance imaging; Midwest Research Institute; Meteorological Research Institute |
| MI | myocardial infarction, "heart attack" | | |
| MIESR | matrix isolation electron spin resonance (spectroscopy) | mRNA | messenger RNA |
| min | minute; minimum | ms | millisecond(s) |
| MIP | macrophage inflammatory protein | MS | mass spectrometry; Mt. Moosilauke site |
| MIP-2 | macrophage inflammatory protein 2 | MSA | Metropolitan Statistical Area; methane sulfonic acid |
| mL | milliliter | MSL | mean sea level |
| mL/min | milliliter(s) per minute | MS/MS | tandem mass spectrometry |
| MLN | mediastinal lymph node | MT | million ton(s); metric ton(s) |
| Mm | megameter | MT, Mt | metallothionein |
| mm | millimeter(s) | MT1 | mitochondria |
| MM Mt. | Mt. Mitchell site | MTBE | methyl-tertiary-butyl ether |
| MM5 | National Center for Atmospheric Research/Penn State Mesoscale Model (version 5) | mtDNA | mitochondrial DNA |
| MMAD | mass median aerodynamic diameter; mass median aerodynamic density | Mtn | mountain |
| MMEF | maximal midexpiratory flow | MW | molecular weight |
| mmHg | millimeters of mercury | MyD88 | myeloid differentiation primary response gene 88 |
| MMMD | mean maximum mixing height depth | n, N | number; number of observations |
| MMP-2 | matrix metalloproteinase-2 | N | nitrogen; North; nasal exposure by natural breathing |
| MMP-3 | matrix metalloproteinase-3 | ¹⁵ N | nitrogen-15, stable isotope of nitrogen |
| MMP-9 | metalloproteinase-9 | N ₂ | molecular nitrogen; nonreactive nitrogen |
| MMSP | Mount Mitchell State Park, NC | Na | sodium |
| Mn | manganese | NA | noradrenaline; North American |
| M/N | pooled data from mouth and nasal exposure | NA; N/A | not available; not applicable |
| MnSOD | Manganese superoxide dismutase | Na ⁺ | sodium ion |
| mo | month(s) | NAAQS | National Ambient Air Quality Standards |
| MOA(s) | mode(s) of Action | NAD | nicotinamide adenine nucleotide |
| MOBILE | (U.S. EPA) mobile vehicle emission factor model (on-road vehicles) | NADH | reduced nicotinamide adenine dinucleotide; nicotinamide adenine dinucleotide dehydrogenase |

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|-------------|--|--|---|
| NADP | National Atmospheric Deposition Program | NH ₃ | ammonia |
| NADPH | reduced nicotinamide adenine dinucleotide phosphate | NH ₄ ⁺ | ammonium ion |
| NADPH-CR | reduced nicotinamide adenine dinucleotide phosphate - cytochrome c reductase | NH ₄ HSO ₄ | ammonium bisulfate |
| NaE | sodium erythorbate | (NH ₄) ₂ HSO ₄ | ammonium sulfate |
| NAG | N-acetyl-glucosaminidase | NHANES | National Health and Nutrition Examination Survey |
| Na-K-ATPase | sodium-potassium-dependent adenosine triphosphatase | NHANES III | National Health and Nutrition Examination Survey III |
| NAMS | National Ambient Monitoring Stations | NHAPS | National Human Activity Pattern Survey |
| NAPAP | National Acid Precipitation Assessment Program | NHEERL | (U.S. EPA) National Health and Environmental Effects Research Laboratory |
| NAPBN | National Air Pollution Background Network | NHIS | National Health Interview Survey |
| NARE | North Atlantic Regional Experiment | (NH ₄) ₂ SO ₄ | ammonium sulfate |
| NARSTO | North American Regional Strategy for Tropospheric Ozone | NIH | National Institutes of Health |
| NAS | National Academy of Sciences; Normative Aging Study | NIST | National Institute of Standards and Technology |
| NASA | National Aeronautics and Space Administration | NK | natural killer cells; neurokinin |
| NBS | National Bureau of Standards | NKT | natural killer T-cells |
| NBTH | 3-methyl-2-benzothiazolinone acetone azine | NL | nasal lavage |
| NCEA | National Center for Environmental Assessment | NLF | nasal lavage fluid |
| NCEA-RTP | NCEA Division in Research Triangle Park, NC | NM | National Monument |
| NCHS | National Center for Health Statistics | NMHC(s) | nonmethane hydrocarbon(s) |
| NCICAS | National Cooperative Inner-City Asthma Study | NMMAPS | National Morbidity, Mortality, and Air Pollution Study |
| NCLAN | National Crop Loss Assessment Network | NMOC(s) | nonmethane organic compound(s) |
| NCore | National Core multi-pollutant monitoring network | NMVOCs | nonmethane volatile organic compounds |
| NC-R | resistant clones of white clover | NN | normal-to-normal (NN or RR) time interval between each QRS complex in the EKG |
| NC-S | sensitive clones of white clover | NNK | 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone |
| ND; n.d. | not detectable; not detected; no data | nNOS | neuronal nitric oxide synthase (NOS) |
| 2ndHDM | second-highest daily maximum | NO | nitric oxide |
| NDF | neutral detergent fiber | ·NO | nitric oxide concentration (interpunct NO) |
| NEE | net ecosystem CO ₂ exchange | NO ₂ | nitrogen dioxide |
| NEI | National Emissions Inventory | NO ₃ ; NO ₃ • | nitrate, nitrate radical |
| NEM | National Ambient Air Quality Standards Exposure Model | NO ₃ ⁻ | nitrate, nitrate ion |
| NEP | Net Ecosystem Production | N ₂ O | nitrous oxide |
| NERL | National Exposure Research Laboratory | N ₂ O ₅ | dinitrogen pentoxide |
| NESCAUM | Northeast States for Coordinated Air Use Management | NOAA | National Oceanic and Atmospheric Administration |
| NF | National Forest; non-filtered air | NOAEL | no observed adverse effect level |
| NF-kB | nuclear factor kappa B | NOS | nitric oxide synthase (types, NOS-1, NOS-2, NOS-3) |
| ng | nanogram(s) | NO _x | nitrogen oxides, oxides of nitrogen (NO + NO ₂) |
| NGF | nerve growth factor | NO _y | sum of NO _x and NO _z ; odd nitrogen species; total oxidized nitrogen |
| NH | northern hemisphere | NO _z | sum of all inorganic and organic reaction products of NO _x (HONO, HNO ₃ , HNO ₄ , organic nitrates, particulate nitrate, nitro-PAHs, etc.) |
| | | NP | National Park |

| | | | |
|------------------------------|--|------------------|---|
| NPP | net primary production | OPECs | Outdoor Plant Environment Chambers |
| NPS | National Park Service, U.S. Department of the Interior | OR | odds ratio |
| NQO1 | NAD(P)H-quinone oxidoreductase (genotype) | ORD | Office of Research and Development |
| NQO1wt | NAD(P)H-quinone oxidoreductase wild type (genotype) | OSHA | Occupational Safety and Health Administration |
| NR | not reported | OTC | open-top chamber |
| Nr | reactive nitrogen | OuJ | O ₃ -sensitive C3H mouse strain (C3H/OuJ) |
| NRC | National Research Council | OVA | ovalbumin |
| Nrf-2 | nuclear factor erythroid 2-related factor 2 | OX | odd oxygen species; total oxidants |
| Nrf2-ARE | NF- ϵ 2-related factor 2-antioxidant response element | OxComp | oxidative capacity of the atmosphere |
| NS; n.s. | nonsignificant; non-smoker; national seashore; natural spline | oz | ounce(s) |
| NSAID | non-steroidal anti-inflammatory agent | P | pressure in atmospheres; plants grown in pots; phosphorus; penetration fraction of O ₃ into the microenvironment; pulmonary region |
| NSBR | nonspecific bronchial responsiveness | p | probability value |
| NSF | National Science Foundation | P450 | cytochrome P450 |
| NTE | nasal turbinate epithelial (cells) | p53 | cell cycle protein gene |
| NTN | National Trends Network | P90 | 90th percentile of the absolute difference in concentrations |
| NTP | National Toxicology Program | PACF | partial autocorrelation function of the model residuals |
| NTRMs | NIST Traceable Reference Materials | PAD | peripheral arterial disease; pollutant-applied dose |
| NTS | nucleus of the solitary tract (in brainstem) | PAF | platelet-activating factor; paroxysmal atrial fibrillation |
| NWR | national wildlife refuge | PAH(s) | polycyclic aromatic hydrocarbon(s) |
| NWS | National Weather Service | PAI-1 | plasminogen activator fibrinogen inhibitor-1 |
| NZW | New Zealand white (rabbit) | PAL | phenylalanine ammonia lyase |
| O | oxygen; horizon forest floor | PAMS | Photochemical Assessment Monitoring Stations network |
| ¹⁸ O | oxygen-18, stable isotope of oxygen | PAN | peroxyacetyl nitrate |
| O ₂ | molecular oxygen | PaO ₂ | arterial oxygen pressure |
| O ₂ ⁻ | superoxide | PAPA | Public Health and Air Pollution in Asia |
| O ₂ [•] | superoxide radical | PAR | photosynthetically active radiation; proximal alveolar region |
| ¹ O ₂ | singlet oxygen | P _{atm} | Pressure in atmospheres |
| O ₃ | ozone | p-ATP | para-acetamidophenol |
| ¹⁸ O ₃ | (oxygen-18 labeled) ozone | Pb | Lead |
| O ₃ [*] | electronically excited ozone | PBL | planetary boundary layer; peripheral blood lymphocytes |
| OAQPS | Office of Air Quality Planning and Standards | PBM | population-based model or modeling |
| OAR | Office of Air and Radiation | PBN | C-phenyl N-tert-butyl nitrene |
| OBM _s | observationally based methods | PBPK | physiologically based pharmacokinetic (model) |
| OC | organic carbon | PBS | phosphate buffered saline |
| OD | outer diameter; optical density | PC | phosphatidylcholine |
| O(¹ D) | electronically excited oxygen atom | PC ₂₀ | provocative concentration that produces a 20% decrease in forced expiratory volume in 1 second |
| OH, OH [•] | hydroxyl group, hydroxyl radical | | |
| 8-OHdG | 8-hydroxy-2'-deoxyguanosine | | |
| OLS | ordinary least squares | | |
| OMI | Ozone Monitoring Instrument | | |
| ON | Ontario | | |
| ONOO ⁻ | peroxynitrate ion | | |
| O(³ P) | ground-state oxygen atom | | |
| OPE | ozone production efficiency | | |

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|------------------------------------|--|-------------------|--|
| PC ₂₀ FEV ₁ | provocative concentration that produces a 20% decrease in FEV ₁ | pH | relative acidity; Log of the reciprocal of the hydrogen ion concentration |
| PC ₅₀ | provocative concentration that produces a 50% decrease in forced expiratory volume in 1 second | PHA | phytohemagglutinin A |
| PCA | principal component analysis | PI | phosphatidylinositol; probability interval; posterior interval |
| PC-ALF | 1-palmitoyl-2-(9-oxonononyl)-sn-glycero-3-phosphocholine | PIF | peak inspiratory flow |
| PCD | programmed cell death | PIZZ | respiratory phenotype |
| PCI | picryl chloride | PK | pharmacokinetics |
| pCNEM | Canadian version of National Ambient Air Quality Standards Exposure Model | pKa | dissociation constant |
| PCO ₂ | Average partial pressure of O ₂ in lung capillaries | PLFA | phospholipid fatty acid |
| pCO ₂ | partial pressure of carbon dioxide | PM | particulate matter |
| PCR | polymerase chain reaction | PM _x | Particulate matter of a specific size range not defined for regulatory use. Usually X refers to the 50% cut point, the aerodynamic diameter at which the sampler collects 50% of the particles and rejects 50% of the particles. The collection efficiency, given by a penetration curve, increases for particles with smaller diameters and decreases for particles with larger diameters. The definition of PM _x is sometimes abbreviated as "particles with a nominal aerodynamic diameter less than or equal to X μm" although X is usually a 50% cut point. |
| PCR-DGGE | PCR–denaturing gradient gel electrophoresis | | |
| PD | pregnancy day | | |
| PD ₂₀ | provocative dose that produces a 20% decrease in FEV ₁ | | |
| PD ₂₀ FEV ₁ | provocative dose that produces a 20% decrease in FEV ₁ | | |
| PD ₁₀₀ | provocative dose that produces a 100% increase in sRAW | | |
| PD ₁₀₀ S _{Raw} | provocative dose that produces a 100% increase in S _{Raw} | PM _{2.5} | In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 2.5 μm; a measurement of fine particles in regulatory terms, particles with an upper 50% cut-point of 2.5 μm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix L of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53, by an equivalent method designated in accordance with 40 CFR Part 53, or by an approved regional method designated in accordance with Appendix C of 40 CFR Part 58. |
| PDI | pain on deep inspiration | | |
| PE | postexposure, phosphatidylethanolamine | | |
| PEF | peak expiratory flow | | |
| PEF _{0.75} | peak expiratory flow in 0.75 second | | |
| PEFR | peak expiratory flow rate | | |
| PEFT | time to peak flow | | |
| PEG-CAT | polyethylene glycol-catalase | | |
| PEG-SOD | polyethylene glycol-superoxide dismutase | | |
| PEM(s) | personal exposure monitor(s) | | |
| Penh | enhanced pause | | |
| PEPc | phosphoenolpyruvate carboxylase | | |
| PFD | photosynthetic flux density | | |
| PFT | pulmonary function test | | |
| pg | picogram(s) | | |
| PG | prostaglandin (e.g., PGE ₂ , PGF ₂); phosphatidylglycerol | | |
| 6PGD | 6-phosphogluconate dehydrogenase | | |
| PGE ₂ | prostaglandin E ₂ | | |
| PGF ₂ α | prostaglandin F ₂ -alpha | | |
| PGHS-2 | prostaglandin endoperoxide G/H synthase 2 | | |
| PGP | protein gene product (e.g., PGP9.5) | | |
| PGSM | Plant Growth Stress Model | | |

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| PM ₁₀ | In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 10 µm; a measurement of thoracic particles (i.e., that subset of inhalable particles thought small enough to penetrate beyond the larynx into the thoracic region of the respiratory tract) in regulatory terms, particles with an upper 50% cut-point of 10 ± 0.5 µm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) and a penetration curve as measured by a reference method based on Appendix J of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53. | PNN50 | proportion of interval differences of successive normal-beat intervals greater than 50 ms in EKG |
| | | PO ₂ | partial pressure of oxygen |
| | | POC | particulate organic carbon |
| | | POD | peroxidase |
| | | polyADPR | poly(adenosinediphosphate-ribose) |
| | | POMS | Portable Ozone Monitoring Systems |
| | | ppb | parts per billion |
| | | ppb-h | parts per billion per hour |
| | | ppbv | parts per billion by volume |
| | | pphm | parts per hundred million |
| | | ppm | parts per million |
| | | ppm-h | parts per million hours; weighted concentration values based on hourly concentrations: usually summed over a certain number of hours, day(s), months, and/or season. |
| PM _{10-2.5} | In general terms, particulate matter with an aerodynamic diameter less than or equal to a nominal 10 µm and greater than a nominal 2.5 µm; a measurement of thoracic coarse particulate matter or the coarse fraction of PM ₁₀ in regulatory terms, particles with an upper 50% cut-point of 10 µm aerodynamic diameter and a lower 50% cut-point of 2.5 µm aerodynamic diameter (the 50% cut point diameter is the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles) as measured by a reference method based on Appendix O of 40 CFR Part 50 and designated in accordance with 40 CFR Part 53 or by an equivalent method designated in accordance with 40 CFR Part 53. | ppmv | parts per million by volume |
| | | PPN | peroxypropionyl nitrate; peroxypropionic nitric anhydride |
| | | PPPs | power plant plumes |
| | | ppt | parts per trillion |
| | | pptv | parts per trillion by volume |
| | | PQH2 | plastoquinone |
| | | PR | pathogenesis-related (protein) |
| | | PR-1 | promoter region 1 |
| | | PRB | policy-relevant background |
| | | preproET-1 | pre-protein form of ET-1 mRNA |
| | | PRYL | predicted relative yield (biomass) loss |
| | | PS | penalized spline |
| | | PS | paradoxical sleep |
| | | PS II | Photosystem II: enzyme that uses light to obtain electrons from water (for photosynthesis). |
| PM _{10c} | The PM _{10-2.5} concentration of PM _{10-2.5} measured by the 40 CFR Part 50 Appendix O reference method which consists of currently operated, co-located low-volume (16.7 Lpm) PM ₁₀ and PM _{2.5} reference method samplers. | PSA | picryl sulfonic acid |
| | | PSC | polar stratospheric clouds |
| | | PTB | preterm birth |
| | | PTR-MS | proton-transfer-reaction mass spectroscopy |
| p38MAPK | p38 mitogen-activated protein kinase(s) | PU, PUL | pulmonary |
| PM-CAMx | Comprehensive Air Quality Model with extensions and with particulate matter chemistry | PUFA(s) | polyunsaturated fatty acid(s) |
| | | PV | potential vorticity |
| PMN(s) | polymorphonuclear leukocyte(s) | PVCD | peripheral vascular and cerebrovascular disease |
| PMT | photomultiplier tube | PVD | peripheral vascular disease |
| PND | post natal day | PVOCs | photochemical volatile organic compounds |
| pNEM | probabilistic National Exposure Model | PWM | pokeweed mitogen |
| PnET | Photosynthetic EvapoTranspiration model | PWTES | (left ventricular) posterior wall thickness at end systole |
| PNN | proportion of interval differences of successive normal-beat intervals in EKG | Pxase | peroxidase |
| | | QA | Quality Assurance |
| | | QC | quality control |

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|---------------------------------|---|--|--|
| QCE | quasi continuous exercise | Rn | nasal resistance |
| qNP | non-photochemical quenching | RNA | ribonucleic acid |
| q _{NP} | non-photochemical quenching | RO ₂ | organic peroxy; organic peroxy |
| qP | photochemical quenching | ROG | reactive organic gases |
| QRS | A complex of three distinct electrocardiogram waves which represent the beginning of ventricular contraction | ROI | reactive oxygen intermediate/superoxide anion |
| QT | interval measure of the time interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle | RONO ₂ | organic nitrate |
| QTc | corrected QT interval | ROOH | organic peroxides |
| r | Pearson correlation coefficient | ROONO ₂ , RO ₂ NO ₂ | peroxy nitrate |
| R, r | correlation coefficient | ROS | reactive oxygen species |
| r ² | correlation coefficient | RPD | relative percent difference |
| R ² | multiple regression correlation coefficient | RR | normal-to-normal (NN or RR) time interval between each QRS complex in the EKG; risk ratio; relative risk; respiratory rate |
| R ² , r ² | coefficient of determination | RRMS | relatively remote monitoring sites |
| RACM | Regional Atmospheric Chemistry Mechanism | RT | respiratory tract |
| RADM | Regional Acid Deposition Model | RT | transepithelial resistance |
| rALP | recombinant antileukoprotease | RTLFL | respiratory tract lining fluid |
| RAMS | Regional Atmospheric Modeling System | RuBisCO; Rubisco | ribulose-1,5-bisphosphate carboxylase/oxygenase |
| RANTES | regulated upon activation, normal T-cell expressed and secreted (cells) | RuBP | ribulose bisphosphate |
| Raw | airway resistance | σ | sigma, standard deviation |
| RB | respiratory bronchiole | σg | sigma-g; (geometric standard deviation) |
| RBC(s) | red blood cell(s); erythrocyte(s) | s | second |
| rbcL | Rubisco large subunit | S | Short; smoker; sulfur; South |
| rbcS | Rubisco small subunit | s.c. | subcutaneous (route) |
| R'CO acyl | acyl carrier protein | SA | salicylic acid |
| R'C(O)-O ₂ | acyl peroxy | SAB | Science Advisory Board |
| rcd1 | Arabidopsis mutant radical induced cell death | SAC | Staphylococcus aureus Cowan 1 strain |
| RCD3 | rod-cone dysplasia 3 | SAG21 | senescence |
| RCP | Representative Concentration Pathways | SAI | Systems Applications International |
| RDBMS | Relational Database Management Systems | S-allele | short-allele |
| Re | Reynolds number | SAMD | S-adenosyl methionine decarboxylase |
| REHEX | Regional Human Exposure Model | SaO ₂ | oxygen saturation of arterial blood |
| RER | rough endoplasmic reticulum; Respiratory exchange ratio | SAPALDIA | Study of Air Pollution and Lung Diseases in Adults |
| RF | radiative forcing | SAPRC | Stratospheric Processes and their Role in Climate; Statewide Air Pollution Research Center, University of California, Riverside |
| RGR | relative growth rate | SAR | systemic acquired resistance |
| RH | relative humidity | SAROAD | Storage and Retrieval of Aerometric Data (U.S. EPA centralized database; superseded by Aerometric Information Retrieval System [AIRS]) |
| RIOPA | Relationship of Indoor, Outdoor, and Personal Air (study) | SAWgrp | small airway function group |
| RL | total pulmonary resistance | SBNF | San Bernardino National Forest, California |
| RLKs | receptor-like/Pelle kinase group | SBP | systolic blood pressure |
| RMNP | Rocky Mountain National Park, Colorado | SBUV | Solar Backscatter Ultraviolet Spectrometer |
| RMR | resting metabolic rate | SC | stratum corneum |
| rMSSD | root mean squared differences between adjacent normal-to-normal heartbeat intervals | Sc | scandium |

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| SCAQS | Southern California Air Quality Study | SOS | Southern Oxidant Study |
| SCE(s) | sister chromatid exchange(s) | SO _x | sulfur oxides |
| SD | standard deviation; Sprague-Dawley rat | SoyFACE | Soybean Free Air gas Concentration Enrichment (Facility) |
| SDNN | standard deviation normal-to-normal (NN or RR) time interval between each QRS complex in the EKG | SP | surfactant protein (e.g., SPA, SPD); substance P |
| SE | standard error | SP-A | surfactant protein-A |
| SEBAS | Social Environment and Biomarkers of Aging Study | SPF | specific pathogen free |
| sec | second | SPMs | special purpose monitors |
| Sess. | session | SP-NK | substance P – neurokinin receptor complex |
| SEM | simultaneously extracted metal; standard error of the mean; scanning electron microscopy | sRaw, | specific airway resistance |
| SENP | Sequoia National Park, California | SRBC | sheep red blood cell |
| SES | socioeconomic status | SRES | Special Report on Emissions Scenarios |
| SF | San Francisco Bay Area | SRM | standard reference method |
| SF6 | sulfur hexafluoride (tracer gas) | SRP | standard reference photometers |
| SGA | small for gestational age | SSCP | single-strand conformation polymorphism |
| sRaw | specific airway conductance | 129S1/SvlmJ | mouse strain |
| SH | Shenandoah National Park site | STE | stratosphere-troposphere exchange |
| SHEDS | Stochastic Human Exposure and Dose Simulation | STEP | Stratospheric-Tropospheric-exchange Project |
| SHEN | Shenandoah National Park | STN | speciation trends network |
| sICAM-1 | soluble intercellular adhesion molecule | sTNFR1 | soluble tumor necrosis factor receptor 1 |
| SIDS | sudden infant death syndrome | STP | standard temperature and pressure |
| SIGMOID | sigmoid weighted summed concentration | STPD | standard temperature and pressure, dry |
| SINIC | Simple Nitrogen Cycle model | STRF | Spatio-Temporal Random Field (theory) |
| SIP | State Implementation Plan | subscript i | Index of indoor microenvironments |
| SIPK | salicylic acid (SA) induced protein kinase | subscript o | Index of outdoor microenvironments |
| SK | shikimate kinase | subscript o,i | Index of outdoor microenvironments adjacent to a given indoor microenvironment / |
| SLA | specific leaf area | SUM00 | sum of all hourly average concentrations |
| SLAC1 | (protein) slow anion channel associated 1 | SUM06 | seasonal sum of all hourly average concentrations ≥ 0.06 ppm |
| SLAMS | State and Local Air Monitoring Stations | SUM07 | seasonal sum of all hourly average concentrations ≥ 0.07 ppm |
| SM | smooth muscle | SUM08 | seasonal sum of all hourly average concentrations ≥ 0.08 ppm |
| SMD | soil moisture deficit | SURE | Sulfate Regional Experiment Program |
| SME | soybean oil methyl ester | SVE | supraventricular ectopy |
| SMNP | Great Smoky Mountain National Park (North Carolina and Tennessee) | S-W | square-wave |
| SMOKE | Spare-Matrix Operator Kernel Emissions | SWS | slow wave sleep |
| S _N | normalized slope of the alveolar plateau | SZA | solar zenith angle |
| SNAAQs | Secondary National Ambient Air Quality Standards | τ | tau, photochemical lifetime; atmospheric lifetime |
| SNP(s) | single-nucleotide polymorphism | t | t-test statistical value; t statistic |
| SO ₂ | sulfur dioxide | T | time; duration of exposure |
| SO ₄ ²⁻ | sulfate | | |
| SOC | soil organic carbon | | |
| SOD | superoxide dismutase | | |

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| T-cell(s) | T lymphocyte(s), thymus-dependent lymphocytes | TOMS | Total Ozone Mapping/Monitoring Satellite; total ozone mapping spectrometer |
| T1 | first trimester | TOPSE | Tropospheric Ozone Production About the Spring Equinox |
| T2 | second trimester | tPA | tissue plasminogen activator |
| T ₃ | triiodothyronine | TPLIF | two-photon laser-induced fluorescence |
| T3 | third trimester | TRAMP | TexAQS-II Radical and Aerosol Measurement Project |
| T ₄ | thyroxine | TREGRO | Tree Growth Model |
| TAR | IPCC Third Assessment Report | TRIFFID | Top-down Representation of Interactive Foliage and Flora Including Dynamics |
| TAR WGI | IPCC Third Assessment Report of Working Group I | TRIM | Total Risk Integrated Methodology (model) |
| TB | tracheobronchial; terminal bronchioles; tuberculosis | TRIM.Expo | Total Risk Integrated Methodology Exposure Event (model) |
| TBA | thiobarbituric acid | TRP | transient receptor potential (ion channel[s], ex., TRP-A1, TRP-V1, TRP-M8) |
| TBARS | thiobarbituric acid reactive substances | TSH | thyroid stimulating hormone |
| TC | total carbon | TSP | total suspended particles |
| ^{99m} Tc | Technetium-99m | TTFMS | two-tone frequency-modulated spectroscopy |
| T-cells | T-lymphocytes, Thymus-derived lymphocytes | TWA | time-weighted average |
| ^{99m} Tc-DTPA | ^{99m} Tc-diethylenetriaminepentaacetic acid | TX | thromboxane (e.g., TXB ₂) |
| Tco | core temperature | TXB ₂ | thromboxane B2 |
| TDLAS | Tunable Diode Laser Absorption Spectrometer | UA | uric acid; urate |
| Te | expiratory time | UAM | Urban Airshed Model |
| TEM | transmission electron microscopy; Terrestrial Ecosystem Model | UCL | upper 95th% confidence limit |
| TES | Tropospheric Emission Spectrometer | UDGT | UDP -galactose-1,2,-diacylglycerol galactosyltransferase |
| TexAQS | Texas Air Quality Field Study | UDP | uridine diphosphate |
| Tg | teragram(s) | U.K. | United Kingdom |
| TGF | transforming growth factor | UNECE | United Nations Economic Commission for Europe |
| TGF β | transforming growth factor beta | UNEP | United Nations Environmental Programme |
| Th | T helper cell type | UNFCCC | United Nations Framework Convention on Climate Change |
| Th2 | T helper cell type 2 | U-O | epioxides formed from uric acid |
| THC | Total hydrocarbon content | U-O ₂ ⁻ | peroxides formed from uric acid |
| tHcy | total homocysteine | U-O ₃ ⁻ | ozonides formed from uric acid |
| Ti | inspiratory time | URI | upper respiratory infection |
| Ti | titanium | URS | upper respiratory symptoms |
| TIA | transient ischemic attack | URT | upper respiratory tract; upper airways |
| TIMP-2 | tissue inhibitor of matrix metalloprotease-2 | U.S. | United States (of America) |
| TiO ₂ | titanium dioxide | USC; U.S.C. | U.S. Code |
| TLC | total lung capacity | USDA | U.S. Department of Agriculture |
| TLNISE | two-level normal independent sampling estimation | USFS | U.S. Forest Service |
| Tlr | Toll-like receptor gene | USGCRP | U.S. Global Change Research Program |
| TLR | Toll-like receptor protein (ex., TLR2, TLR4) | USGS | U.S. Geological Survey |
| TMPO | tetramethylphrrolise 1-oxide | UV | ultraviolet radiation |
| TNC | total nonstructural carbohydrate | UV-A | ultraviolet radiation at wavelengths of 320 to 400 nm |
| TNF | tumor necrosis factor (e.g., TNF-α) | | |
| TNF-308 | tumor necrosis factor genotype | | |
| TNF-α | tumor necrosis factor alpha | | |
| TNFR | tumor necrosis factor receptor | | |

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| UV-B | ultraviolet radiation at wavelengths of 280 to 320 nm | WED | (U.S. EPA NHEERL) Western Ecology Division |
| UV-C | ultraviolet radiation at wavelengths of 200 to 280 nm | WF, WFM | White Face Mountain site |
| UV-DIAL | Ultraviolet Differential Absorption Lidar | WHI | Women's Health Initiative |
| V | vanadium | WHO | World Health Organization |
| V, mV, μ V | volt, millivolt, microvolt | W/m ² , W m ⁻² | watts per square meter |
| VA | alveolar ventilation | WMO | World Meteorological Organization |
| Val | valine | WMO/UNEP | World Meteorological Organization/United Nations Environment Program |
| VC | vital capacity | WRF | Weather Research and Forecasting model |
| VCAM | vascular cell adhesion molecule | Ws | Wassilewskija Arabidopsis ecotype |
| V _d | deposition rate, deposition velocity (cm/sec) | WS | wood smoke |
| V _D | volume of the anatomic or physiological dead space | WT | wild type; White Top Mountain site |
| \dot{V}_E | ventilation rate; minute ventilation; ventilatory volume | wt % | percent by weight |
| VEGF | vascular endothelial growth factor | WUS | western U.S. |
| \dot{V}_E max | maximum minute ventilation | w/v | weight per volume |
| Vmax | maximum velocity | Y | three parameter Weibull model |
| Vmax _{25%} | maximum expiratory flow at 25% of the vital capacity | yr | year |
| Vmax _{50%} | maximum expiratory flow at 50% of the vital capacity | Z | Airway generation |
| Vmax _{75%} | maximum expiratory flow at 75% of the vital capacity | ZAPS | Zonal Air Pollution System |
| VMD | volume median diameter | ZELIG | a forest succession simulation model |
| V _n | nasal volume | Zn | zinc |
| VO ₂ | oxygen consumption | | |
| VO ₂ max | maximum volume per time, of oxygen (maximal oxygen consumption, maximal oxygen uptake or aerobic capacity) | | |
| VOC(s) | volatile organic compound(s) | | |
| VP | volumetric penetration | | |
| VP _{50%} | volume at which 50% of an inhaled bolus is absorbed | | |
| VPD | vapor pressure deficit; Vehicles per day; Ventricular premature depolarization | | |
| VT | tidal volume | | |
| VTB | terminal bronchiole region volume | | |
| VTmax | maximum tidal volume | | |
| VUA | volume of the upper airways | | |
| vWF | von Willebrand factor | | |
| W | width; wilderness; week(s) | | |
| W126 | cumulative integrated exposure index with a sigmoidal weighting function | | |
| W95 | cumulative integrated exposure index with a sigmoidal weighting function | | |
| WBC | white blood cell | | |
| WBGT | wet bulb globe temperature | | |
| wc | sigmoidal weighting of hourly O ₃ concentration | | |
| WCB | warm conveyor belt | | |

PREAMBLE

Process of ISA Development

1 This preamble outlines the general process for developing an Integrated Science
2 Assessment (ISA) including the framework for evaluating weight of evidence and
3 drawing scientific conclusions and causal judgments. The ISA provides a concise review,
4 synthesis, and evaluation of the most policy-relevant science to serve as a scientific
5 foundation for the review of the National Ambient Air Quality Standards (NAAQS). The
6 general process for NAAQS reviews is described at
7 <http://www.epa.gov/ttn/naaqs/review.html>. Figure I depicts the general NAAQS review
8 process and information for individual NAAQS reviews is available at
9 www.epa.gov/ttn/naaqs. This preamble is a general discussion of the basic steps and
10 criteria used in developing an ISA; for each ISA, specific details and considerations are
11 included in the introductory section for that assessment.

12 The fundamental process for developing an ISA includes:

- 13 ▪ literature searches;
- 14 ▪ study selection;
- 15 ▪ evaluation and integration of the evidence; and
- 16 ▪ development of scientific conclusions and causal judgments.

17 An initial step in this process is publication of a call for information in the Federal
18 Register that invites the public to provide information relevant to the assessment, such as
19 new publications on health or welfare¹ effects of the pollutant, or from atmospheric and
20 exposure sciences fields. EPA maintains an ongoing literature search process for
21 identification of relevant scientific studies published since the last review of the NAAQS.
22 Search strategies are designed for pollutants and scientific disciplines and iteratively
23 modified to optimize identification of pertinent publications. Papers are identified for
24 inclusion in several additional ways: specialized searches on specific topics; independent
25 review of tables of contents for journals in which relevant papers may be published;
26 independent identification of relevant literature by expert scientists; review of citations in
27 previous assessments and identification by the public and CASAC during the external
28 review process. This literature search and study selection process is depicted in Figure II.
29 Publications considered for inclusion in the ISA are added to the Health and

¹ Welfare effects as defined in Clean Air Act section 302(h) [42 U.S.C. 7602(h)] include, but are not limited to, “effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being.”

1 Environmental Research Online (HERO) database developed by EPA
2 (<http://hero.epa.gov/>); the references in the ISA include a hyperlink to the database.

3 Studies that have undergone scientific peer review and have been published or accepted
4 for publication and reports that have undergone review are considered for inclusion in the
5 ISA. Analyses conducted by EPA using publicly available data are also considered for
6 inclusion in the ISA. All relevant epidemiologic, controlled human exposure,
7 toxicological, and ecological and welfare effects studies published since the last review
8 are considered, including those related to exposure-response relationships, mode(s) of
9 action (MOA), and potentially at-risk populations and lifestyles. Studies on atmospheric
10 chemistry, environmental fate and transport, dosimetry, toxicokinetics and exposure are
11 also considered for inclusion in the document, as well as analyses of air quality and
12 emissions data. References that were considered for inclusion in a specific ISA can be
13 found using the HERO website (<http://hero.epa.gov/>).

National Ambient Air Quality Standard Review Process

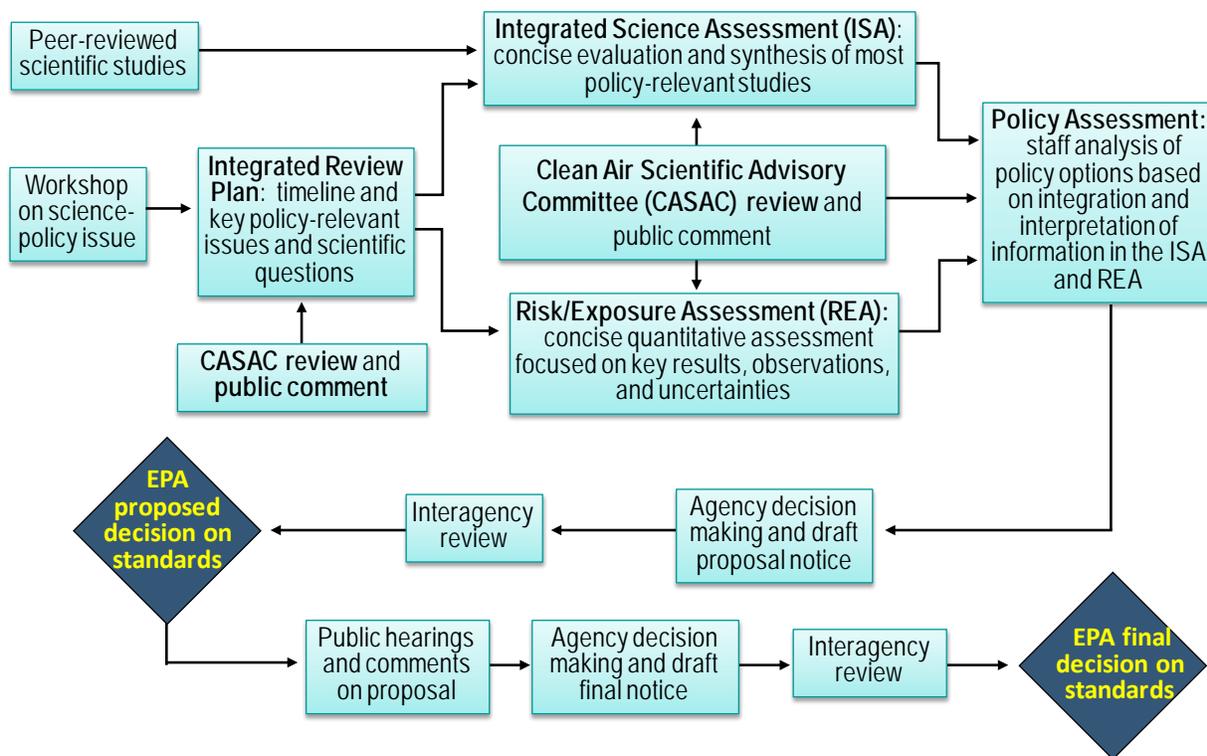


Figure 1 Illustration of the key steps in the process of the review of National Ambient Air Quality Standards.

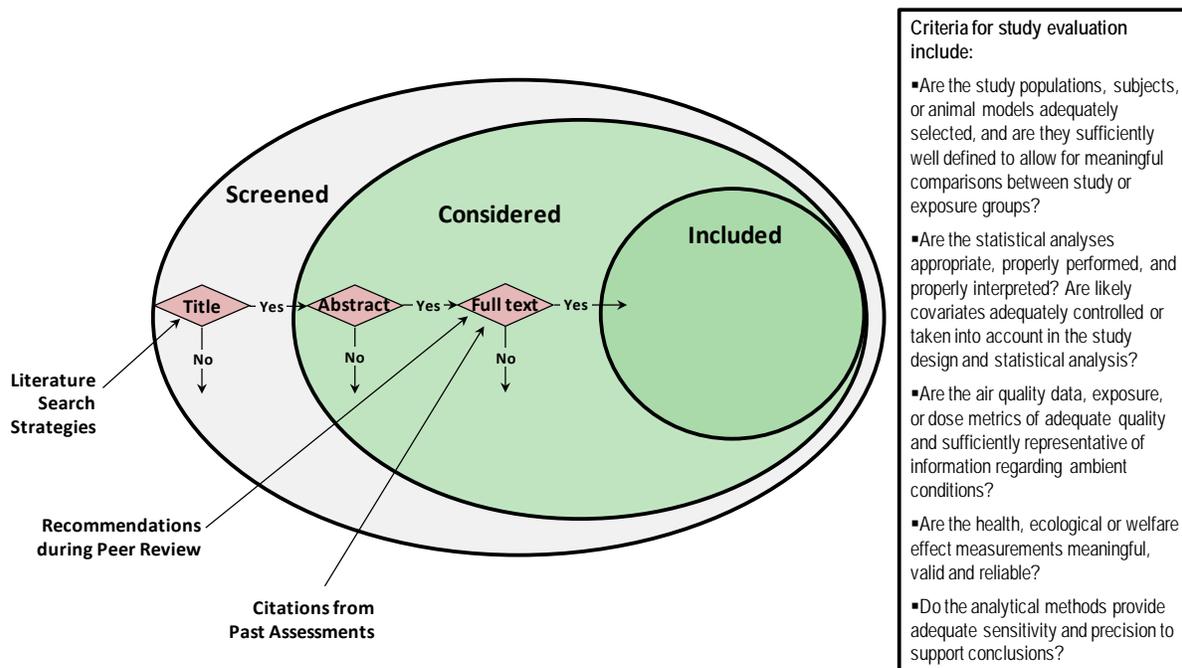


Figure II Illustration of processes for literature search and study selection used for development of ISAs.

1 Each ISA builds upon the conclusions of previous assessments for the pollutant under
 2 review. EPA focuses on peer reviewed literature published following the completion of
 3 the previous review and on any new interpretations of previous literature, integrating the
 4 results of recent scientific studies with previous findings. Important earlier studies may
 5 be discussed in detail to reinforce key concepts and conclusions or for reinterpretation in
 6 light of newer data. Earlier studies also are the primary focus in some areas of the
 7 document where research efforts have subsided, or if these earlier studies remain the
 8 definitive works available in the literature.

9 Selection of studies for inclusion in the ISA is based on the general scientific quality of
 10 the study, and consideration of the extent to which the study is informative and policy-
 11 relevant. Policy relevant and informative studies include those that provide a basis for or
 12 describe the relationship between the criteria pollutant and effects, including studies that
 13 offer innovation in method or design and studies that reduce uncertainty on critical issues,
 14 such as analyses of confounding or effect modification by copollutants or other variables,
 15 analyses of concentration-response or dose-response relationships, or analyses related to
 16 time between exposure and response. Emphasis is placed on studies that examine effects
 17 associated with pollutant concentrations relevant to current population and ecosystem

1 exposures, and particularly those pertaining to concentrations currently found in ambient
2 air. Other studies are included if they contain unique data, such as a previously
3 unreported effect or MOA for an observed effect, or examine multiple concentrations to
4 elucidate exposure-response relationships. In general, in assessing the scientific quality
5 and relevance of health and welfare effects studies, the following considerations have
6 been taken into account when selecting studies for inclusion in the ISA.

- 7 ▪ Are the study populations, subjects, or animal models adequately selected, and
8 are they sufficiently well defined to allow for meaningful comparisons
9 between study or exposure groups?
- 10 ▪ Are the statistical analyses appropriate, properly performed, and properly
11 interpreted? Are likely covariates adequately controlled or taken into account
12 in the study design and statistical analysis?
- 13 ▪ Are the air quality data, exposure, or dose metrics of adequate quality and
14 sufficiently representative of information regarding ambient conditions?
- 15 ▪ Are the health, ecological or welfare effect measurements meaningful, valid
16 and reliable?
- 17 ▪ Do the analytical methods provide adequate sensitivity and precision to
18 support conclusions?

19 Considerations specific to particular disciplines include the following. In selecting
20 epidemiologic studies, EPA considers whether a given study: (1) presents information on
21 associations with short- or long-term pollutant exposures at or near conditions relevant to
22 ambient exposures; (2) addresses potential confounding by other pollutants; (3) assesses
23 potential effect modifiers; (4) evaluates health endpoints and populations not previously
24 extensively researched; and (5) evaluates important methodological issues related to
25 interpretation of the health evidence (e.g., lag or time period between exposure and
26 effects, model specifications, thresholds, mortality displacement).

27 Considerations for the selection of research evaluating controlled human exposure or
28 animal toxicological studies includes a focus on studies conducted using relevant
29 pollutant exposures. For both types of studies, relevant pollutant exposures are
30 considered to be those generally within one or two orders of magnitude of ambient
31 concentrations. Studies in which higher doses were used may also be considered if they
32 provide information relevant to understanding MOA or mechanisms, as noted below.

33 Evaluation of controlled human exposure studies focuses on those that approximated
34 expected human exposure conditions in terms of concentration and duration. Studies
35 should include control exposures to filtered air, as appropriate. In the selection of
36 controlled human exposure studies, emphasis is placed on studies that: (1) investigate

1 potentially at-risk populations and lifestages such as people with asthma or
2 cardiovascular diseases, children or older adults; (2) address issues such as concentration-
3 response or time-course of responses; and (3) have sufficient statistical power to assess
4 findings.

5 Review of the animal toxicological evidence focuses on studies that approximate
6 expected human dose conditions, which vary depending on the dosimetry, toxicokinetics
7 and biological sensitivity of the particular laboratory animal species or strains studied.
8 Emphasis is placed on studies that: (1) investigate animal models of disease that can
9 provide information on populations potentially at increased risk of effects; (2) address
10 issues such as concentration-response or time-course of responses; and (3) have sufficient
11 statistical power to assess findings. Due to resource constraints on exposure duration and
12 numbers of animals tested, animal studies typically utilize high-concentration exposures
13 to acquire data relating to mechanisms and assure a measurable response. Emphasis is
14 placed on studies using doses or concentrations generally within 1-2 orders of magnitude
15 of current levels. Studies with higher concentration exposures or doses are considered to
16 the extent that they provide useful information to inform understanding of interspecies
17 differences and potential differences between healthy and potentially at-risk human
18 populations. Results from in vitro studies may also be included if they provide
19 mechanistic insight or further support for results demonstrated in vivo.

20 These criteria provide benchmarks for evaluating various studies and for focusing on the
21 policy-relevant studies in assessing the body of health, ecological and welfare effects
22 evidence. As stated initially, the intent of the ISA is to provide a concise review,
23 synthesis, and evaluation of the most policy-relevant science to serve as a scientific
24 foundation for the review of the NAAQS, not extensive summaries of all health,
25 ecological and welfare effects studies for a pollutant. Of most relevance for inclusion of
26 studies is whether they provide useful qualitative or quantitative information on
27 exposure-effect or exposure-response relationships for effects associated with pollutant
28 exposures at doses or concentrations relevant to ambient conditions that can inform
29 decisions on whether to retain or revise the standards.

30 In developing an ISA, EPA reviews and summarizes the evidence from: studies of
31 atmospheric sciences and exposure; the health effects evidence from toxicological,
32 controlled human exposure and epidemiologic studies; and ecological and welfare effects
33 evidence. In the process of developing the first draft ISA, EPA may convene a public
34 workshop in which EPA and non-EPA experts review the scientific content of
35 preliminary draft materials to ensure that the ISA is up to date and focused on the most
36 policy-relevant findings, and to assist EPA with integration of evidence within and across
37 disciplines. The general process for ISA development is illustrated in Figure III.

1 EPA integrates the evidence from across scientific disciplines or study types and
2 characterizes the weight of evidence for relationships between the pollutant and various
3 outcomes. The integration of evidence on health, and ecological or welfare effects,
4 involves collaboration between scientists from various disciplines. As an example, an
5 evaluation of health effects evidence would include the integration of the results from
6 epidemiologic, controlled human exposure, and toxicological studies, and application of
7 the causal framework (described below) to draw conclusions. Using the causal
8 framework described in the following section, EPA scientists consider aspects such as
9 strength, consistency, coherence, and biological plausibility of the evidence, and develop
10 causality determinations on the nature of the relationships. Causality determinations often
11 entail an iterative process of review and evaluation of the evidence. Two drafts of the ISA
12 are typically released for review by the CASAC and the public, and comments received
13 on the characterization of the science as well as the implementation of the causal
14 framework are carefully considered in revising and completing the final ISA.

Integrated Science Assessment Development Process

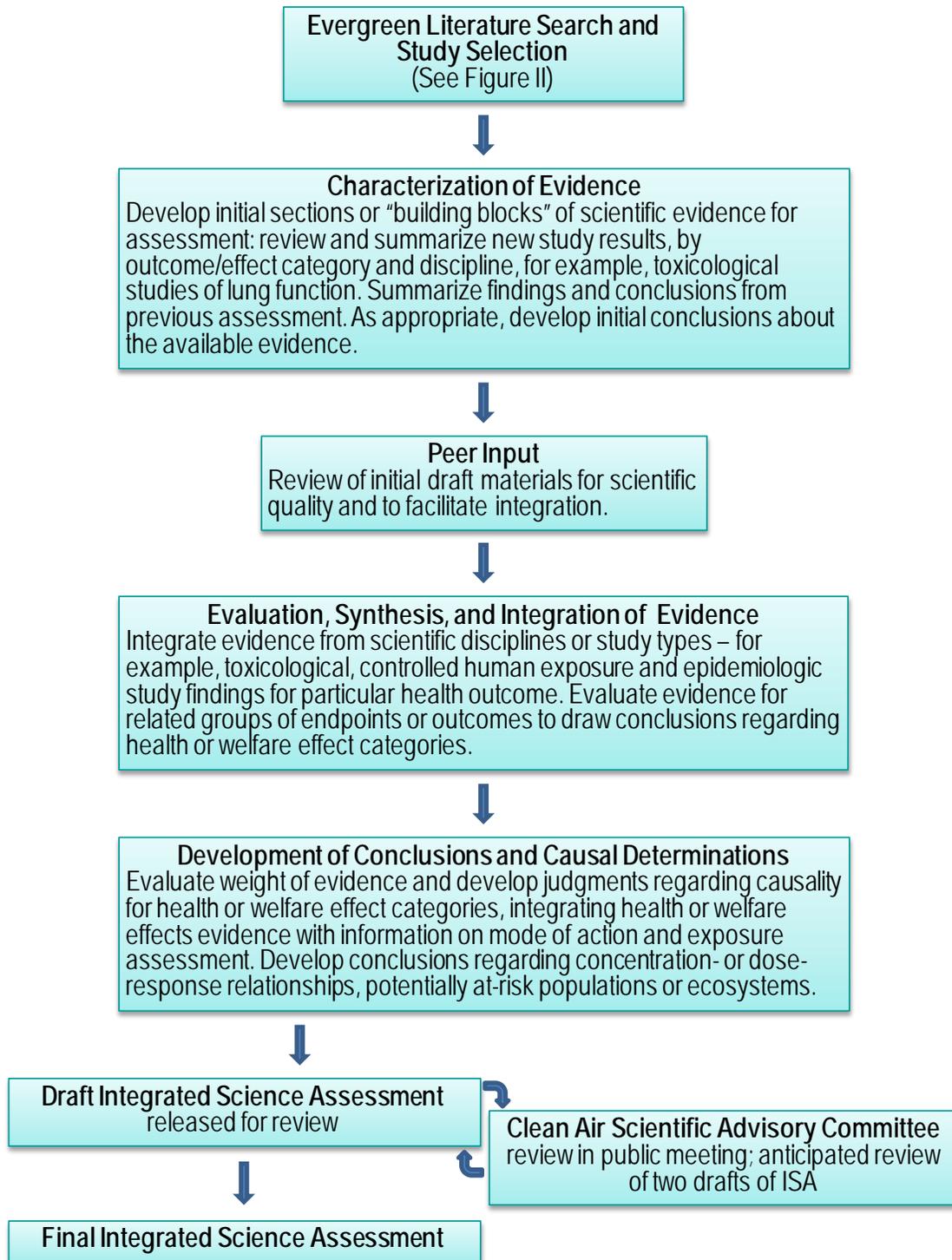


Figure III Characterization of the general process of ISA development.

EPA Framework for Causal Determination

1 EPA has developed a consistent and transparent basis to evaluate the causal nature of air
2 pollution-related health or welfare effects for use in developing ISAs. The framework
3 described below establishes uniform language concerning causality and brings more
4 specificity to the findings. This standardized language was drawn from sources across the
5 federal government and wider scientific community, especially the National Academy of
6 Sciences (NAS) Institute of Medicine (IOM) document, *Improving the Presumptive*
7 *Disability Decision-Making Process for Veterans* ([2008](#)), a comprehensive report on
8 evaluating causality. This framework:

- 9 ▪ describes the kinds of scientific evidence used in establishing a general causal
10 relationship between exposure and health effects;
- 11 ▪ characterizes the evidence necessary to reach a conclusion about the existence
12 of a causal relationship;
- 13 ▪ identifies issues and approaches related to uncertainty; and
- 14 ▪ provides a framework for classifying and characterizing the weight of
15 evidence in support of a general causal relationship.

16 Approaches to assessing the separate and combined lines of evidence
17 (e.g., epidemiologic, controlled human exposure, and animal toxicological studies) have
18 been formulated by a number of regulatory and science agencies, including the IOM of
19 the NAS ([2008](#)), International Agency for Research on Cancer ([2006](#)), U.S. EPA ([2005](#)),
20 and Centers for Disease Control and Prevention ([2004](#)). Causal inference criteria have
21 also been described for ecological effects evidence ([U.S. EPA, 1998a](#); [Fox, 1991](#)). These
22 formalized approaches offer guidance for assessing causality. The frameworks are similar
23 in nature, although adapted to different purposes, and have proven effective in providing
24 a uniform structure and language for causal determinations.

Evaluating Evidence for Inferring Causation

25 The 1964 Surgeon General’s report defined “cause” as a “significant, effectual
26 relationship between an agent and an associated disorder or disease in the host” ([HEW,
27 1964](#)); more generally, a cause is defined as an agent that brings about an effect or a
28 result. An association is the statistical relationship among variables; alone, however, it is
29 insufficient proof of a causal relationship between an exposure and a health outcome.
30 Unlike an association, a causal claim supports the creation of counterfactual claims, that

1 is, a claim about what the world would have been like under different or changed
2 circumstances ([Samet and Bodurow, 2008](#)).

3 Many of the health and environmental outcomes reported in these studies have complex
4 etiologies. Diseases such as asthma, coronary heart disease (CHD) or cancer are typically
5 initiated by multiple agents. Outcomes depend on a variety of factors, such as age,
6 genetic susceptibility, nutritional status, immune competence, and social factors ([Samet
7 and Bodurow, 2008](#); [Gee and Payne-Sturges, 2004](#)). Effects on ecosystems are often also
8 multifactorial with a complex web of causation. Further, exposure to a combination of
9 agents could cause synergistic or antagonistic effects. Thus, the observed risk may
10 represent the net effect of many actions and counteractions.

11 In estimating the causal influence of an exposure on health or environmental effects, it is
12 recognized that scientific findings incorporate uncertainty. “Uncertainty” can be defined
13 as having limited knowledge to exactly describe an existing state or future outcome,
14 e.g., the lack of knowledge about the correct value for a specific measure or estimate.
15 Uncertainty analysis may be qualitative or quantitative in nature. In many cases, the
16 analysis is qualitative, and can include professional judgment or inferences based on
17 analogy with similar situations. Quantitative uncertainty analysis may include use of
18 simple measures (e.g., ranges) and analytical techniques. Quantitative uncertainty
19 analysis might progress to more complex measures and techniques, if needed for decision
20 support. Various approaches to evaluating uncertainty include classical statistical
21 methods, sensitivity analysis, or probabilistic uncertainty analysis, in order of increasing
22 complexity and data requirements. However, data may not be available for all aspects of
23 an assessment and those data that are available may be of questionable or unknown
24 quality. Ultimately, the assessment is based on a number of assumptions with varying
25 degrees of uncertainty. The ISA generally evaluates uncertainties qualitatively in
26 assessing the evidence from across studies; in some situations quantitative analysis
27 approaches, such as meta-regression, may be used.

28 Publication bias is a source of uncertainty regarding the magnitude of health risk
29 estimates. It is well understood that studies reporting non-null findings are more likely to
30 be published than reports of null findings, and publication bias can also result in
31 overestimation of effect estimate sizes ([Ioannidis, 2008](#)). For example, effect estimates
32 from single-city epidemiologic studies have been found to be generally larger than those
33 from multicity studies ([Bell et al., 2005](#)).

Consideration of Evidence from Scientific Disciplines

1 Moving from association to causation involves the elimination of alternative explanations
2 for the association. The ISA focuses on evaluation of the findings from the body of
3 evidence, drawing upon the results of all studies determined to meet the criteria described
4 previously. Causality determinations are based on the evaluation and synthesis of
5 evidence from across scientific disciplines. The relative importance of different types of
6 evidence varies by pollutant or assessment, as does the availability of different types of
7 evidence for causality determination. Three general types of studies inform consideration
8 of human health effects: controlled human exposure, epidemiologic and toxicological
9 studies. Evidence on ecological or welfare effects may be drawn from a variety of
10 experimental approaches (e.g., greenhouse, laboratory, field) and numerous disciplines
11 (e.g., community ecology, biogeochemistry and paleontological/historical
12 reconstructions).

13 Direct evidence of a relationship between pollutant exposures and human health effects
14 comes from controlled human exposure studies. Controlled human exposure studies
15 experimentally evaluate the health effects of administered exposures in human volunteers
16 under highly controlled laboratory conditions. Also referred to as human clinical studies,
17 these experiments allow investigators to expose subjects to known concentrations of air
18 pollutants under carefully regulated environmental conditions and activity levels. In some
19 instances, controlled human exposure studies can also be used to characterize
20 concentration-response relationships at pollutant concentrations relevant to ambient
21 conditions. Controlled human exposures are typically conducted using a randomized
22 crossover design, with subjects exposed both to the pollutant and a clean air control. In
23 this way, subjects serve as their own controls, effectively controlling for many potential
24 confounders. However, controlled human exposure studies are limited by a number of
25 factors, including small sample size and short exposure time. For example, exposure
26 patterns relevant to understanding real-world exposures, especially long-term exposures,
27 are generally not practical to replicate in a laboratory setting. In addition, although
28 subjects do serve as their own controls, personal exposure to pollutants in the hours and
29 days preceding the controlled exposures may vary significantly between and within
30 individuals. Finally, controlled human exposure studies require investigators to adhere to
31 stringent health criteria for subjects included in the study, and therefore the results often
32 cannot be generalized to an entire population. Although some controlled human exposure
33 studies have included health-compromised individuals such as those with respiratory or
34 cardiovascular disease, these individuals must also be relatively healthy and may not
35 represent the most sensitive individuals in the population. In addition, the study design is
36 limited to exposures and endpoints that are not expected to result in severe health
37 outcomes. Thus, not observing an effect in controlled human exposure studies does not

1 necessarily mean that a causal relationship does not exist. While controlled human
2 exposure studies provide important information on the biological plausibility of
3 associations observed in epidemiologic studies, observed effects in these studies may
4 underestimate the response in certain populations.

5 Epidemiologic studies provide important information on the associations between health
6 effects and exposure of human populations to ambient air pollution. In epidemiologic or
7 observational studies of humans, the investigator generally does not control exposures or
8 intervene with the study population. Broadly, observational studies can describe
9 associations between exposures and effects. These studies fall into several categories:
10 e.g., cross-sectional, prospective cohort, panel and time-series studies. “Natural
11 experiments” offer the opportunity to investigate changes in health related to a change in
12 exposure, such as closure of a pollution source.

13 In evaluating epidemiologic studies, consideration of many study design factors and
14 issues must be taken into account to properly inform their interpretation. One key
15 consideration is evaluation of the potential contribution of the pollutant to a health
16 outcome when it is a component of a complex air pollutant mixture. Reported effect
17 estimates in epidemiologic studies may reflect: independent effects on health outcomes;
18 effects of the pollutant acting as an indicator of a copollutant or a complex ambient air
19 pollution mixture; effects resulting from interactions between that pollutant and
20 copollutants.

21 In the evaluation of epidemiologic evidence, one important consideration is potential
22 confounding. Confounding is “... a confusion of effects. Specifically, the apparent effect
23 of the exposure of interest is distorted because the effect of an extraneous factor is
24 mistaken for or mixed with the actual exposure effect (which may be null)” ([Rothman
25 and Greenland, 1998](#)). One approach to remove spurious associations due to possible
26 confounders is to control for characteristics that may differ between exposed and
27 unexposed persons; this is frequently termed “adjustment.” Scientific judgment is needed
28 to evaluate likely sources and extent of confounding, together with consideration of how
29 well the existing constellation of study designs, results, and analyses address this
30 potential threat to inferential validity. A confounder is associated with both the exposure
31 and the effect; for example, confounding can occur between correlated pollutants that are
32 associated with the same effect.

33 Several statistical methods are available to detect and control for potential confounders,
34 with none of them being completely satisfactory. Multivariable regression models
35 constitute one tool for estimating the association between exposure and outcome after
36 adjusting for characteristics of participants that might confound the results. The use of
37 multipollutant regression models has been the prevailing approach for controlling

1 potential confounding by copollutants in air pollution health effects studies. Finding the
2 likely causal pollutant from multipollutant regression models is made difficult by the
3 possibility that one or more air pollutants may be acting as a surrogate for an unmeasured
4 or poorly measured pollutant or for a particular mixture of pollutants. In addition, more
5 than one pollutant may exert similar health effects, resulting in independently observed
6 associations for multiple pollutants. The number and degree of diversity of covariates, as
7 well as their relevance to the potential confounders, remain matters of scientific
8 judgment. Despite these limitations, the use of multipollutant models is still the
9 prevailing approach employed in most air pollution epidemiologic studies and provides
10 some insight into the potential for confounding or interaction among pollutants.

11 Confidence that unmeasured confounders are not producing the findings is increased
12 when multiple studies are conducted in various settings using different subjects or
13 exposures, each of which might eliminate another source of confounding from
14 consideration. For example, multicity studies can provide insight on potential
15 confounding through the use of a consistent method to analyze data from across locations
16 with different levels of copollutants and other covariates. Intervention studies, because of
17 their quasi-experimental nature, can be particularly useful in characterizing causation.

18 Another important consideration in the evaluation of epidemiologic evidence is effect
19 modification, which occurs when the effect differs between subgroups or strata; for
20 example, effect estimates that vary by age group or potential risk factor. “Effect-measure
21 modification differs from confounding in several ways. The main difference is that,
22 whereas confounding is a bias that the investigator hopes to prevent or remove from the
23 effect estimate, effect-measure modification is a property of the effect under study ... In
24 epidemiologic analysis one tries to eliminate confounding but one tries to detect and
25 estimate effect-measure modification” ([Rothman and Greenland, 1998](#)). When a risk
26 factor is a confounder, it is the true cause of the association observed between the
27 exposure and the outcome; when a risk factor is an effect modifier, it changes the
28 magnitude of the association between the exposure and the outcome in stratified analyses.
29 For example, the presence of a preexisting disease or indicator of low socioeconomic
30 status may be an effect modifier in causing increased risk of effects related to air
31 pollution exposure. It is often possible to stratify the relationship between health outcome
32 and exposure by one or more of these potential effect modifiers. For variables that
33 modify the association, effect estimates in each stratum will be different from one another
34 and different from the overall estimate, indicating a different exposure-response
35 relationship may exist in populations represented by these variables.

36 Exposure measurement error, which refers to the uncertainty associated with using
37 exposure metrics to represent the actual exposure of an individual or population, can be

1 an important contributor to variability in air pollution epidemiologic study results.
2 Exposure error can under- or over-estimate epidemiologic associations between ambient
3 pollutant concentrations and health outcomes by biasing effect estimates toward or away
4 from the null, and tends to widen confidence intervals around those estimates. There are
5 several components that contribute to exposure measurement error in air pollution
6 epidemiologic studies, including the difference between true and measured ambient
7 concentrations, the difference between average personal exposure to ambient pollutants
8 and ambient concentrations at central monitoring sites, and the use of average population
9 exposure rather than individual exposure estimates. Factors that could influence exposure
10 estimates include nonambient sources of exposure, topography of the natural and built
11 environment, meteorology, measurement errors, time-location-activity patterns and extent
12 to which ambient pollutants penetrate indoor environments. The importance of exposure
13 misclassification varies with study design and is dependent on the spatial and temporal
14 aspects of the design.

15 The third main type of health effects evidence, animal toxicological studies, provides
16 information on the pollutant's biological action under controlled and monitored exposure
17 circumstances. Taking into account physiological differences of the experimental species
18 from humans, these studies inform characterization of health effects of concern,
19 exposure-response relationships and MOAs. Further, animal models can inform
20 determinations of at-risk populations. These studies evaluate the effects of exposures to a
21 variety of pollutants in a highly controlled laboratory setting and allow exploration of
22 toxicological pathways or mechanisms by which a pollutant may cause effects.
23 Understanding the biological mechanisms underlying various health outcomes can prove
24 crucial in establishing or negating causality. In the absence of human studies data,
25 extensive, well-conducted animal toxicological studies can support determinations of
26 causality, if the evidence base indicates that similar responses are expected in humans
27 under ambient exposure conditions.

28 Interpretations of animal toxicological studies are affected by limitations associated with
29 extrapolation between animal and human responses. The differences between humans
30 and other species have to be taken into consideration, including metabolism, hormonal
31 regulation, breathing pattern, and differences in lung structure and anatomy. Also, in spite
32 of a high degree of homology and the existence of a high percentage of orthologous
33 genes across humans and rodents (particularly mice), extrapolation of molecular
34 alterations at the gene level is complicated by species-specific differences in
35 transcriptional regulation. Given these differences, there are uncertainties associated with
36 quantitative extrapolations of observed pollutant-induced pathophysiological alterations
37 between laboratory animals and humans, as those alterations are under the control of
38 widely varying biochemical, endocrine, and neuronal factors.

1 For ecological effects assessment, both laboratory and field studies (including field
2 experiments and observational studies) can provide useful data for causality
3 determination. Because conditions can be controlled in laboratory studies, responses may
4 be less variable and smaller differences easier to detect. However, the control conditions
5 may limit the range of responses (e.g., animals may not be able to seek alternative food
6 sources), so they may not reflect responses that would occur in the natural environment.
7 In addition, larger-scale processes are difficult to reproduce in the laboratory.

8 Field observational studies measure biological changes in uncontrolled situations, and
9 describe an association between a disturbance and an ecological effect. Field data can
10 provide important information for assessments of multiple stressors or where site-specific
11 factors significantly influence exposure. They are also often useful for analyses of larger
12 geographic scales and higher levels of biological organization. However, because
13 conditions are not controlled, variability is expected to be higher and differences harder
14 to detect. Field surveys are most useful for linking stressors with effects when stressor
15 and effect levels are measured concurrently. The presence of confounding factors can
16 make it difficult to attribute observed effects to specific stressors.

17 Intermediate between laboratory and field are studies that use environmental media
18 collected from the field to examine response in the laboratory, and experiments that are
19 performed in the natural environment while controlling for some environmental
20 conditions (i.e., mesocosm studies). This type of study in manipulated natural
21 environments can be considered a hybrid between a field experiment and laboratory study
22 since some aspects are performed under controlled conditions but others are not. They
23 make it possible to observe community and/or ecosystem dynamics, and provide strong
24 evidence for causality when combined with findings of studies that have been made
25 under more controlled conditions.

Application of Framework for Causal Determination

26 In its evaluation of the scientific evidence on health or welfare effects of criteria
27 pollutants, EPA determines the weight of evidence in support of causation and
28 characterizes the strength of any resulting causal classification. EPA also evaluates the
29 quantitative evidence and draws scientific conclusions, to the extent possible, regarding
30 the concentration-response relationships and the loads to ecosystems, exposure doses or
31 concentrations, duration and pattern of exposures at which effects are observed.

Table I Aspects to aid in judging causality

| | |
|--|---|
| Consistency of the observed association | An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered. |
| Coherence | An inference of causality from one line of evidence (e.g., epidemiologic, clinical or animal studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. Evidence on ecological or welfare effects may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and subdisciplines of ecology (e.g., community ecology, biogeochemistry and paleontological/historical reconstructions). The coherence of evidence from various fields greatly adds to the strength of an inference of causality. In addition, there may be coherence in demonstrating effects across multiple study designs or related health endpoints within one scientific line of evidence. |
| Biological plausibility. | An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A proposed mechanistic linking between an effect and exposure to the agent is an important source of support for causality, especially when data establishing the existence and functioning of those mechanistic links are available. |
| Biological gradient (exposure-response relationship) | A well-characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times). |
| Strength of the observed association | The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, it is noted that a small magnitude in an effect estimate may represent a substantial effect in a population. |
| Experimental evidence | Strong evidence for causality can be provided through “natural experiments” when a change in exposure is found to result in a change in occurrence or frequency of health or welfare effects. |
| Temporal relationship of the observed association | Evidence of a temporal sequence between the introduction of an agent, and appearance of the effect, constitutes another argument in favor of causality. |
| Specificity of the observed association | Evidence linking a specific outcome to an exposure can provide a strong argument for causation. However, it must be recognized that rarely, if ever, does exposure to a pollutant invariably predict the occurrence of an outcome, and that a given outcome may have multiple causes. |
| Analogy | Structure activity relationships and information on the agent’s structural analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality. |

1 To aid judgment, various “aspects”¹ of causality have been discussed by many
2 philosophers and scientists. The 1964 Surgeon General’s report on tobacco smoking
3 discussed criteria for the evaluation of epidemiologic studies, focusing on consistency,
4 strength, specificity, temporal relationship, and coherence (HEW, 1964). Sir Austin
5 Bradford Hill (Hill, 1965) articulated aspects of causality in epidemiology and public
6 health that have been widely used (Samet and Bodurow, 2008; IARC, 2006; U.S. EPA,
7 2005; CDC, 2004). These aspects (Hill, 1965) have been modified (Table I) for use in
8 causal determinations specific to health and welfare effects for pollutant exposures (U.S.
9 EPA, 2009d).² Although these aspects provide a framework for assessing the evidence,
10 they do not lend themselves to being considered in terms of simple formulas or fixed

¹ The “aspects” described by Sir Austin Bradford Hill (Hill, 1965) have become, in the subsequent literature, more commonly described as “criteria.” The original term “aspects” is used here to avoid confusion with “criteria” as it is used, with different meaning, in the Clean Air Act.

² The Hill aspects were developed for interpretation of epidemiologic results. They have been modified here for use with a broader array of data, i.e., epidemiologic, controlled human exposure, ecological, and animal toxicological studies, as well as in vitro data, and to be more consistent with EPA’s Guidelines for Carcinogen Risk Assessment.

1 rules of evidence leading to conclusions about causality ([Hill, 1965](#)). For example, one
2 cannot simply count the number of studies reporting statistically significant results or
3 statistically nonsignificant results and reach credible conclusions about the relative
4 weight of the evidence and the likelihood of causality. Rather, these aspects are taken into
5 account with the goal of producing an objective appraisal of the evidence, informed by
6 peer and public comment and advice, which includes weighing alternative views on
7 controversial issues. In addition, it is important to note that the aspects in Table I cannot
8 be used as a strict checklist, but rather to determine the weight of the evidence for
9 inferring causality. In particular, not meeting one or more of the principles does not
10 automatically preclude a determination of causality [see discussion in ([CDC, 2004](#))].

Determination of Causality

11 In the ISA, EPA assesses the body of relevant literature, building upon evidence available
12 during previous NAAQS reviews, to draw conclusions on the causal relationships
13 between relevant pollutant exposures and health or environmental effects. ISAs use a
14 five-level hierarchy that classifies the weight of evidence for causation¹. In developing
15 this hierarchy, EPA has drawn on the work of previous evaluations, most prominently the
16 IOM's *Improving the Presumptive Disability Decision-Making Process for Veterans*
17 ([Samet and Bodurow, 2008](#)), EPA's Guidelines for Carcinogen Risk Assessment ([U.S.
18 EPA, 2005](#)), and the U.S. Surgeon General's smoking report ([CDC, 2004](#)). This weight
19 of evidence evaluation is based on various lines of evidence from across the health and
20 environmental effects disciplines. These separate judgments are integrated into a
21 qualitative statement about the overall weight of the evidence and causality. The five
22 descriptors for causal determination are described in Table II.

23 Determination of causality involves the evaluation of evidence for different types of
24 health, ecological or welfare effects associated with short- and long-term exposure
25 periods. In making determinations of causality, evidence is evaluated for major outcome
26 categories and then conclusions are drawn based upon the integration of evidence from
27 across disciplines and also across the spectrum of related endpoints. In making causal
28 judgments, the ISA focuses on major outcome categories (e.g., respiratory effects,
29 vegetation growth), by evaluating the coherence of evidence across a spectrum of related
30 endpoints (e.g., health effects ranging from inflammatory effects to respiratory mortality)
31 to draw conclusions regarding causality. In discussing the causal determination, EPA

¹ The Center for Disease Control (CDC) and IOM frameworks use a four-category hierarchy for the strength of the evidence. A five-level hierarchy is used here to be consistent with the EPA Guidelines for Carcinogen Risk Assessment and to provide a more nuanced set of categories.

1 characterizes the evidence on which the judgment is based, including strength of
2 evidence for individual endpoints within the major outcome category.

3 In drawing judgments regarding causality for the criteria air pollutants, the ISA focuses
4 on evidence of effects in the range of relevant pollutant exposures or doses, and not on
5 determination of causality at any dose. Emphasis is placed on evidence of effects at doses
6 (e.g., blood lead concentration) or exposures (e.g., air concentrations) that are relevant to,
7 or somewhat above, those currently experienced by the population. The extent to which
8 studies of higher concentrations are considered varies by pollutant and major outcome
9 category, but generally includes those with doses or exposures in the range of one to two
10 orders of magnitude above current or ambient conditions. Studies that use higher doses or
11 exposures may also be considered to the extent that they provide useful information to
12 inform understanding of mode of action, interspecies differences, or factors that may
13 increase risk of effects for a population. Thus, a causality determination is based on
14 weight of evidence evaluation for health, ecological or welfare effects, focusing on the
15 evidence from exposures or doses generally ranging from current levels to one or two
16 orders of magnitude above current levels.

17 In addition, EPA evaluates evidence relevant to understand the quantitative relationships
18 between pollutant exposures and health, ecological or welfare effects. This includes
19 evaluation of the form of concentration-response or dose-response relationships and, to
20 the extent possible, drawing conclusions on the levels at which effects are observed. The
21 ISA also draws scientific conclusions regarding important exposure conditions for effects
22 and populations that may be at greater risk for effects, as described in the following
23 section.

Table II Weight of evidence for causal determination

| | Health Effects | Ecological and Welfare Effects |
|--|--|--|
| Causal relationship | Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes multiple high-quality studies | Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. Controlled exposure studies (laboratory or small- to medium-scale field studies) provide the strongest evidence for causality, but the scope of inference may be limited. Generally, determination is based on multiple studies conducted by multiple research groups, and evidence that is considered sufficient to infer a causal relationship is usually obtained from the joint consideration of many lines of evidence that reinforce each other. |
| Likely to be a causal relationship | Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes multiple high-quality studies. | Evidence is sufficient to conclude that there is a likely causal association with relevant pollutant exposures. That is, an association has been observed between the pollutant and the outcome in studies in which chance, bias and confounding are minimized, but uncertainties remain. For example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, determination is based on multiple studies in multiple research groups. |
| Suggestive of a causal relationship | Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited. For example, (a) at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent; or (b) a well-conducted toxicological study, such as those conducted in the National Toxicology Program (NTP), shows effects in animal species. | Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, bias and confounding cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent. |
| Inadequate to infer a causal relationship | Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect. | The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect. |
| Not likely to be a causal relationship | Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations, are mutually consistent in not showing an effect at any level of exposure. | Several adequate studies, examining relationships with relevant exposures, are consistent in failing to show an effect at any level of exposure. |

Quantitative Relationships: Effects on Human Populations

1 Once a determination is made regarding the causal relationship between the pollutant and
2 outcome category, important questions regarding quantitative relationships include:

- 3 ▪ What is the concentration-response, exposure-response, or dose-response
4 relationship in the human population?
- 5 ▪ What is the interrelationship between incidence and severity of effect?
- 6 ▪ What exposure conditions (dose or exposure, duration and pattern) are
7 important?
- 8 ▪ What populations and lifestages appear to be differentially affected (i.e., more
9 at risk of experiencing effects)?

10 To address these questions, the entirety of quantitative evidence is evaluated to
11 characterize pollutant concentrations and exposure durations at which effects were
12 observed for exposed populations, including populations and lifestages potentially at
13 increased risk. To accomplish this, evidence is considered from multiple and diverse
14 types of studies, and a study or set of studies that best approximates the concentration-
15 response relationships between health outcomes and the pollutant may be identified.
16 Controlled human exposure studies provide the most direct and quantifiable exposure-
17 response data on the human health effects of pollutant exposures. To the extent available,
18 the ISA evaluates results from across epidemiologic studies that use various methods to
19 characterize the form of relationships between the pollutant and health outcomes and
20 draws conclusions on the shape of these relationships. Animal data may also inform
21 evaluation of concentration-response relationships, particularly relative to MOAs and
22 characteristics of at-risk populations.

23 An important consideration in characterizing the public health impacts associated with
24 exposure to a pollutant is whether the concentration-response relationship is linear across
25 the range of concentrations or if nonlinear relationships exist along any part of this range.
26 Of particular interest is the shape of the concentration-response curve at and below the
27 level of the current standards. Various sources of variability and uncertainty, such as low
28 data density in the lower concentration range, possible influence of exposure
29 measurement error, and variability between individuals in susceptibility to air pollution
30 health effects, tend to smooth and “linearize” the concentration-response function, and
31 thus can obscure the existence of a threshold or nonlinear relationship. Since individual
32 thresholds vary from person to person due to individual differences such as genetic level
33 susceptibility or preexisting disease conditions (and even can vary from one time to
34 another for a given person), it can be difficult to demonstrate that a threshold exists in a
35 population study. These sources of variability and uncertainty may explain why the

1 available human data at ambient concentrations for some environmental pollutants
2 (e.g., particulate matter [PM], O₃, lead [Pb], environmental tobacco smoke [ETS],
3 radiation) do not exhibit thresholds for cancer or noncancer health effects, even though
4 likely mechanisms include nonlinear processes for some key events. These attributes of
5 human population dose-response relationships have been extensively discussed in the
6 broader epidemiologic literature ([Rothman and Greenland, 1998](#)).

7 Finally, identification of the population groups or lifestages that may be at greater risk of
8 health effects from air pollutant exposures contributes to an understanding of the public
9 health impact of pollutant exposures. In the ISA, the term “at-risk population” is used to
10 encompass populations or lifestages that have a greater likelihood of experiencing health
11 effects related to exposure to an air pollutant due to a variety of factors; other terms used
12 in the literature include susceptible, vulnerable, and sensitive. These factors may be
13 intrinsic, such as genetic or developmental factors, race, gender, lifestage, or the presence
14 of preexisting diseases, or they may be extrinsic, such as socioeconomic status (SES),
15 activity pattern and exercise level, reduced access to health care, low educational
16 attainment, or increased pollutant exposures (e.g., near roadways). Epidemiologic studies
17 can help identify populations potentially at increased risk of effects by evaluating health
18 responses in the study population. Examples include testing for interactions or effect
19 modification by factors such as gender, age group, or health status. Experimental studies
20 using animal models of susceptibility or disease can also inform the extent to which
21 health risks are likely greater in specific population groups.

Quantitative Relationships: Effects on Ecosystems or Public Welfare

22 Key questions for understanding the quantitative relationships between exposure (or
23 concentration or deposition) to a pollutant and risk to ecosystems or the public welfare
24 include:

- 25 ▪ What elements of the ecosystem (e.g., types, regions, taxonomic groups,
26 populations, functions, etc.) appear to be affected, or are more sensitive to
27 effects? Are there differences between locations or materials in welfare effects
28 responses, such as impaired visibility or materials damage?
- 29 ▪ Under what exposure conditions (amount deposited or concentration, duration
30 and pattern) are effects seen?
- 31 ▪ What is the shape of the concentration-response or exposure-response
32 relationship?

33 Evaluations of causality generally consider the probability of quantitative changes in
34 ecological and welfare effects in response to exposure. A challenge to the quantification

1 of exposure-response relationships for ecological effects is the great regional and local
2 spatial variability, as well as temporal variability, in ecosystems. Thus, exposure-
3 response relationships are often determined for a specific ecological system and scale,
4 rather than at the national or even regional scale. Quantitative relationships therefore are
5 available site by site and may differ greatly between ecosystems.

Concepts in Evaluating Adversity of Health Effects

6 In evaluating health evidence, a number of factors can be considered in delineating
7 between adverse and nonadverse health effects resulting from exposure to air pollution.
8 Some health outcomes, such as hospitalization for respiratory or cardiovascular diseases,
9 are clearly considered adverse. It is more difficult to determine the extent of change that
10 constitutes adversity in more subtle health measures. These include a wide variety of
11 responses, such as alterations in markers of inflammation or oxidative stress, changes in
12 pulmonary function or heart rate variability, or alterations in neurocognitive function
13 measures. The challenge is determining the magnitude of change in these measures when
14 there is no clear point at which a change become adverse; for example, what percentage
15 change in a lung function measure represents an adverse effect. What constitutes an
16 adverse health effect may vary between populations. Some changes that may not be
17 considered adverse in healthy individuals would be potentially adverse in more at-risk
18 individuals.

19 For example, the extent to which changes in lung function are adverse has been discussed
20 by the American Thoracic Society (ATS) in an official statement titled *What Constitutes*
21 *an Adverse Health Effect of Air Pollution?* (2000b). An air pollution-induced shift in the
22 population distribution of a given risk factor for a health outcome was viewed as adverse,
23 even though it may not increase the risk of any one individual to an unacceptable level.
24 For example, a population of asthmatics could have a distribution of lung function such
25 that no identifiable individual has a level associated with significant impairment.
26 Exposure to air pollution could shift the distribution such that no identifiable individual
27 experiences clinically relevant effects. This shift toward decreased lung function,
28 however, would be considered adverse because individuals within the population would
29 have diminished reserve function and therefore would be at increased risk to further
30 environmental insult. The committee also observed that elevations of biomarkers, such as
31 cell number and types, cytokines and reactive oxygen species, may signal risk for ongoing
32 injury and clinical effects or may simply indicate transient responses that can provide
33 insights into mechanisms of injury, thus illustrating the lack of clear boundaries that
34 separate adverse from nonadverse effects.

1 The more subtle health outcomes may be connected mechanistically to health events that
2 are clearly adverse. For example, air pollution may affect markers of transient myocardial
3 ischemia such as ST-segment abnormalities and onset of exertional angina. These effects
4 may not be apparent to the individual, yet may still increase the risk of a number of
5 cardiac events, including myocardial infarction and sudden death. Thus, small changes in
6 physiological measures may not appear to be clearly adverse when considered alone, but
7 may be a part of a coherent and biologically plausible chain of related health outcomes
8 that range up to responses that are very clearly adverse, such as hospitalization or
9 mortality.

Concepts in Evaluating Adversity of Ecological Effects

10 Adversity of ecological effects can be understood in terms ranging in scale from the
11 cellular level to the individual organism and to the population, community, and
12 ecosystem levels. In the context of ecology, a population is a group of individuals of the
13 same species, and a community is an assemblage of populations of different species
14 interacting with one another that inhabit an area. An ecosystem is the interactive system
15 formed from all living organisms and their abiotic (physical and chemical) environment
16 within a given area ([IPCC, 2007a](#)). The boundaries of what could be called an ecosystem
17 are somewhat arbitrary, depending on the focus of interest or study. Thus, the extent of an
18 ecosystem may range from very small spatial scales to, ultimately, the entire Earth
19 ([IPCC, 2007a](#)).

20 Effects on an individual organism are generally not considered to be adverse to public
21 welfare. However if effects occur to enough individuals within a population, then
22 communities and ecosystems may be disrupted. Changes to populations, communities
23 and ecosystems can in turn result in an alteration of ecosystem processes. Ecosystem
24 processes are defined as the metabolic functions of ecosystems including energy flow,
25 elemental cycling, and the production, consumption and decomposition of organic matter
26 ([U.S. EPA, 2002](#)). Growth, reproduction, and mortality are species-level endpoints that
27 can be clearly linked to community and ecosystem effects and are considered to be
28 adverse when negatively affected. Other endpoints such as changes in behavior and
29 physiological stress can decrease ecological fitness of an organism, but are harder to link
30 unequivocally to effects at the population, community, and ecosystem level. The degree
31 to which pollutant exposure is considered adverse may also depend on the location and its
32 intended use (i.e., city park, commercial, cropland). Support for consideration of
33 adversity beyond the species level by making explicit the linkages between stress-related
34 effects at the species and effects at the ecosystem level is found in *A Framework for*
35 *Assessing and Reporting on Ecological Condition: an SAB report* ([U.S. EPA, 2002](#)).
36 Additionally, the National Acid Precipitation Assessment Program (NAPAP) uses the

1 following working definition of “adverse ecological effects” in the preparation of reports
2 to Congress mandated by the Clean Air Act: “any injury (i.e., loss of chemical or physical
3 quality or viability) to any ecological or ecosystem component, up to and including at the
4 regional level, over both long and short terms.”

5 On a broader scale, ecosystem services may provide indicators for ecological impacts.
6 Ecosystem services are the benefits that people obtain from ecosystems ([UNEP, 2003](#)).
7 According to the Millennium Ecosystem Assessment, ecosystem services include:
8 “provisioning services such as food and water; regulating services such as regulation of
9 floods, drought, land degradation, and disease; supporting services such as soil formation
10 and nutrient cycling; and cultural services such as recreational, spiritual, religious and
11 other nonmaterial benefits.” For example, a more subtle ecological effect of pollution
12 exposure may result in a clearly adverse impact on ecosystem services if it results in a
13 population decline in a species that is recreationally or culturally important.

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LEGISLATIVE AND HISTORICAL BACKGROUND

Legislative Requirements for the NAAQS Review

1 Two sections of the Clean Air Act (CAA) govern the establishment and revision of
2 the National Ambient Air Quality Standards (NAAQS). Section 108 (42 USC §7408)
3 directs the Administrator to identify and list certain air pollutants and then to issue air
4 quality criteria for those pollutants. The Administrator is to list those air pollutants
5 that in her “judgement; cause or contribute to air pollution which may reasonably be
6 anticipated to endanger public health or welfare;” ... ”the presence of which in the
7 ambient air results from numerous or diverse mobile or stationary sources” and “for
8 which ... [the Administrator] plans to issue air quality criteria...” ([CAA, 1990a](#)). Air
9 quality criteria are intended to “accurately reflect the latest scientific knowledge
10 useful in indicating the kind and extent of identifiable effects on public health or
11 welfare, which may be expected from the presence of [a] pollutant in ambient air ...”
12 [42 USC §7408(b)].

13 Section 109 ([CAA, 1990b](#)) directs the Administrator to propose and promulgate
14 “primary” and “secondary” NAAQS for pollutants for which air quality criteria have
15 been issued. Section 109(b)(1) defines a primary standard as one “the attainment and
16 maintenance of which in the judgment of the Administrator, based on such criteria
17 and allowing an adequate margin of safety, are requisite to protect the public
18 health.”¹ A secondary standard, as defined in section 109(b)(2), must “specify a level
19 of air quality the attainment and maintenance of which, in the judgment of the
20 Administrator, based on such criteria, is required to protect the public welfare from
21 any known or anticipated adverse effects associated with the presence of [the]
22 pollutant in the ambient air.”²

23 The requirement that primary standards include an adequate margin of safety was
24 intended to address uncertainties associated with inconclusive scientific and technical
25 information available at the time of standard setting. It was also intended to provide a
26 reasonable degree of protection against hazards that research has not yet identified.
27 See *Lead Industries Association v. EPA*, 647 F.2d 1130, 1154 (D.C. Cir 1980), cert.
28 denied, 449 U.S. 1042 (1980); *American Petroleum Institute v. Costle*, 665 F.2d
29 1176, 1186 (D.C. Cir. (1981), cert. denied, 455 U.S. 1034 (1982). Both kinds of

¹ The legislative history of section 109 indicates that a primary standard is to be set at “the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population,” and that for this purpose “reference should be made to a representative sample of persons comprising the sensitive group rather than to a single person in such a group” [S. Rep. No. 91-1196, 91st Cong., 2d Sess. 10 (1970)].

² Welfare effects as defined in section 302(h) include, but are not limited to, “effects on soils, water, crops, vegetation, man-made materials, animals, wildlife, weather, visibility and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being” ([CAA, 2005](#)).

1 uncertainties are components of the risk associated with pollution at levels below
2 those at which human health effects can be said to occur with reasonable scientific
3 certainty. Thus, in selecting primary standards that include an adequate margin of
4 safety, the Administrator is seeking not only to prevent pollution levels that have
5 been demonstrated to be harmful but also to prevent lower pollutant levels that may
6 pose an unacceptable risk of harm, even if the risk is not precisely identified as to
7 nature or degree. The CAA does not require the Administrator to establish a primary
8 NAAQS at a zero-risk level or at background concentration levels, see *Lead*
9 *Industries v. EPA*, 647 F.2d at 1156 n.51, but rather at a level that reduces risk
10 sufficiently so as to protect public health with an adequate margin of safety.

11 In addressing the requirement for a margin of safety, EPA considers such factors as
12 the nature and severity of the health effects involved, the size of the sensitive
13 population(s) at risk, and the kind and degree of the uncertainties that must be
14 addressed. The selection of any particular approach to providing an adequate margin
15 of safety is a policy choice left specifically to the Administrator’s judgment. See
16 *Lead Industries Association v. EPA*, supra, 647 F.2d at 1161-1162; *Whitman v.*
17 *American Trucking Associations*, 531 U.S. 457, 495 (2001).

18 In setting standards that are “requisite” to protect public health and welfare, as
19 provided in Section 109(b), EPA’s task is to establish standards that are neither more
20 nor less stringent than necessary for these purposes. In so doing, EPA may not
21 consider the costs of implementing the standards. [See generally, *Whitman v.*
22 *American Trucking Associations*, 531 U.S. 457, 465-472, 475-76. (2001)]. Likewise,
23 “[a]ttainability and technological feasibility are not relevant considerations in the
24 promulgation of national ambient air quality standards.” *American Petroleum*
25 *Institute v. Costle*, 665 F. 2d at 1185.

26 Section 109(d)(1) requires that “not later than December 31, 1980, and at 5-year
27 intervals thereafter, the Administrator shall complete a thorough review of the
28 criteria published under section 108 and the national ambient air quality standards ...
29 and shall make such revisions in such criteria and standards and promulgate such
30 new standards as may be appropriate...” Section 109(d)(2) requires that an
31 independent scientific review committee “shall complete a review of the criteria ...
32 and the national primary and secondary ambient air quality standards ... and shall
33 recommend to the Administrator any new ... standards and revisions of existing
34 criteria and standards as may be appropriate ...” Since the early 1980s, this
35 independent review function has been performed by CASAC.

History of the NAAQS for Ozone

Tropospheric (ground-level) O₃ is the indicator for the mix of photochemical oxidants (e.g., peroxyacetyl nitrate, hydrogen peroxide) formed from biogenic and anthropogenic precursor emissions. Naturally occurring O₃ in the troposphere can result from biogenic organic precursors reacting with naturally occurring nitrogen oxides (NO_x) and by stratospheric O₃ intrusion into the troposphere. Anthropogenic precursors of O₃, especially NO_x, and volatile organic compounds (VOCs), originate from a wide variety of stationary and mobile sources. Ambient O₃ concentrations produced by these emissions are directly affected by temperature, solar radiation, wind speed, and other meteorological factors.

NAAQS are comprised of four basic elements: indicator, averaging time, level, and form. The indicator defines the pollutant to be measured in the ambient air for the purpose of determining compliance with the standard. The averaging time defines the time period over which air quality measurements are to be obtained and averaged or cumulated, considering evidence of effects associated with various time periods of exposure. The level of a standard defines the air quality concentration used (i.e., an ambient concentration of the indicator pollutant) in determining whether the standard is achieved. The form of the standard specifies the air quality measurements that are to be used for compliance purposes (e.g., the annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years), and whether the statistic is to be averaged across multiple years. These four elements taken together determine the degree of public health and welfare protection afforded by the NAAQS.

Table III Summary of primary and secondary NAAQS promulgated for ozone during the period 1971-2008

| Final Rule | Indicator | Avg Time | Level (ppm) | Form |
|--------------------|---|----------|-------------|---|
| 1971 (36 FR 8186) | Total photochemical oxidants | 1-h | 0.08 | Not to be exceeded more than 1 hour per year |
| 1979 (44 FR 8202) | O ₃ | 1-h | 0.12 | Attainment is defined when the expected number of days per calendar year, with maximum hourly average concentration greater than 0.12 ppm, is ≤ 1 |
| 1993 (58 FR 13008) | EPA decided that revisions to the standards were not warranted at the time. | | | |
| 1997 (62 FR 38856) | O ₃ | 8-h | 0.08 | Annual fourth-highest daily maximum 8-h concentration averaged over 3 years |
| 2008 (73 FR 16483) | O ₃ | 8-h | 0.075 | Form of the standards remained unchanged relative to the 1997 standard |

1 Table III summarizes the O₃ NAAQS that have been promulgated to date. In each
2 review, the secondary standard has been set to be identical to the primary standard.
3 These reviews are briefly described below.

4 EPA first established primary and secondary NAAQS for photochemical oxidants in
5 1971 . Both primary and secondary standards were set at a level of 0.08 parts per
6 million (ppm), 1-h avg, total photochemical oxidants, not to be exceeded more than
7 1 hour per year. The standards were based on scientific information contained in the
8 1970 AQCD.

9 In 1977, EPA announced the first periodic review of the 1970 AQCD in accordance
10 with Section 109(d)(1) of the Clean Air Act. In 1978, EPA published an AQCD.
11 Based on the 1978 AQCD, EPA published proposed revisions to the original
12 NAAQS in 1978 ([U.S. EPA, 1978b](#)) and final revisions in 1979 ([U.S. EPA, 1979a](#)).
13 The level of the primary and secondary standards was revised from 0.08 to 0.12 ppm;
14 the indicator was revised from photochemical oxidants to O₃; and the form of the
15 standards was revised from a deterministic to a statistical form, which defined
16 attainment of the standards as occurring when the expected number of days per
17 calendar year with maximum hourly average concentration greater than 0.12 ppm is
18 equal to or less than one.

19 In 1982, EPA announced plans to revise the 1978 AQCD ([U.S. EPA, 1978a](#)). In
20 1983, EPA announced that the second periodic review of the primary and secondary
21 standards for O₃ had been initiated ([U.S. EPA, 1983](#)). EPA subsequently published
22 the 1986 O₃ AQCD ([U.S. EPA, 1986](#)) and 1989 Staff Paper ([U.S. EPA, 1989](#)).
23 Following publication of the 1986 O₃ AQCD, a number of scientific abstracts and
24 articles were published that appeared to be of sufficient importance concerning
25 potential health and welfare effects of O₃ to warrant preparation of a Supplement to
26 the 1986 O₃ AQCD ([Costa et al., 1992](#)). Under the terms of a court order, on August
27 10, 1992, EPA published a proposed decision ([U.S. EPA, 1992](#)) stating that revisions
28 to the existing primary and secondary standards were not appropriate at the time
29 ([U.S. EPA, 1992](#)). This notice explained that the proposed decision would complete
30 EPA's review of information on health and welfare effects of O₃ assembled over a
31 7-year period and contained in the 1986 O₃ AQCD ([U.S. EPA, 1986](#)) and its
32 Supplement to the 1986 O₃ AQCD ([Costa et al., 1992](#)). The proposal also announced
33 EPA's intention to proceed as rapidly as possible with the next review of the air
34 quality criteria and standards for O₃ in light of emerging evidence of health effects
35 related to 6- to 8-hour O₃ exposures. On March 9, 1993, EPA concluded the review
36 by deciding that revisions to the standards were not warranted at that time ([U.S.
37 EPA, 1993](#)).

1 In August 1992, EPA announced plans to initiate the third periodic review of the air
2 quality criteria and O₃ NAAQS ([U.S. EPA, 1992](#)). On the basis of the scientific
3 evidence contained in the 1996 O₃ AQCD and the 1996 Staff Paper ([U.S. EPA,
4 1996e](#)), and related technical support documents, linking exposures to ambient O₃ to
5 adverse health and welfare effects at levels allowed by the then existing standards,
6 EPA proposed to revise the primary and secondary O₃ standards on December 13,
7 1996 ([U.S. EPA, 1996d](#)). The EPA proposed to replace the then existing 1-hour
8 primary and secondary standards with 8-h avg O₃ standards set at a level of 0.08 ppm
9 (equivalent to 0.084 ppm using standard rounding conventions). The EPA also
10 proposed, in the alternative, to establish a new distinct secondary standard using a
11 biologically based cumulative seasonal form. The EPA completed the review on July
12 18, 1997 by setting the primary standard at a level of 0.08 ppm, based on the annual
13 fourth-highest daily maximum 8-h avg concentration, averaged over 3 years, and
14 setting the secondary standard identical to the revised primary standard ([U.S. EPA,
15 1997](#)).

16 On May 14, 1999, in response to challenges to EPA's 1997 decision by industry and
17 others, the U.S. Court of Appeals for the District of Columbia Circuit (D.C. Cir.)
18 remanded the O₃ NAAQS to EPA, finding that Section 109 of the CAA, as
19 interpreted by EPA, effected an unconstitutional delegation of legislative authority.
20 In addition, the D.C. Cir. directed that, in responding to the remand, EPA should
21 consider the potential beneficial health effects of O₃ pollution in shielding the public
22 from the effects of solar ultraviolet (UV) radiation, as well as adverse health effects.
23 On January 27, 2000, EPA petitioned the U.S. Supreme Court for certiorari on the
24 constitutional issue (and two other issues) but did not request review of the D.C. Cir.,
25 ruling regarding the potential beneficial health effects of O₃. On February 27, 2001,
26 the U.S. Supreme Court unanimously reversed the judgment of the D.C. Cir. on the
27 constitutional issue, holding that Section 109 of the CAA does not delegate
28 legislative power to the EPA in contravention of the Constitution, and remanded the
29 case to the D.C. Cir. to consider challenges to the O₃ NAAQS that had not been
30 addressed by that Court's earlier decisions. On March 26, 2002, the D.C. Cir. issued
31 its final decision, finding the 1997 O₃ NAAQS to be "neither arbitrary nor
32 capricious," and denied the remaining petitions for review. On November 14, 2001,
33 in response to the D.C. Cir. remand to consider the potential beneficial health effects
34 of O₃ pollution in shielding the public from effects of solar (UV) radiation, EPA
35 proposed to leave the 1997 8-h O₃ NAAQS unchanged ([U.S. EPA, 2001](#)). After
36 considering public comment on the proposed decision, EPA published its final
37 response to this remand on January 6, 2003, reaffirming the 8-h O₃ NAAQS set in
38 1997 ([U.S. EPA, 2003](#)). On April 30, 2004, EPA announced the decision to make the
39 1-h O₃ NAAQS no longer applicable to areas 1 year after the effective date of the

1 designation of those areas for the 8-h NAAQS (2004). For most areas, the date that
2 the 1-h NAAQS no longer applied was June 15, 2005.

3 EPA initiated the next periodic review of the air quality criteria and O₃ standards in
4 September 2000 with a call for information (U.S. EPA, 2000). The schedule for
5 completion of that rulemaking later became governed by a consent decree resolving a
6 lawsuit filed in March 2003 by a group of plaintiffs representing national
7 environmental and public health organizations. Based on the 2006 O₃ AQCD (U.S.
8 EPA, 2006b) published in March 2006, the Staff Paper (U.S. EPA, 2007b) and
9 related technical support documents, the proposed decision was published in the
10 Federal Register on July 11, 2007 (U.S. EPA, 2007a). The EPA proposed to revise
11 the level of the primary standard to a level within the range of 0.075 to 0.070 ppm.
12 Two options were proposed for the secondary standard: (1) replacing the current
13 standard with a cumulative, seasonal standard, expressed as an index of the annual
14 sum of weighted hourly concentrations cumulated over 12 daylight hours during the
15 consecutive 3-month period within the O₃ season with the maximum index value, set
16 at a level within the range of 7 to 21 ppm-h; and (2) setting the secondary standard
17 identical to the revised primary standard. The EPA completed the rulemaking with
18 publication of a final decision on March 27, 2008 (U.S. EPA, 2008e), revising the
19 level of the 8-hour primary O₃ standard from 0.08 ppm to 0.075 ppm and revising the
20 secondary standard to be identical to the primary standard.

21 In May 2008, state, public health, environmental, and industry petitioners filed suit
22 against EPA regarding that final decision. At EPA's request the consolidated cases
23 were held in abeyance pending EPA's reconsideration of the 2008 decision. A notice
24 of proposed rulemaking to reconsider the 2008 final decision was issued by the
25 Administrator on January 6, 2010. Three public hearings were held. The Agency
26 solicited CASAC review of the proposed rule on January 25, 2010 and additional
27 CASAC advice on January 26, 2011. On September 2, 2011, the Office of
28 Management and Budget returned the draft final rule on reconsideration to EPA for
29 further consideration. EPA decided to coordinate further proceedings on its voluntary
30 rulemaking on reconsideration with the ongoing periodic review, by deferring the
31 completion of its voluntary rulemaking on reconsideration until it completes its
32 statutorily-required periodic review. In light of that, the litigation on the 2008 final
33 decision is no longer being held in abeyance and is proceeding. The 2008 ozone
34 standards remain in effect.

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1 EXECUTIVE SUMMARY

Introduction and Purpose

1 The purpose of this Integrated Science Assessment (ISA) is to provide a synthesis and
2 evaluation of the most policy-relevant science that forms the scientific foundation for the
3 review of the primary (health-based) and secondary (welfare-based) national ambient air
4 quality standard (NAAQS) for ozone (O₃) and related photochemical oxidants. The ISA
5 is intended to inform the EPA Risk and Exposure Assessment and Policy Assessment and
6 thereby support decisions by the EPA Administrator on the NAAQS for O₃ (See Figure I
7 in Preamble). The current primary O₃ standard includes an 8-hour average standard set in
8 2008 at 75 parts per billion (ppb). The secondary standard for O₃ is equal to the primary
9 standard. The current primary NAAQS protects against respiratory health effects incurred
10 after short-term exposure to O₃, while the secondary NAAQS protects against damage to
11 vegetation and ecosystems.

Scope and Methods

12 EPA has developed an extensive and robust process for evaluating the scientific evidence
13 and drawing conclusions regarding air pollution-related health and welfare effects, which
14 is applied to the health and welfare effects resulting from current ambient concentrations
15 of O₃. Building upon the findings of previous assessments, this review includes
16 identification, selection, evaluation, and integration of the relevant results pertaining to
17 the atmospheric science of O₃; short- and long-term exposure to ambient O₃; health
18 effects due to relevant O₃ concentrations as characterized in epidemiologic, controlled
19 human exposure, and toxicological studies; and ecological or welfare effects; as well as
20 O₃ concentration-response relationships, mode(s) of action, and populations at increased
21 risk for O₃-related health effects. The conclusions and key findings from previous
22 reviews provide the foundation for the consideration of evidence from recent studies (i.e.,
23 studies published since the completion of the 2006 O₃ AQCD). Conclusions are drawn
24 based on the synthesis of evidence across disciplines from recent studies and building
25 upon the extensive evidence presented in previous reviews.

26 EPA has developed a consistent and transparent approach to evaluate the causal nature of
27 air pollution-related health and environmental effects for use in developing ISAs; the
28 framework for causal determinations is described in the Preamble to this document.
29 Causality determinations are based on the evaluation and synthesis of evidence across
30 scientific disciplines; however, the type of evidence that is most important for such
31 determinations will vary by pollutant or assessment. EPA assesses the entire body of

1 peer-reviewed literature, building upon evidence available during the previous NAAQS
2 reviews, to draw conclusions on the causal relationships between relevant pollutant
3 concentrations and health or welfare effects. EPA also evaluates the quantitative evidence
4 and draws scientific conclusions, to the extent possible, regarding the
5 concentration-response relationships and the loads to ecosystems, exposure doses or
6 concentrations, duration and pattern of exposures at which effects are observed.
7 A five-level hierarchy is used to classify the weight of evidence for causation, not just
8 association. This weight of evidence evaluation is based on various lines of evidence
9 from across the health and environmental effects disciplines. These separate judgments
10 are integrated into a qualitative statement about the overall weight of the evidence and
11 causality. The causal determinations are:

- 12 ▪ Causal relationship
- 13 ▪ Likely to be a causal relationship
- 14 ▪ Suggestive of a causal relationship
- 15 ▪ Inadequate to infer a causal relationship
- 16 ▪ Not likely to be a causal relationship

Ambient Ozone Concentrations

17 Ozone is naturally present in the stratosphere, where it serves the beneficial role of
18 blocking harmful ultraviolet radiation from the Sun, and preventing the majority of this
19 radiation from reaching the surface of the Earth. However, in the troposphere, O₃ acts as
20 a powerful oxidant and can harm living organisms and materials. Tropospheric O₃ is
21 present not only in polluted urban air, but throughout the globe. Ozone can be influenced
22 by local meteorological conditions, circulation patterns, emissions, and topographic
23 barriers, resulting in heterogeneous concentrations across an individual urban area. On a
24 larger scale, O₃ persists in the atmosphere long enough that it can be transported from
25 continent to continent.

26 Ozone in the troposphere originates from both anthropogenic (i.e., man-made) and
27 natural source categories. Ozone attributed to anthropogenic sources is formed in the
28 atmosphere by photochemical reactions involving sunlight and precursor pollutants
29 including volatile organic compounds, nitrogen oxides, and carbon monoxide. Ozone
30 attributed to natural sources is formed through the same photochemical reactions
31 involving natural emissions of precursor pollutants from vegetation, microbes, animals,
32 biomass burning, and lightning. Because O₃ is produced downwind of urban source areas
33 and O₃ tends to persist longer in rural than in urban areas as a result of lower chemical

1 scavenge, resulting in concentrations in rural areas that are often higher than those in
2 urban areas.

3 In the context of a review of the NAAQS, it is useful to define background O₃
4 concentrations in a way that distinguishes between concentrations that result from
5 precursor emissions that are relatively less controllable from those that are relatively
6 more controllable through U.S. policies. North American (NA) background can be
7 defined as those concentrations resulting from natural sources everywhere in the world
8 and from anthropogenic sources outside the U.S., Canada and Mexico. Since NA
9 background is a construct that cannot be measured, NA background O₃ concentrations are
10 estimated using chemistry transport models. Seasonal mean daily maximum 8-h average
11 NA background O₃ concentrations are generally higher in spring than in summer across
12 the U.S. The highest estimates are found in the Intermountain West during the spring and
13 in the Southwest during the summer. The lowest estimates occur over the East in the
14 spring and over the Northeast in the summer (See Section [3.4](#)).

Human Exposure to Ozone

15 The widespread presence of O₃ in the environment results in exposure as people
16 participate in normal daily activities. The relationship between personal exposure and
17 ambient concentration measured at fixed-site monitors can be described in terms of
18 correlation, or how they covary in time, and ratio, which describes their relative
19 magnitude. Personal-ambient O₃ correlations are generally moderate (0.3-0.8), although
20 low correlations have been observed with increased time spent indoors, low air exchange
21 rate, and concentrations below the personal sampler detection limit (See Section [4.3](#)).
22 Ratios of 0.1-0.3 between personal exposure and ambient concentration have been
23 observed for the general population, with ratios of up to 0.9 observed for outdoor
24 workers. Evidence suggests that some groups, particularly children, older adults, and
25 those with respiratory problems, change their behavior on high-O₃ days to reduce
26 exposure (See Section [4.4.2](#)). Such behavioral changes may result in reduced effect
27 estimates in epidemiologic studies that do not account for averting behavior on high-O₃
28 days. Variation in O₃ concentrations occurs over multiple spatial and temporal scales, and
29 this introduces exposure error into epidemiologic results (See Section [4.6.2](#)). However,
30 epidemiologic studies evaluating the influence of spatial scale and monitor selection find
31 little difference among effect estimates, and comparable risk estimates have been
32 reported in studies using a variety of exposure assessment techniques expected to produce
33 different levels of personal-ambient associations. This suggests that there is no clear
34 indication that a particular method of exposure assessment produces stronger
35 epidemiologic results.

Dosimetry and Modes of Action

1 When O₃ is inhaled, the amount of O₃ that is absorbed is affected by a number of factors
2 including the shape and size of the respiratory tract, route of breathing (nose or mouth),
3 as well as how quickly and deeply a person is breathing. The site of the greatest O₃ dose
4 to the lung tissue is the junction of the conducting airway and the gas exchange region, in
5 the deeper portion of the respiratory tract. Additionally, the primary site of O₃ uptake
6 moves deeper into the respiratory tract during exercise when breathing becomes faster
7 and the breathing route changes from the nose only to oronasal breathing (i.e., through
8 the nose and mouth) (See Section [5.2](#)).

9 Once O₃ has been absorbed, there are several key events in the toxicity pathway of O₃ in
10 the respiratory tract that lead to O₃-induced health effects (See Section [5.3](#)). These
11 include formation of secondary oxidation products in the lung, activation of neural
12 reflexes, initiation of inflammation, alterations of epithelial barrier function, sensitization
13 of bronchial smooth muscle, modification of innate and adaptive immunity, and airway
14 remodeling. Another key event, systemic inflammation and vascular oxidative/nitrosative
15 stress, may be critical to the extrapulmonary effects of O₃.

16 Overall, biological responses to O₃ exposure are common across many species (See
17 Section [5.5](#)). Thus, animal studies are used to add to the understanding of the full range
18 of potential O₃-mediated health effects.

Integration of Ozone Health Effects

19 The body of evidence from short-term (i.e., hours, days, weeks) or long-term
20 (i.e., months to years) exposure studies is evaluated and integrated across scientific
21 disciplines (i.e., controlled human exposure studies, toxicology, and epidemiology) and
22 interpreted for the health effects evidence that spans all lifestages, and which vary in
23 severity from minor subclinical effects to death. The results from the health studies,
24 supported by the evidence from atmospheric chemistry and exposure assessment studies,
25 contribute to the causal determinations made for the health outcomes. The conclusions
26 from the previous NAAQS review and the causality determinations from this review are
27 summarized in [Table 1-1](#). Additional details are provided here for respiratory health
28 effects and mortality, for which there is the strongest evidence of an effect from O₃;
29 details for a wider range of health effects are provided subsequent chapters.

Table 1-1 Summary of ozone causal determinations by exposure duration and health outcome

| Health Outcome | Conclusions from Previous Review | Conclusions from 2012 3rd Draft ISA |
|---|--|---|
| Short-Term Exposure to O₃ | | |
| Respiratory effects | The overall evidence supports a causal relationship between acute ambient O ₃ exposures and increased respiratory morbidity outcomes. | Causal Relationship |
| Cardiovascular effects | The limited evidence is highly suggestive that O ₃ directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association. | Suggestive of a Causal Relationship |
| Central nervous system effects | Toxicological studies report that acute exposures to O ₃ are associated with alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration. | Suggestive of a Causal Relationship |
| Total Mortality | The evidence is highly suggestive that O ₃ directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality. | Likely to be a Causal Relationship |
| Long-term Exposure to O₃ | | |
| Respiratory effects | The current evidence is suggestive but inconclusive for respiratory health effects from long-term O ₃ exposure. | Likely to be a Causal Relationship |
| Cardiovascular effects | No studies from previous review. | Suggestive of a Causal Relationship |
| Reproductive and developmental effects | Limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for O ₃ effects. | Suggestive of a Causal Relationship |
| Central nervous system effects | Evidence regarding chronic exposure and neurobehavioral effects was not available. | Suggestive of a Causal Relationship |
| Cancer | Little evidence for a relationship between chronic O ₃ exposure and increased risk of lung cancer. | Inadequate to infer a Causal Relationship |
| Total Mortality | There is little evidence to suggest a causal relationship between chronic O ₃ exposure and increased risk for mortality in humans. | Suggestive of a Causal Relationship |

Respiratory Effects

1 The clearest evidence for health effects associated with exposure to O₃ is provided by
2 studies of respiratory effects. Collectively, a very large amount of evidence spanning
3 several decades supports a relationship between exposure to O₃ and a broad range of
4 respiratory effects (See Section [6.2.9](#) and Section [7.2.8](#)). The majority of this evidence is
5 derived from studies investigating short-term exposure (i.e., hours to weeks) to O₃,
6 although animal toxicological studies and recent epidemiologic evidence demonstrate
7 that long-term exposure (i.e., months to years) may also be detrimental to the respiratory
8 system.

9 The last review concluded that there was clear, consistent evidence of a causal
10 relationship between short-term exposure to O₃ and respiratory health effects. This causal
11 association is substantiated by the coherence of effects observed across recent controlled
12 human exposure, epidemiologic, and toxicological studies indicating associations of

1 short-term O₃ exposures with a range of respiratory health endpoints from respiratory
2 tract inflammation to respiratory-related emergency department (ED) visits and hospital
3 admissions. Across disciplines, short-term O₃ exposures induced or were associated with
4 statistically significant declines in lung function. An equally strong body of evidence
5 from controlled human exposure and toxicological studies demonstrated O₃-induced
6 inflammatory responses, increased epithelial permeability, and airway
7 hyperresponsiveness. Toxicological studies provided additional evidence for O₃-induced
8 impairment of host defenses. Combined, these findings from experimental studies
9 provided support for epidemiologic evidence, in which short-term increases in O₃
10 concentration were consistently associated with increases in respiratory symptoms and
11 asthma medication use in children with asthma, respiratory-related hospital admissions,
12 and ED visits for COPD and asthma. Additionally, recent evidence supports the range of
13 respiratory effects induced by O₃ by demonstrating that short-term increases in ambient
14 O₃ concentrations can lead to respiratory mortality. The combined evidence across
15 disciplines supports **a causal relationship between short-term O₃ exposure and**
16 **respiratory effects.**

17 Taken together, the recent epidemiologic studies of respiratory health effects (including
18 respiratory symptoms, new-onset asthma and respiratory mortality) combined with
19 toxicological studies in rodents and nonhuman primates, provide biologically plausible
20 evidence that there **is likely to be a causal relationship between long-term exposure**
21 **to O₃ and respiratory effects.** The strongest epidemiologic evidence for a relationship
22 between long-term O₃ exposure and respiratory effects is provided by studies that
23 demonstrate interactions between exercise or different genetic variants and long-term
24 measures of O₃ exposure on new-onset asthma in children; and increased respiratory
25 symptom effects in asthmatics. Additional studies of respiratory health effects and a
26 study of respiratory mortality provide a collective body of evidence supporting these
27 relationships. Studies considering other pollutants provide data suggesting that the effects
28 related to O₃ are independent from potential effects of the other pollutants. Some studies
29 provide evidence for a positive concentration-response relationship. Short-term studies
30 provide supportive evidence with increases in respiratory symptoms and asthma
31 medication use, hospital admissions and ED visits for all respiratory outcomes and
32 asthma, and decrements in lung function in children. The recent epidemiologic and
33 toxicological data base provides a compelling case to support the hypothesis that a
34 relationship exists between long-term exposure to ambient O₃ and measures of
35 respiratory health effects.

Mortality Effects

1 The last review concluded that the overall body of evidence was highly suggestive that
2 short-term exposure to O₃ directly or indirectly contributes to non-accidental and
3 cardiopulmonary-related mortality; but that additional research was needed to more fully
4 establish underlying mechanisms by which such effects occur. The evaluation of recent
5 multicity studies and a multicontinent study that have examined the association between
6 short-term O₃ exposure and mortality found evidence that supports the conclusions of the
7 last review (See Section [6.6](#)). These recent studies reported consistent positive
8 associations between short-term O₃ exposure and total (nonaccidental) mortality, with
9 associations being stronger during the warm season. They also added support for
10 associations between O₃ exposure and cardiovascular mortality being similar to or
11 stronger than those between O₃ exposure and respiratory mortality. Additionally, these
12 recent studies examined previously identified areas of uncertainty in the O₃-mortality
13 relationship, and provide evidence that continues to support an association between short-
14 term O₃ exposure and mortality. The body of evidence indicates that there **is likely to be**
15 **a causal relationship between short-term exposures to O₃ and total mortality.**

Populations Potentially at Increased Risk

16 The examination of populations potentially at increased risk for O₃ exposure identifies
17 populations that are at increased risk for O₃-related health effects; these studies do so by
18 examining groups within the study population, such as those with an underlying health
19 condition or genetic variant; categories of age, race, or sex; or by developing animal
20 models that mimic the conditions associated with a health effect. Such studies have
21 identified a multitude of factors that could potentially contribute to whether an individual
22 is at increased risk for O₃-related health effects (See Chapter [8](#)). The populations
23 identified as having adequate evidence for increased risk of O₃-related health effects are
24 individuals with asthma, younger and older age groups, individuals with reduced intake
25 of certain nutrients (i.e., Vitamins C and E), and outdoor workers. The evidence for other
26 potential factors, including variations in multiple genes related to oxidative metabolism
27 or inflammation, sex, socioeconomic status, and obesity is suggestive of an increased
28 risk, but further evidence is needed.

Integration of Effects on Vegetation and Ecosystems

29 The most policy-relevant information pertaining to the review of the NAAQS for the
30 effects of O₃ on vegetation and ecosystems are evaluated and synthesized, integrating key
31 findings about plant physiology, biochemistry, whole plant biology, ecosystems and

1 exposure-response relationships. The welfare effects of O₃ can be observed across spatial
 2 scales, starting at the cellular and subcellular level, then the whole plant and finally,
 3 ecosystem-level processes. Ozone effects at small spatial scales, such as the leaf of an
 4 individual plant, can result in effects at a continuum of larger spatial scales. These effects
 5 include altered rates of leaf gas exchange, growth and reproduction at the individual plant
 6 level and can result in changes in ecosystems, such as productivity, carbon storage, water
 7 cycling, nutrient cycling, and community composition. The conclusions from the
 8 previous NAAQS review and the causality determinations from this review are
 9 summarized in the table below. Further discussion of these conclusions is provided below
 10 for visible foliar injury, growth, productivity, and carbon storage, reduced yield and
 11 quality of agricultural crops, water cycling, below-ground processing, community
 12 composition, and O₃ exposure-response relationships; discussion for all relevant welfare
 13 effects is provided in Chapter 9.

Table 1-2 Summary of ozone causal determination for welfare effects

| Vegetation and Ecosystem Effects | Conclusions from Previous Review | Conclusions from 2012 3rd Draft ISA |
|--|---|-------------------------------------|
| Visible Foliar Injury Effects on Vegetation | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause impaired aesthetic quality of many native plants and trees by increasing foliar injury. | Causal Relationship |
| Reduced Vegetation Growth | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O₃ concentrations cause decreased growth and biomass accumulation in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees. | Causal Relationship |
| Reduced Productivity in Terrestrial Ecosystems | There is evidence that O₃ is an important stressor of ecosystems and that the effects of O ₃ on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity. | Causal Relationship |
| Reduced Carbon (C) Sequestration in Terrestrial Ecosystems | Limited studies from previous review | Likely to be a Causal Relationship |
| Reduced Yield and Quality of Agricultural Crops | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O₃ concentrations cause decreased yield and/or nutritive quality in a large number of agronomic and forage crops. | Causal Relationship |
| Alteration of Terrestrial Ecosystem Water Cycling | Ecosystem water quantity may be affected by O₃ exposure at the landscape level. | Likely to be a Causal Relationship |
| Alteration of Below-ground Biogeochemical Cycles | Ozone-sensitive species have well known responses to O₃ exposure , including altered C allocation to below-ground tissues, and altered rates of leaf and root production, turnover, and decomposition. These shifts can affect overall C and N loss from the ecosystem in terms of respired C, and leached aqueous dissolved organic and inorganic C and N. | Causal Relationship |
| Alteration of Terrestrial Community Composition | Ozone may be affecting above- and below -ground community composition through impacts on both growth and reproduction. Significant changes in plant community composition resulting directly from O₃ exposure have been demonstrated. | Likely to be a Causal Relationship |

Visible Foliar Injury

1 Visible foliar injury resulting from exposure to O₃ has been well characterized and
2 documented over several decades on many tree, shrub, herbaceous and crop species.
3 Ozone-induced visible foliar injury symptoms on certain plant species are considered
4 diagnostic of exposure to O₃, as experimental evidence has clearly established a
5 consistent association, with greater exposure often resulting in greater and more prevalent
6 injury. Additional sensitive species showing visible foliar injury continue to be identified
7 from field surveys and verified in controlled exposure studies (See Section [9.4.2](#)).
8 Overall, evidence is sufficient to conclude that there **is a causal relationship between**
9 **ambient O₃ exposure and the occurrence of O₃ induced visible foliar injury on**
10 **sensitive vegetation across the U.S.**

Growth, Productivity, Carbon Storage and Agriculture

11 Ambient O₃ concentrations have long been known to cause decreases in photosynthetic
12 rates and plant growth. The O₃-induced effects at the plant scale may translate to the
13 ecosystem scale, and cause changes in productivity and C storage. The effects of O₃
14 exposure on photosynthesis, growth, biomass allocation, ecosystem production and
15 ecosystem C sequestration were reviewed for natural ecosystems (See Section [9.4.3](#)), and
16 crop productivity and crop quality were reviewed for agricultural ecosystems (See
17 Section [9.4.4](#)). There is strong and consistent evidence that ambient concentrations of O₃
18 decrease plant photosynthesis and growth in numerous plant species across the U.S.
19 Studies conducted during the past four decades have also demonstrated unequivocally
20 that O₃ alters biomass allocation and plant reproduction. Studies at the leaf and plant
21 scales showed that O₃ reduced photosynthesis and plant growth, providing coherence and
22 biological plausibility for the reported decreases in ecosystem productivity. In addition to
23 primary productivity, other indicators such as net ecosystem CO₂ exchange and
24 C sequestration were often assessed by modeling studies. Model simulations consistently
25 found that O₃ exposure caused negative impacts on those indicators, but the severity of
26 these impacts was influenced by multiple interactions of biological and environmental
27 factors. Although O₃ generally causes negative effects on ecosystem productivity, the
28 magnitude of the response varies among plant communities. Overall, evidence is
29 sufficient to conclude that there **is a causal relationship between ambient O₃**
30 **exposure and reduced native plant growth and productivity, and a likely causal**
31 **relationship between O₃ exposure and reduced carbon sequestration in terrestrial**
32 **ecosystems.**

33 The detrimental effect of O₃ on crop production has been recognized since the 1960's,
34 and current O₃ concentrations across the U.S. are high enough to cause yield loss for a

1 variety of agricultural crops including, but not limited to, soybean, wheat, potato,
2 watermelon, beans, turnip, onion, lettuce, and tomato. Continued increases in O₃
3 concentration may further decrease yield in these sensitive crops while also initiating
4 yield losses in less sensitive crops. Research has linked increasing O₃ concentration to
5 decreased photosynthetic rates and accelerated senescence, which are related to yield
6 (See Section [9.4.4](#)). Evidence is sufficient to conclude that there **is a causal relationship**
7 **between O₃ exposure and reduced yield and quality of agricultural crops.**

Water Cycling

8 Ozone can affect water use in plants and ecosystems through several mechanisms
9 including damage to stomatal functioning and loss of leaf area. Possible mechanisms for
10 O₃ exposure effects on stomatal functioning include the build-up of CO₂ in the
11 substomatal cavity, impacts on signal transduction pathways and direct O₃ impact on
12 guard cells. Regardless of the mechanism, O₃ exposure has been shown to alter stomatal
13 performance, which may affect plant and stand transpiration and therefore may affect
14 hydrological cycling (See Section [9.4.5](#)). Although the direction of the response differed
15 among studies, the evidence is sufficient to conclude that there **is likely to be a causal**
16 **relationship between O₃ exposure and the alteration of ecosystem water cycling.**

Below Ground Processes

17 Below-ground processes are tightly linked with above-ground processes. The responses
18 of above-ground process to O₃ exposure, such as reduced photosynthetic rates, increased
19 metabolic cost, and reduced root C allocation, have provided biologically plausible
20 mechanisms for the alteration of below-ground processes. These include altered quality
21 and quantity of C input to soil, microbial community composition, and C and nutrient
22 cycling (See Section [9.4.6](#)). The evidence is sufficient to conclude that there **is a causal**
23 **relationship between O₃ exposure and the alteration of below-ground**
24 **biogeochemical cycles.**

Community Composition

25 Ozone exposure changes competitive interactions and leads to loss of O₃-sensitive
26 species or genotypes. Studies at the plant level found that the severity of O₃ damage to
27 growth, reproduction, and foliar injury varied among species, which provided the
28 biological plausibility for the alteration of community composition (See Section [9.4.3](#) and
29 Section [9.4.7](#)). For example, there is a tendency for O₃ exposure to shift the biomass of
30 grass-legume mixtures in favor of grass species. Ozone exposure not only altered

1 community composition of plant species, but also microorganisms: research since the last
2 review has shown that O₃ can also alter community composition and diversity of soil
3 microbial communities. Shifts in community composition of bacteria and fungi have been
4 observed in both natural and agricultural ecosystems, although no general patterns could
5 be identified. The evidence is sufficient to conclude that there **is likely to be a causal**
6 **relationship between O₃ exposure and the alteration of community composition of**
7 **some ecosystems.**

Ozone Exposure-Response Relationships

8 Previous reviews of the NAAQs have included exposure-response functions for the yield
9 of many crop species, and for the biomass accumulation of tree species. They were based
10 on large-scale experiments designed to obtain clear exposure-response data, and are
11 updated by using the W126 metric to quantify exposure. In recent years, extensive
12 exposure-response data obtained in more naturalistic settings have become available for
13 yield of soybean and growth of aspen. The exposure-response median functions are
14 validated based on previous data by comparing their predictions with the newer
15 observations (See Section [9.6](#)). The functions supply very accurate predictions of effects
16 in naturalistic settings. Recent meta-analyses of large sets of crop and tree studies do not
17 give rise to exposure-response functions, but their results are consistent with the
18 functions presented in Section [9.6](#). It is important to note that although these median
19 functions provide reliable models for groups of species or group of genotypes within a
20 species, the original data and recent results consistently show that some species, and
21 some genotypes within species are much more severely affected by exposure to O₃.

The Role of Tropospheric Ozone in Climate Change and UV-B Effects

22 Atmospheric O₃ plays an important role in the Earth's energy budget by interacting with
23 incoming solar radiation and outgoing infrared radiation. Tropospheric O₃ makes up only
24 a small portion of the total column of O₃, but it has important incremental effects on the
25 overall radiation budget. Perturbations in tropospheric O₃ concentrations can have direct
26 effects on climate and indirect effects on health, ecology, and welfare by shielding the
27 earth's surface from solar ultraviolet (UV) radiation.

Radiative Forcing and Climate Change

28 Tropospheric O₃ is a major greenhouse gas, third in importance after CO₂ and CH₄
29 according to the IPCC (See Section [10.3](#)). Models calculate that the global average

1 concentration of tropospheric O₃ has doubled since the preindustrial era, while
2 observations indicate that in some regions O₃ may have increased by factors as great as 4
3 or 5. These increases are tied to the rise in emissions of O₃ precursors from human
4 activity, mainly fossil fuel consumption and agricultural processes. There are large
5 uncertainties in the radiative forcing estimate attributed to tropospheric O₃, making the
6 effect of tropospheric O₃ on climate more uncertain than the effect of the long-lived
7 greenhouse gases. Overall, the evidence supports a **causal relationship between**
8 **changes in tropospheric O₃ concentrations and radiative forcing.**

9 Radiative forcing does not take into account the climate feedbacks that could amplify or
10 dampen the actual surface temperature response. Quantifying the change in surface
11 temperature requires a complex climate simulation in which all important feedbacks and
12 interactions are accounted for. As these processes are not well understood or easily
13 modeled, the surface temperature response to a given radiative forcing is highly uncertain
14 and can vary greatly among models and from region to region within the same model. In
15 light of these uncertainties, the evidence indicates that there **is likely to be a causal**
16 **relationship between changes in tropospheric O₃ concentrations and effects on**
17 **climate.**

UV-B Effects

18 UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to
19 have damaging effects on living organisms and materials (see Section [10.4](#)). Atmospheric
20 O₃ plays a crucial role in reducing exposure to UV radiation at the Earth's surface. Ozone
21 in the stratosphere is responsible for the majority of this shielding, but O₃ in the
22 troposphere provides supplemental shielding of UV radiation in the mid-wavelength
23 range (UV-B), thereby influencing human and ecosystem health and materials damage.
24 There is a lack of published studies that critically examine the incremental health or
25 welfare effects (adverse or beneficial) attributable specifically to changes in UV-B
26 exposure resulting from perturbations in tropospheric O₃ concentrations. While the
27 effects are expected to be small, they cannot yet be critically assessed within reasonable
28 uncertainty. Overall, the evidence is inadequate to determine if a causal relationship
29 exists between changes in tropospheric O₃ concentrations and effects on health and
30 welfare related to UV-B shielding.

31 The conclusions from the previous NAAQS review and the causality determinations from
32 this review relating climate change and UV-B effects are summarized in the table below
33 ([Table 1-3](#)), with details provided in Chapter [10](#).

Table 1-3 Summary of ozone causal determination for climate change and UV-B effects.

| Effects | Conclusions from Previous Review | Conclusions from 2012 3rd Draft ISA |
|--|---|---|
| Radiative Forcing | Climate forcing by O ₃ at the regional scale may be its most important impact on climate. | Causal Relationship |
| Climate Change | While more certain estimates of the overall importance of global-scale forcing due to tropospheric O ₃ await further advances in monitoring and chemical transport modeling, the overall body of scientific evidence suggests that high concentrations of O ₃ on the regional scale could have a discernible influence on climate, leading to surface temperature and hydrological cycle changes. | Likely to be a Causal Relationship |
| Health and Welfare Effects Related to UV-B Shielding | UV-B has not been studied in sufficient detail to allow for a credible health benefits assessment. In conclusion, the effect of changes in surface-level O ₃ concentrations on UV-induced health outcomes cannot yet be critically assessed within reasonable uncertainty. | Inadequate to Determine if a Causal Relationship Exists |

Conclusion

1 The clearest evidence for human health effects associated with exposure to O₃ is provided
2 by studies of respiratory effects. Collectively, there is a very large amount of evidence
3 spanning several decades in support of a causal association between exposure to O₃ and a
4 broad range of respiratory effects. The majority of this evidence is derived from studies
5 investigating short-term O₃ exposure (i.e., hours to weeks), although animal toxicological
6 studies and recent epidemiologic evidence demonstrate that long-term exposure
7 (i.e., months to years) may also be detrimental to the respiratory system. Additionally,
8 consistent positive associations between short-term O₃ exposure and total (nonaccidental)
9 mortality have helped to resolve previously identified areas of uncertainty in the
10 O₃-mortality relationship, indicating that there **is likely to be a causal relationship**
11 **between short-term exposures to O₃ and total mortality**. Taken together, the recent
12 epidemiologic studies of respiratory health effects (including respiratory symptoms, new-
13 onset asthma and respiratory mortality) combined with toxicological studies in rodents
14 and nonhuman primates, provide biologically plausible evidence that there **is likely to be**
15 **a causal relationship between long-term exposure to O₃ and respiratory effects**.
16 Recent evidence **is suggestive of a causal relationship between long-term O₃**
17 **exposures and total mortality**. The evidence for these health effects indicates that the
18 relationship between concentration and response is linear along the range of O₃
19 concentrations observed in the U.S., with no indication of a threshold. However, there is
20 less certainty in the shape of the concentration-response curve at O₃ concentrations
21 generally below 20 ppb. The populations identified as having increased risk of O₃-related
22 health effects are individuals with asthma, younger and older age groups, individuals with
23 certain dietary deficiencies, and outdoor workers.

1 There has been over 40 years of research on the effects of O₃ exposure on vegetation and
2 ecosystems. The best evidence for effects is from controlled exposure studies. These
3 studies have clearly shown that exposure to O₃ is causally linked to visible foliar injury,
4 decreased photosynthesis, changes in reproduction, and decreased growth. Recently,
5 studies at larger spatial scales support the results from controlled studies and indicate that
6 ambient O₃ exposures can affect ecosystem productivity, crop yield, water cycling, and
7 ecosystem community composition. And on a global scale, tropospheric O₃ is the third
8 most important greenhouse gas, playing an important role in climate change.

2 INTEGRATIVE SUMMARY

1 This Integrated Science Assessment (ISA) forms the scientific foundation for the review
2 of the national ambient air quality standards (NAAQS) for ozone (O₃). The ISA is a
3 concise evaluation and synthesis of the most policy-relevant science—and it
4 communicates critical science judgments relevant to the review of the NAAQS for O₃.
5 The ISA accurately reflects “the latest scientific knowledge useful in indicating the kind
6 and extent of identifiable effects on public health or welfare which may be expected from
7 the presence of [a] pollutant in ambient air” ([CAA, 1990a](#)). Key information and
8 judgments contained in prior Air Quality Criteria Documents (AQCD) for O₃ are
9 incorporated into this assessment. Additional details of the pertinent scientific literature
10 published since the last review, as well as selected earlier studies of particular interest,
11 are included. This ISA thus serves to update and revise the evaluation of the scientific
12 evidence available at the time of the completion of the 2006 O₃ AQCD. The current
13 primary O₃ standard includes an 8-hour (h) average (avg) standard set at 75 parts per
14 billion (ppb). The secondary standard for O₃ is set equal to the primary standard. Further
15 information on the legislative and historical background for the O₃ NAAQS is contained
16 in the Preface to this ISA.

17 This chapter summarizes and synthesizes the available scientific evidence and is intended
18 to provide a concise synopsis of the ISA conclusions and findings that best inform
19 consideration of the policy-relevant questions that frame this assessment ([U.S. EPA,](#)
20 [2009c](#)). It includes:

- 21 ▪ An integration of the evidence on the health effects associated with short- and
22 long-term exposure to O₃, discussion of important uncertainties identified in
23 the interpretation of the scientific evidence, and an integration of health
24 evidence from the different scientific disciplines and exposure durations.
- 25 ▪ An integration of the evidence on the welfare effects associated with exposure
26 to O₃, including those associated with vegetation and ecosystems, and
27 discussion of important uncertainties identified in the interpretation of the
28 scientific evidence.
- 29 ▪ Discussion of policy-relevant considerations, such as potentially at-risk
30 populations and concentration-response relationships and how they inform
31 selection of appropriate exposure metrics/indices.

2.1 ISA Development and Scope

1 EPA has developed a robust, consistent, and transparent process for evaluating the
2 scientific evidence and drawing conclusions and causal judgments regarding air
3 pollution-related health and environmental effects. The ISA development process
4 includes literature search strategies, criteria for selecting and evaluating studies,
5 approaches for evaluating weight of the evidence, and a framework for making causality
6 determinations. The process and causality framework are described in more detail in the
7 Preamble to the ISA. This section provides a brief overview of the process for
8 development of this ISA.

9 EPA initiated the current review of the NAAQS for O₃ on September 29, 2008, with a
10 call for information from the public ([U.S. EPA, 2008f](#)). Literature searches were
11 conducted routinely to identify studies published since the last review, focusing on
12 studies published from 2005 (close of previous scientific assessment) through July 2011.
13 References that were considered for inclusion in this ISA can be found using the HERO
14 website (<http://hero.epa.gov/ozone>). This site contains HERO links to lists of references
15 that are cited in the ISA, as well as those that were considered for inclusion, but not cited
16 in the ISA, with bibliographic information and abstracts.

17 This review has endeavored to evaluate all relevant data published since the last review;
18 this includes studies pertaining to the atmospheric science of O₃, human exposure to
19 ambient O₃, and health, ecological, climate and UV-B effects studies. These include
20 studies that are related to concentration-response relationships, mode(s) of action (MOA),
21 and understanding of at-risk populations for effects of O₃ exposure. Added to the body of
22 research were EPA's analyses of air quality and emissions data, studies on atmospheric
23 chemistry, transport, and fate of these emissions.

24 Previous AQCDs ([U.S. EPA, 2006b](#), [1996a, b](#), [1984](#), [1978a](#)) have included an extensive
25 body of evidence on both health and welfare effects of O₃ exposure, as well as an
26 understanding of the atmospheric chemistry of O₃ ([U.S. EPA, 2006b](#)). In this ISA, the
27 conclusions and key findings from previous reviews are summarized at the beginning of
28 each section, to provide the foundation for consideration of evidence from recent studies.
29 Results of key studies from previous reviews are included in discussions or tables and
30 figures, as appropriate, and conclusions are drawn based on the synthesis of evidence
31 from recent studies with the extensive literature summarized in previous reviews.

32 The Preamble discusses the general framework for conducting the science assessment
33 and developing an ISA, including criteria for evaluating studies and developing scientific
34 conclusions. For selection of epidemiologic studies in the O₃ ISA, particular emphasis is
35 placed on those studies most relevant to the review of the NAAQS. Studies conducted in

1 the United States (U.S.) or Canada are discussed in more detail than those from other
2 geographical regions, and in regard to human health, particular emphasis is placed on:
3 (1) recent multicity studies that employ standardized analysis methods for evaluating
4 effects of O₃ and that provide overall estimates for effects, based on combined analyses
5 of information pooled across multiple cities; (2) studies that help understand quantitative
6 relationships between exposure concentrations and effects; (3) new studies that provide
7 evidence on effects in at-risk populations; and (4) studies that consider and report O₃ as a
8 component of a complex mixture of air pollutants. In evaluating toxicological and
9 controlled human exposure studies, emphasis is placed on studies using concentrations
10 that are within about an order of magnitude of ambient O₃ concentrations. Consideration
11 of studies important for evaluation of human exposure to ambient O₃ places emphasis on
12 those evaluating the relationship between O₃ measured at central site monitors and
13 personal exposure to ambient O₃. Important factors affecting this relationship include
14 spatial and temporal variations in ambient O₃ concentration, and time spent outdoors,
15 since penetrations of O₃ into indoor environments may be limited.

16 Epidemiologic studies generally present O₃-related effect estimates for mortality and
17 morbidity health outcomes based on an incremental change in exposure, traditionally
18 equal to the interquartile range in O₃ concentrations or some other arbitrary value
19 (e.g., 10 ppb). Additionally, various averaging times are used in O₃ epidemiologic studies,
20 with the three most common being the maximum 1-hour average within a 24-hour period
21 (1-h max), the maximum 8-hour average within a 24-h period (8-h max), and 24-hour
22 average (24-h avg). For the purpose of presenting results from studies that use different
23 exposure metrics, EPA consistently applies the same O₃ increments to facilitate
24 comparisons between the results of various studies that may use different indices. These
25 increments were derived using the nationwide distributional data for O₃ monitors in U.S.
26 Metropolitan Statistical Areas and are representative of a low-to-high change in O₃
27 concentrations and were approximated on the basis of annual mean to 95th percentile
28 differences ([Langstaff, 2003](#)). Therefore, throughout Chapter [6](#), efforts were made to
29 standardize O₃-related effect estimates using the increments of 20 ppb for 24-h avg,
30 30 ppb for 8-h max, and 40 ppb for 1-h max O₃ concentrations, except as noted. In long-
31 term exposure studies, typically, O₃ concentrations are lower and less variable when
32 averaged across longer exposure periods, and differences due to the use of varying
33 averaging times (e.g., 1-h max, 24-h avg) become less apparent. As such, in the long-term
34 exposure chapter (Chapter [7](#)) an increment of 10 ppb was consistently applied across
35 studies, regardless of averaging time, to facilitate comparisons between the results from
36 these studies.

1 This ISA uses a five-level hierarchy that classifies the weight of evidence for causation:

- 2 ▪ Causal relationship
- 3 ▪ Likely to be a causal relationship
- 4 ▪ Suggestive of a causal relationship
- 5 ▪ Inadequate to infer a causal relationship
- 6 ▪ Not likely to be a causal relationship

7 Beyond judgments regarding causality are questions relevant to quantifying health or
8 environmental risks based on the understanding of the quantitative relationships between
9 pollutant exposures and health or welfare effects. Once a determination is made regarding
10 the causal relationship between the pollutant and outcome category, important questions
11 regarding quantitative relationships include:

- 12 ▪ What is the concentration-response, exposure-response, or dose-response
13 relationship?
- 14 ▪ Under what exposure conditions (dose or concentration, duration and pattern)
15 are effects observed?
- 16 ▪ What populations appear to be differentially affected i.e., at-risk to effects?
- 17 ▪ What elements of the ecosystem (e.g., types, regions, taxonomic groups,
18 populations, functions, etc.) appear to be affected or are more sensitive to
19 effects?

20 This chapter summarizes and integrates the newly available scientific evidence that best
21 informs consideration of the policy-relevant questions that frame this assessment.
22 Section [2.2](#) discusses the trends in ambient concentrations and sources of O₃ and provides
23 a brief summary of ambient air quality for short- and long-term exposure durations.
24 Section [2.3](#) presents the evidence regarding personal exposure to ambient O₃ in outdoor
25 and indoor microenvironments, and it discusses the relationship between ambient O₃
26 concentrations and personal exposure to ambient O₃. Section [2.4](#) provides a discussion of
27 the dosimetry and mode of action evidence for O₃ exposure. Section [2.5](#) integrates the
28 evidence for studies that examine the health effects associated with short- and long-term
29 exposure to O₃ and discusses important uncertainties identified in the interpretation of the
30 scientific evidence. A discussion of policy-relevant considerations, such as potentially at-
31 risk populations, lag structure, and the O₃ concentration-response relationship is also
32 included in Section [2.5](#). Finally, Section [2.6](#) summarizes the evidence for welfare effects
33 related to O₃ exposure, and Section [2.7](#) reviews the literature on the influence of
34 tropospheric O₃ on climate and exposure to solar ultraviolet radiation.

2.2 Atmospheric Chemistry and Ambient Concentrations

2.2.1 Physical and Chemical Processes

1 Ozone in the troposphere is a secondary pollutant; it is formed by photochemical
2 reactions of precursor gases and is not directly emitted from specific sources. Ozone
3 precursor gases originate from both anthropogenic (i.e., man-made) and natural source
4 categories. Ozone attributed to anthropogenic sources is formed in the atmosphere by
5 photochemical reactions involving sunlight and precursor pollutants including volatile
6 organic compounds (VOCs), nitrogen oxides (NO_x), and carbon monoxide (CO). Ozone
7 attributed to natural sources is formed through similar photochemical reactions involving
8 natural emissions of precursor pollutants from vegetation, microbes, animals, biomass
9 burning, lightning, and geogenic sources. The distinction between natural and
10 anthropogenic sources of O₃ precursors is often difficult to make in practice, as human
11 activities affect directly or indirectly emissions from what would have been considered
12 natural sources during the pre-industrial era. A schematic overview of the major
13 photochemical cycles influencing O₃ in the troposphere and the stratosphere is shown in
14 [Figure 2-1](#). The processes depicted in this figure are fairly well understood, and were
15 covered in detail in the previous O₃ AQCD. The formation of O₃, other oxidants, and
16 oxidation products from these precursors is a complex, nonlinear function of many
17 factors including: (1) the intensity and spectral distribution of sunlight reaching the lower
18 troposphere; (2) atmospheric mixing; (3) concentrations of precursors in the ambient air
19 and the rates of chemical reactions of these precursors; and (4) processing on cloud and
20 aerosol particles.

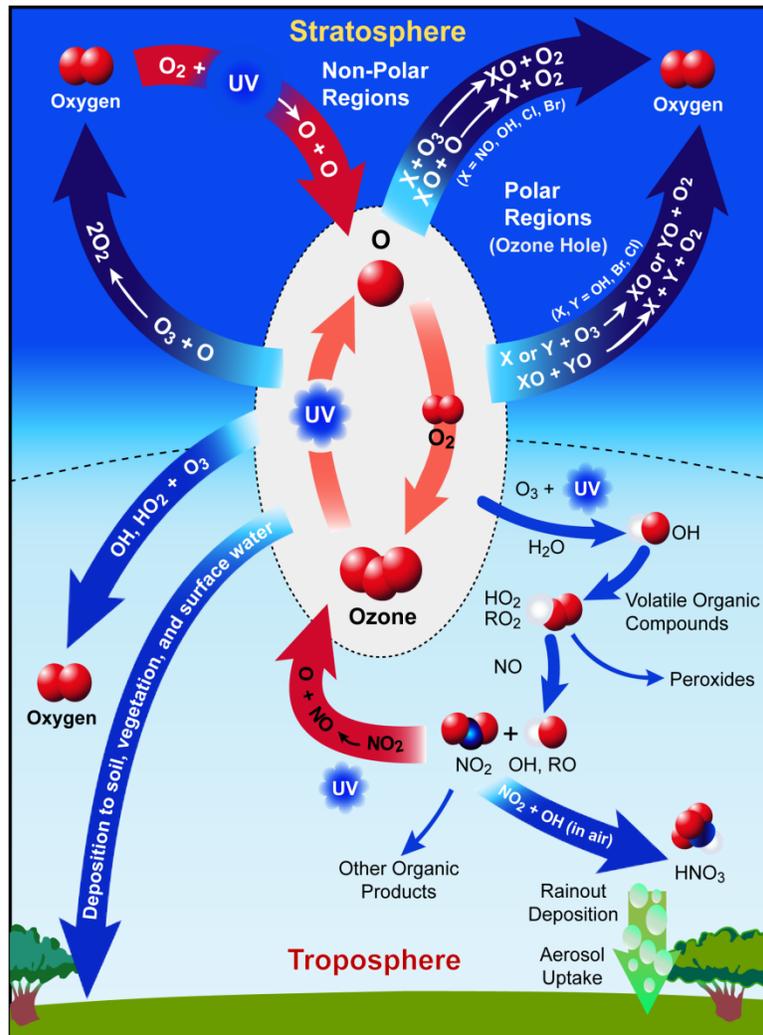


Figure 2-1 Schematic overview of photochemical processes influencing stratospheric and tropospheric ozone.

1 Ozone is present not only in polluted urban atmospheres but throughout the troposphere,
 2 even in remote areas of the globe. Similar basic processes involving sunlight-driven
 3 reactions of NO_x , VOCs and CO contribute to O_3 formation throughout the troposphere.
 4 These processes also lead to the formation of other photochemical products, such as
 5 peroxyacetyl nitrate, nitric acid, and sulfuric acid, and to other compounds, such as
 6 formaldehyde and other carbonyl compounds. In urban areas, NO_x , VOCs, and CO are
 7 all important for O_3 formation. In non-urban vegetated areas, biogenic VOCs emitted
 8 from vegetation tend to be the most important precursor to O_3 formation. In the remote
 9 troposphere, methane—structurally the simplest VOC—and CO are the main carbon-
 10 containing precursors to O_3 formation. Ozone is subsequently removed from the

1 troposphere through a number of gas phase reactions and deposition to surfaces as shown
2 in [Figure 2-1](#).

3 Convective processes and turbulence transport O₃ and other pollutants both upward and
4 downward throughout the planetary boundary layer and the free troposphere. In many
5 areas of the U.S., O₃ and its precursors can be transported over long distances, aided by
6 vertical mixing. The transport of pollutants downwind of major urban centers is
7 characterized by the development of urban plumes. Meteorological conditions, small-
8 scale circulation patterns, localized chemistry, and mountain barriers can influence
9 mixing on a smaller scale, resulting in frequent heterogeneous O₃ concentrations across
10 individual urban areas.

11 Furthermore, because the mean tropospheric lifetime of O₃ is a few weeks, O₃ can be
12 transported from continent to continent. The degree of influence from intercontinental
13 transport varies greatly by location and time. For instance, high elevation sites are most
14 susceptible to the intercontinental transport of pollution, particularly during spring.
15 However, because the atmospheric chemistry of O₃ is quite complex and can be highly
16 non-linear in environments close to sources of precursors, isolating the influence of
17 intercontinental transport of O₃ and O₃ precursors on urban air quality is particularly
18 problematic.

2.2.2 Atmospheric Modeling of Background Ozone Concentrations

19 A number of recent studies indicate that natural sources such as wildfires and
20 stratospheric intrusions and the intercontinental transport of pollution can affect O₃ air
21 quality at specific times and in specific locations in the United States. These contributions
22 are in addition to contributions from dominant local pollution sources. To gain a broader
23 perspective and to isolate the influence of natural or transported O₃, estimates from
24 chemical transport models (CTMs) must be used. This is because observations within the
25 U.S.—even at relatively remote monitoring sites—are impacted by transport from
26 anthropogenic source regions within U.S. borders.

27 In the context of a review of the NAAQS, it is useful to define background O₃
28 concentrations in a way that distinguishes between concentrations that result from
29 precursor emissions that are relatively less controllable from those that are relatively
30 more controllable through U.S. policies. For this assessment, three definitions of
31 background O₃ concentrations are considered, including (1) North American (NA)
32 background (simulated O₃ concentrations that would exist in the absence of
33 anthropogenic emissions from the U.S., Canada and Mexico), (2) United States (U.S.)
34 background (simulated O₃ concentrations that would exist in the absence of

1 anthropogenic emissions from the U.S.), and (3) natural background (simulated O₃
 2 concentrations in the absence of all anthropogenic emissions globally). Each definition of
 3 background O₃ includes contributions resulting from emissions from natural sources
 4 (e.g., stratospheric intrusion, wildfires, biogenic methane and more short-lived VOC
 5 emissions) throughout the globe. There is no chemical difference between background O₃
 6 and O₃ attributable to U.S. or North American anthropogenic sources. However, to
 7 inform policy considerations regarding the current or potential alternative standards, it is
 8 useful to understand how total O₃ concentrations (i.e., O₃ from all sources) can be
 9 attributed to different sources.

10 Since background O₃ concentrations as defined above are a construct that cannot be
 11 directly measured, the range of background O₃ concentrations is estimated using CTMs.
 12 For the current assessment, the GEOS-Chem model at 0.5°×0.667° (~50 km×50 km)
 13 horizontal resolution and a nested, hybrid GEOS-Chem/CAMx model at finer horizontal
 14 resolution (12 km × 12 km) were used. Results from these two models represent the latest
 15 estimates for background O₃ concentrations documented in the peer-reviewed literature
 16 and are shown in [Table 2-1](#). The R² for both models are generally <0.5, with CAMx
 17 showing generally higher values than GEOS-Chem ([Table 3-1](#)). The GEOS-Chem
 18 model-predicted seasonal mean daily maximum 8-h average O₃ concentrations for the
 19 base case (i.e., including all anthropogenic and natural sources globally), U.S.
 20 background, and NA background simulations during spring and summer 2006 are shown
 21 in [Figure 2-2](#).

Table 2-1 Comparison of seasonal mean MDA8 ozone concentrations simulated by the GEOS-Chem and CAMx base case models for 2006, with measurements at CASTNET sites.

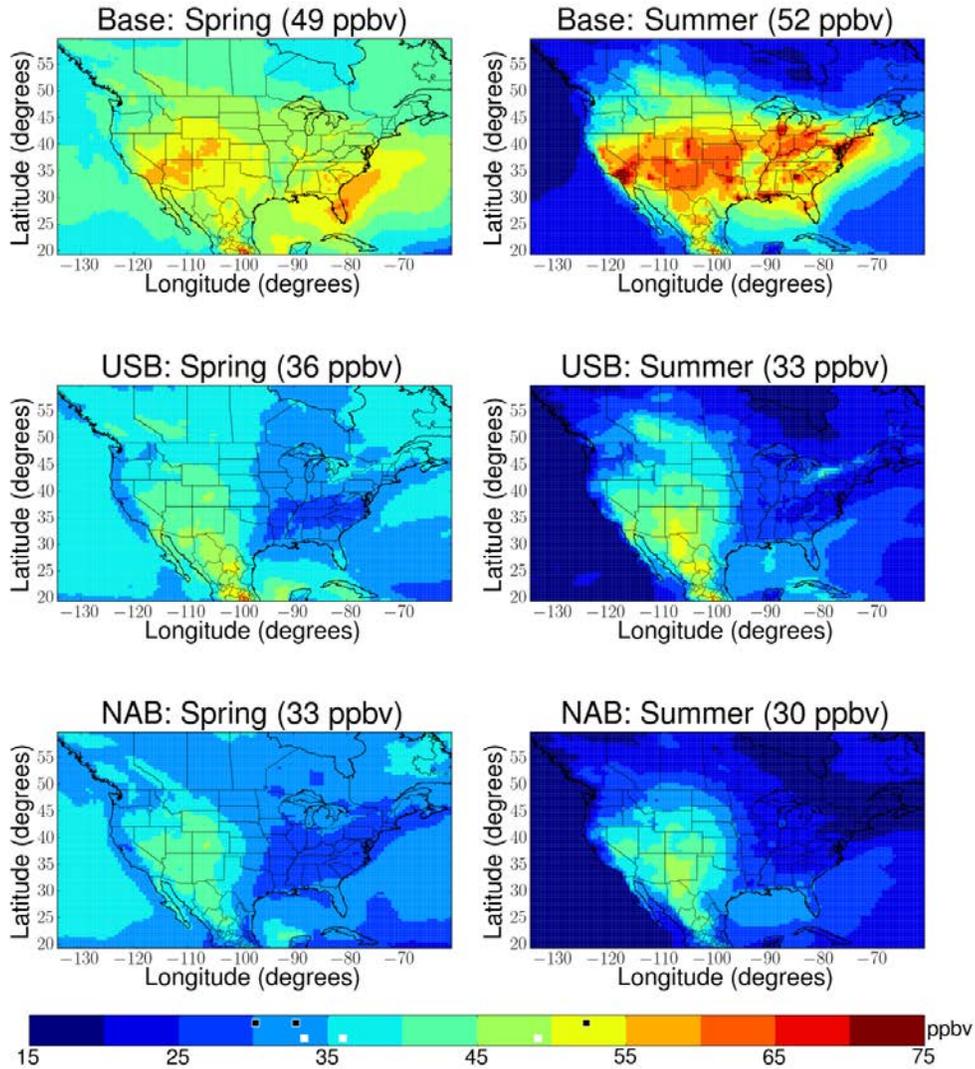
| Region | CASTNET | | GEOS-Chem | | GEOS-Chem/CAMx | |
|-----------------------------|----------------------|---------|--------------------------------|-------------------|-------------------|-------------------|
| | Spring | Summer | Spring | Summer | Spring | Summer |
| California (5) ^a | 58 ± 12 ^b | 69 ± 14 | 52 ± 11 38 ± 7 ^c | 66 ± 18 37 ± 9 | 50 ± 10 39 ± 6 | 66 ± 13 42 ± 6 |
| West (14) | 54 ± 9 | 55 ± 11 | 53 ± 7 42 ± 6 | 55 ± 11 40 ± 9 | 49 ± 8 40 ± 7 | 57 ± 10 41 ± 8 |
| North Central (6) | 47 ± 10 | 50 ± 12 | 47 ± 8 33 ± 6 | 51 ± 14 27 ± 7 | 45 ± 11 30 ± 6 | 54 ± 13 31 ± 5 |
| Northeast (5) | 48 ± 10 | 45 ± 14 | 45 ± 7 33 ± 7 | 45 ± 13 24 ± 7 | 46 ± 11 30 ± 5 | 53 ± 14 27 ± 6 |
| Southeast (9) | 52 ± 11 | 52 ± 16 | 51 ± 7 32 ± 7 | 54 ± 9 29 ± 10 | 54 ± 9 33 ± 6 | 61 ± 12 30 ± 6 |

^aValues in parentheses after each region name refer to the number of sites.

^bShown are seasonal (spring, summer) mean daily maximum 8-h avg O₃ concentrations in ppb ± standard deviation.

^cNorth American background mean daily maximum 8-h avg O₃ concentrations (ppb ± standard deviation) are shown beneath the

base case means.



Note: Mean daily average 8-h O_3 concentrations were calculated by GEOS-Chem for the base case (top, Base), United States background (middle, USB) and North American Background (lower, NAB). Values in parentheses (above each map) refer to continental U.S. means, and are shown in the color bar as black squares for summer and white squares for spring.

Source: Adapted from [Zhang et al. \(2011\)](#).

Figure 2-2 Mean daily average 8-hour ozone concentrations in surface air, for spring and summer 2006.

1 The main results from these modeling efforts can be summarized as follows.

- 2 ▪ Simulated regional and seasonal means of base-case O₃ using both models
3 generally agree to within a few ppb with observations throughout the western
4 and central U.S., except in California; but GEOS-Chem shows better
5 agreement than CAMx in the eastern U.S. However, these results are likely to
6 change with updates to model chemistry and physics.
- 7 ▪ Both models show background concentrations vary spatially and temporally.
8 NA background concentrations are generally higher in spring than in summer
9 across the U.S. Simulated mean NA background concentrations are highest in
10 the Intermountain West (i.e., at high altitude) in spring and in the Southwest in
11 summer. Lowest estimates of NA background occur in the East in the spring
12 and the Northeast in summer.
- 13 ▪ NA background concentrations tend to increase with total (i.e., base case) O₃
14 concentrations at high elevation, but that tendency is not as clear at low
15 elevations.
- 16 ▪ Comparison of NA background and natural background indicate that methane
17 is a major contributor to NA background O₃, accounting for slightly less than
18 half of the increase in background since the preindustrial era and whose
19 relative contribution is projected to grow in the future.
- 20 ▪ U.S. background concentrations are on average 2.6 ppb higher than NA
21 background concentrations during spring and 2.7 ppb during summer across
22 the U.S. with highest increases above NA background over the Northern Tier
23 of New York State (19.1 ppb higher than NA background) in summer. High
24 values for U.S. background are also found in other areas bordering Canada
25 and Mexico.
- 26 ▪ Contributions to background O₃ can be episodic or non-episodic; high
27 background concentrations are driven primarily by the episodic events such as
28 stratospheric intrusions and wildfires. The most pronounced differences
29 between these model results and observations are at the upper end of the
30 concentration distribution, particularly at high elevations.

31 Note that the calculations of background concentrations presented in this chapter were
32 formulated to answer the question, “what would O₃ concentrations be if there were no
33 anthropogenic sources”. This is different from asking, “how much of the O₃ measured or
34 simulated in a given area is due to background contributions”. Because of potentially
35 strong non-linearities—particularly in many urban areas—these estimates should not be
36 used by themselves to answer the second question posed above. The extent of these non-
37 linearities will generally depend on location and time, the strength of concentrated

1 sources, and the nature of the chemical regime. Further work is needed on how these
2 estimates of background concentrations can be used to help determine the contributions
3 of background sources of O₃ to urban concentrations.

2.2.3 Monitoring

4 The federal reference method (FRM) for O₃ measurement is based on the detection of
5 chemiluminescence resulting from the reaction of O₃ with ethylene gas. However, almost
6 all of the state and local air monitoring stations (SLAMS) that reported data to the EPA's
7 Air Quality System (AQS) database from 2005 to 2009 used the federal equivalence
8 method (FEM) UV absorption photometer. More than 96% of O₃ monitors met precision
9 and bias goals during this period.

10 In 2010, there were 1250 SLAMS O₃ monitors reporting data to AQS. Ozone monitoring
11 is required at SLAMS sites during the local "ozone season" which varies by state. In
12 addition, National Core (NCore) is a new multipollutant monitoring network
13 implemented to meet multiple monitoring objectives and each state is required to operate
14 at least one NCore site. The NCore network consists of 60 urban and 20 rural sites
15 nationwide (See [Figure 3-21](#) and [Figure 3-22](#)). The densest concentrations of O₃ sites are
16 located in California and the eastern half of the U.S.

17 The Clean Air Status and Trends Network (CASTNET) is a regional monitoring network
18 established to assess trends in acidic deposition and also provides concentration
19 measurements of O₃. CASTNET O₃ monitors operate year round and are primarily
20 located in rural areas; in 2010, there were 80 CASTNET sites reporting O₃ data to AQS.
21 The National Park Service (NPS) operates 23 CASTNET sites in national parks and other
22 Class-i areas, and provided data to AQS from 20 additional Portable Ozone Monitoring
23 Systems (POMS) in 2010 (See [Figure 3-22](#)). Compared to urban-focused monitors, rural-
24 focused monitors are relatively scarce across the U.S.

2.2.4 Ambient Concentrations

25 Ozone is the only photochemical oxidant other than NO₂ that is routinely monitored and
26 for which a comprehensive database exists. Other photochemical oxidants are typically
27 only measured during special field studies. The concentration analyses in Chapter 3 are
28 limited to widely available O₃ data obtained directly from AQS for the period from 2007
29 to 2009. The median 24-h average, 8-h daily maximum, and 1-h daily maximum O₃
30 concentrations across all U.S. sites reporting data to AQS between 2007 and 2009 were
31 29, 40, and 44 ppb, respectively.

1 To investigate O₃ variability in urban areas across the U.S., 20 combined statistical areas
2 (CSAs) were selected for closer analysis based on their importance in O₃ epidemiology
3 studies and on their location. Several CSAs had relatively little spatial variability in
4 8-hour daily maximum O₃ concentrations (e.g., inter-monitor correlations ranging from
5 0.61 to 0.96 in the Atlanta CSA) while other CSAs exhibited considerably more
6 variability in O₃ concentrations (e.g., inter-monitor correlations ranging from -0.06 to
7 0.97 in the Los Angeles CSA). Uncertainties resulting from the observed variability in O₃
8 concentration fields should be considered when using data from the network of ambient
9 O₃ monitors to approximate community-scale exposures.

10 To investigate O₃ variability in rural settings across the U.S., six focus areas were
11 selected for closer analysis based on the impact of O₃ or O₃ precursor transport from
12 upwind urban areas. The selected rural focus area with the largest number of available
13 AQS monitors was Great Smoky Mountains National Park where the May-September
14 median 8-h daily maximum O₃ concentration ranged from 47 ppb at the lowest elevation
15 (564 m) site to 60 ppb at the highest elevation (2,021 m) site. Correlations between sites
16 within each rural focus area ranged from 0.78 to 0.92. Ozone in rural areas is produced
17 from emissions of O₃ precursors emitted directly within the rural areas, from emissions in
18 urban areas that are processed during transport, and from occasional stratospheric
19 intrusions. Factors contributing to variations observed within these rural focus areas
20 include proximity to local O₃ precursor emissions, local scale circulations related to
21 topography, and possibly stratospheric intrusions as a function of elevation. In addition,
22 O₃ tends to persist longer in rural than in urban areas as a result of less chemical
23 scavenging. This results in a more uniform O₃ concentration throughout the day and night
24 without the typical nocturnal decrease in O₃ concentration observed in urban areas.
25 Persistently high O₃ concentrations observed at many of the rural sites investigated here
26 indicate that cumulative exposures for humans and vegetation in rural areas can
27 frequently exceed cumulative exposures in urban areas.

28 Nation-wide surface level O₃ concentrations have declined over the last decade, with a
29 particularly noticeable decrease between 2003 and 2004 coinciding with NO_x emissions
30 reductions resulting from implementation of the NO_x SIP Call rule, which began in 2003
31 and was fully implemented in 2004. This rule was designed to reduce NO_x emissions
32 from power plants and other large combustion sources in the eastern U.S. The largest
33 density of individual monitors showing downward trends in O₃ concentrations over the
34 last decade occur in the Northeast where this rule was focused. In addition to a downward
35 trend, the nation-wide surface level O₃ concentration data also show a general tightening
36 of the distribution across sites. In contrast to the majority of U.S. surface level monitors
37 reporting downward trends, a few surface-level monitors and elevated observations along
38 the Pacific Coast have shown increases in O₃ concentrations in recent years, possibly

1 resulting from intercontinental transport from Asia. As noted in the 2006 O₃ AQCD,
2 trends in national parks and rural areas are similar to nearby urban areas, reflecting the
3 regional nature of O₃ pollution.

4 Since O₃ is a secondary pollutant, it is not expected to be highly correlated with primary
5 pollutants such as CO and NO_x. Furthermore, O₃ formation is strongly influenced by
6 meteorology, entrainment, and transport of both O₃ and O₃ precursors, resulting in a
7 broad range in correlations with other pollutants which can vary substantially with
8 season. Correlations between 8-h daily maximum O₃ and other criteria pollutants exhibit
9 mostly negative correlations in the winter and mostly positive correlations in the summer.
10 The median seasonal correlations are modest at best with the highest positive correlation
11 at 0.52 for PM_{2.5} in the summer and the highest negative correlation at -0.38 for PM_{2.5} in
12 the winter. As a result, statistical analyses that may be sensitive to correlations between
13 copollutants need to take seasonality into consideration, especially when O₃ is being
14 investigated.

2.3 Human Exposure

15 The widespread presence of O₃ in the environment results in exposure as people
16 participate in normal daily activities. Personal exposure measurements have been found
17 to be moderately associated with fixed-site ambient O₃ concentrations, although a number
18 of factors affect the relationship between ambient concentration and personal exposure.
19 These include: infiltration of ambient O₃ into indoor microenvironments, which is driven
20 by air exchange rate; time spent outdoors and activity pattern, which includes changes in
21 personal behavior by some populations to avoid exposure to O₃; and the variation in O₃
22 concentrations at various spatial and temporal scales. Personal exposure to O₃ is
23 moderately correlated with ambient O₃ concentration, as indicated by studies reporting
24 correlations generally in the range of 0.3-0.8 ([Table 4-2](#)). This suggests that ambient
25 monitor concentrations are representative of day-to-day changes in personal exposure to
26 ambient O₃. Some studies report lower personal-ambient correlations, a result attributable
27 in part to low building air exchange rates and O₃ concentrations below the personal
28 sampler detection limit. Low correlations may also occur for individuals or populations
29 spending increased time indoors. In contrast to correlation, which represents the temporal
30 association between exposure and concentration, the magnitude of exposure can be
31 represented as the ratio between personal exposure and ambient concentration. This ratio
32 varies widely depending on activity patterns, housing characteristics, and season.
33 Personal-ambient ratios are typically 0.1-0.3 for sampling durations of several hours to
34 several days, although individuals spending substantial time outdoors (e.g., outdoor
35 workers) have shown much higher ratios (0.5-0.9) ([Table 4-3](#)). Since there are relatively

1 few indoor sources of O₃, and because of reactions of O₃ with indoor surfaces and
2 airborne constituents, indoor O₃ concentrations are often substantially lower than outdoor
3 concentrations (Section [4.3.2](#)). The lack of indoor sources also suggests that fluctuations
4 in ambient O₃ may be primarily responsible for changes in personal exposure, even under
5 low-ventilation, low-concentration conditions.

6 Another factor that may influence the pattern of exposure is the tendency for people to
7 avoid O₃ exposure by altering their behavior (e.g., reducing outdoor activity levels or
8 time spent being active outdoors) on high-O₃ days. Activity pattern has a substantial
9 effect on ambient O₃ exposure, with time spent outdoors contributing to increased
10 exposure (Section [4.4.2](#)). Air quality alerts and public health recommendations induce
11 reductions in time spent outdoors on high-O₃ days among some populations, particularly
12 for children, older adults, and people with respiratory problems. Such effects are less
13 pronounced in the general population. Limited evidence from an epidemiologic study
14 conducted in the 1990's in Los Angeles, CA reports increased asthma hospital
15 admissions among children and older adults when O₃ alert days (1-h max O₃
16 concentration >200 ppb) were excluded from the analysis of daily hospital admissions
17 and O₃ concentrations (presumably thereby eliminating averting behavior based on high
18 O₃ forecasts). The lower rate of admissions observed when alert days were included in
19 the analysis suggests that estimates of health effects based on concentration-response
20 functions that do not account for averting behavior may be biased towards the null.

21 Variations in O₃ concentrations occur over multiple spatial and temporal scales. Near
22 roadways, O₃ concentrations are reduced due to reaction with NO and other species
23 (Section [4.3.4.2](#)). Over spatial scales of a few kilometers and away from roads, O₃ may
24 be somewhat more homogeneous due to its formation as a secondary pollutant, while
25 over scales of tens of kilometers, additional atmospheric processing can result in higher
26 concentrations downwind of an urban area. Although local-scale variability impacts the
27 magnitude of O₃ concentrations, O₃ formation rates are influenced by factors that vary
28 over larger spatial scales, such as temperature (Section [3.2](#)), suggesting that urban
29 monitors may track one another temporally, but miss small-scale variability. This
30 variation in concentrations changes the pattern of exposure people experience as they
31 move through different microenvironments and affects the magnitude of exposures in
32 different locations within an urban area. The various factors affecting exposure patterns
33 and quantification of exposure result in uncertainty which may contribute to exposure
34 measurement error in epidemiologic studies, which typically use fixed-site monitor data
35 as an indicator of exposure. Low personal-ambient correlations are a source of exposure
36 error for epidemiologic studies, tending to obscure the presence of potential thresholds,
37 bias effect estimates toward the null, and widen confidence intervals, and this impact may
38 be more pronounced among populations spending substantial time indoors. The impact of

1 this exposure error may tend more toward widening confidence intervals than biasing
2 effect estimates, since epidemiologic studies evaluating the influence of monitor selection
3 indicate that effect estimates are similar across different spatial averaging scales and
4 monitoring sites. In addition, in examinations of respiratory endpoints in epidemiologic
5 studies, associations were similar in magnitude across analyses using several different
6 exposure assessment methods that likely vary in how well ambient O₃ concentrations
7 represent personal exposures and between-subject variability in exposures. Respiratory
8 effects were observed with ambient O₃ concentrations found to have stronger personal-
9 ambient relationships, including those measured on-site during long periods of outdoor
10 activity. However, such effects were also found with ambient O₃ measurements expected
11 to have weaker personal-ambient relationships, including those measured at home or
12 school, measured at the closest site, averaged from multiple community sites, and
13 measured at a single site. Overall, there was no clear indication that a particular method
14 of exposure assessment produced stronger findings.

2.4 Dosimetry and Mode of Action

15 Upon inspiration, O₃ uptake in the respiratory tract is affected by a number of factors
16 including respiratory tract morphology, and breathing route, frequency, and volume.
17 Additionally, physicochemical properties of O₃ itself and how it is transported, as well as
18 the physical and chemical properties of the extracellular lining fluid (ELF) and tissue
19 layers in the respiratory tract can influence O₃ uptake. Experimental studies and models
20 have suggested that there are differences between the total absorption of O₃ from the
21 inhaled air and the O₃ dose reaching the respiratory tract tissues. The total O₃ absorption
22 gradually decreases with distal progression into the respiratory tract. In contrast, the
23 primary site of O₃ delivery to the lung epithelium is believed to be the centriacinar region
24 or the junction of the conducting airways with the gas exchange region.

25 Ozone uptake is sensitive to a number of factors including tidal volume, breathing
26 frequency, O₃ concentration, and exposure time. Interindividual variability also accounts
27 for a large amount of the variability in local dose due to differences in pulmonary
28 physiology, anatomy, and biochemistry. An increase in tidal volume and breathing
29 frequency are both associated with increased physical activity. These changes and a
30 switch to oronasal breathing during exercise result in deeper penetration of O₃ into the
31 lower respiratory tract in part due to less oral versus nasal uptake efficiency. For these
32 reasons, increased physical activity acts to move the maximum tissue dose of O₃ distally
33 in the respiratory tract and more into the alveolar region.

1 The ELF is a complex mixture of lipids, proteins, and antioxidants that serves as the first
2 barrier and target for inhaled O₃ (see [Figure 5-7](#)). Distinct products with diverse reactivity
3 (i.e., secondary oxidation products), are mainly formed by reactions of O₃ with soluble
4 ELF components. The thickness of the ELF and that of the mucus layer, within the ELF,
5 are important determinants of the dose of O₃ to the tissues; a thicker ELF generally
6 results in a lower dose of O₃ to the tissues. Additionally, the quenching ability and the
7 concentrations of antioxidants and other ELF components are determinants of the
8 formation of secondary oxidation products. These reactions appear to limit interaction of
9 O₃ with underlying tissues and to reduce penetration of O₃ distally into the respiratory
10 tract.

11 In addition to contributing to the driving force for O₃ uptake, formation of secondary
12 oxidation products contributes to oxidative stress which may lead to cellular injury and
13 altered cell signaling in the respiratory tract. Secondary oxidation products initiate
14 pathways (See [Figure 5-8](#)) that provide the mechanistic basis for short- and long-term
15 health effects described in detail in Chapters 6 and 7. Other key events involved in the
16 mode of action of O₃ in the respiratory tract include the activation of neural reflexes,
17 initiation of inflammation, alterations of epithelial barrier function, sensitization of
18 bronchial smooth muscle, modification of innate and adaptive immunity, and airways
19 remodeling. Another key event, systemic inflammation and vascular oxidative/nitrosative
20 stress, may be critical to the extrapulmonary effects of O₃.

21 Secondary oxidation products can transmit signals to respiratory tract cells resulting in
22 the activation of neural reflexes. Nociceptive sensory nerves mediate the involuntary
23 truncation of respiration, resulting in decreases in lung function (i.e., FVC, FEV₁, and
24 tidal volume), and pain upon deep inspiration. Studies implicate TRPA1 receptors on
25 bronchial C-fibers in this reflex. Another neural reflex involves vagal sensory nerves,
26 which mediate a mild increase in airways obstruction (i.e., bronchoconstriction)
27 following exposure to O₃ via parasympathetic pathways. Substance P release from
28 bronchial C-fibers and the SP-NK receptor pathway may also contribute to this response.

29 Secondary oxidation products also initiate the inflammatory cascade following exposure
30 to O₃. Studies have implicated eicosanoids, chemokines and cytokines, vascular
31 endothelial adhesion molecules, and tachykinins in mediating this response.

32 Inflammation is characterized by airways neutrophilia as well as the influx of other
33 inflammatory cell types. Recent studies demonstrate a later phase of inflammation
34 characterized by increased numbers of macrophages, which is mediated by hyaluronan.
35 Inflammation further contributes to O₃-induced oxidative stress.

36 Alteration of the epithelial barrier function of the respiratory tract also occurs as a result
37 of O₃-induced secondary oxidation product formation. Increased epithelial permeability

1 may lead to enhanced sensitization of bronchial smooth muscle, resulting in airways
2 hyperresponsiveness (AHR). Neurally-mediated sensitization also occurs and is mediated
3 by cholinergic postganglionic pathways and bronchial C-fiber release of substance P.
4 Recent studies implicate hyaluronan and Toll-like receptor 4 (TLR4) signaling in
5 bronchial smooth muscle sensitization, while earlier studies demonstrate roles for
6 eicosanoids, cytokines, and chemokines.

7 Evidence is accumulating that exposure to O₃ modifies innate and adaptive immunity
8 through effects on macrophages, monocytes, and dendritic cells. Enhanced antigen
9 presentation, adjuvant activity, and altered responses to endotoxin have been
10 demonstrated. TLR4 signaling contributes to some of these responses. Effects on innate
11 and adaptive immunity may result in both short- and longer-term consequences related to
12 the exacerbation and/or induction of asthma and to alterations in host defense.

13 Airways remodeling has been demonstrated following chronic and/or intermittent
14 exposure to O₃ by mechanisms that are not well understood. However, the TGF-β
15 signaling pathway has recently been implicated in O₃-induced deposition of collagen in
16 the airways wall. These studies were conducted in adult animal models and their
17 relevance to effects in humans is unknown.

18 Evidence is also accumulating that O₃ exposure results in systemic inflammation and
19 vascular oxidative/nitrosative stress. The release of diffusible mediators from the
20 O₃-exposed lung into the circulation may initiate or propagate inflammatory responses in
21 the vascular or in systemic compartments. This may provide a mechanistic basis for
22 extrapulmonary effects, such as vascular dysfunction.

23 Both dosimetric and mechanistic factors contribute to the understanding of
24 inter-individual variability in response. Inter-individual variability is influenced by
25 variability in respiratory tract volume and thus surface area, breathing route, certain
26 genetic polymorphisms, pre-existing conditions and disease, nutritional status, lifestyles,
27 attenuation, and co-exposures. In particular, very young individuals may be sensitive to
28 developmental effects of O₃ since studies in animal models demonstrated altered
29 development of lung and immune system.

30 Some of these factors are also influential in understanding species homology and
31 sensitivity. Qualitatively, animal models exhibit a similar pattern of tissue dose
32 distribution for O₃ with the largest tissue dose delivered to the centriacinar region.
33 However, due to anatomical and biochemical respiratory tract differences, the actual O₃
34 dose delivered differs between humans and animal models. Animal data obtained in
35 resting conditions underestimates the dose to the respiratory tract tissue relative to
36 exercising humans. Further, it should be noted that, with the exception of airways

1 remodeling, the mechanistic pathways discussed above have been demonstrated in both
2 animals and human subjects in response to the inhalation of O₃. Even though interspecies
3 differences limit quantitative comparison between species, the short- and long-term
4 functional responses of laboratory animals to O₃ appear qualitatively homologous to
5 those of the human making them a useful tool in determining mechanistic and
6 cause-effect relationships with O₃ exposure. Furthermore, animal studies add to a better
7 understanding of the full range of potential O₃-mediated effects.

2.5 Integration of Ozone Health Effects

8 This section evaluates the evidence from toxicological, controlled human exposure, and
9 epidemiologic studies (which examined the health effects associated with short- and
10 long-term exposure to O₃,) and summarizes the main conclusions of this assessment
11 regarding the health effects of O₃ and the concentrations at which those effects are
12 observed. The results from the health studies, supported by the synthesis of atmospheric
13 chemistry (See Section [2.2](#)) and exposure assessment (See Section [2.3](#)) studies, contribute
14 to the causal determinations made for the health outcomes discussed in this assessment
15 (See Preamble to this document for details on the causal framework).

2.5.1 Conclusions from Previous Ozone AQCDs

16 The 2006 O₃ AQCD concluded that there was clear, consistent evidence of a causal
17 relationship between short-term O₃ exposure and respiratory health effects ([U.S. EPA,](#)
18 [2006b](#)). The causal relationship for respiratory health effects was substantiated by the
19 coherence of effects observed across controlled human exposure, epidemiologic, and
20 toxicological studies indicating effects of short-term O₃ exposures on a range of
21 respiratory health endpoints from respiratory tract inflammation to respiratory-related
22 emergency department (ED) visits and hospital admissions.

23 Across disciplines, short-term O₃ exposures induced or were associated with statistically
24 significant declines in lung function. An equally strong body of evidence from controlled
25 human exposure and toxicological studies demonstrated O₃-induced inflammatory
26 responses, increased epithelial permeability, and airway hyperresponsiveness (both
27 specific and nonspecific). Toxicological studies provided additional evidence for
28 O₃-induced impairment of host defenses. Combined, these findings from experimental
29 studies provided support for epidemiologic evidence, in which short-term increases in
30 ambient O₃ concentration were consistently associated with increases in respiratory
31 symptoms and asthma medication use in children with asthma, respiratory-related

1 hospital admissions, and asthma-related ED visits. Although O₃ was consistently
2 associated with nonaccidental and cardiopulmonary mortality, the contribution of
3 respiratory causes to these findings was uncertain.

4 Collectively, there is a vast amount of evidence spanning several decades that
5 demonstrated that exposure to O₃ induces a range of respiratory effects. The majority of
6 this evidence was derived from studies investigating short-term exposure (i.e., hours to
7 weeks) to O₃. The combined evidence across disciplines led to the causal relationship
8 between short-term O₃ exposure and respiratory effects reported in the 2006 O₃ AQCD.

9 Mechanistic evidence for the effects of O₃ on the respiratory system was characterized in
10 the 1996 O₃ AQCD, which identified O₃-induced changes in a variety of lung lipid
11 species whose numerous biologically active metabolites, in turn, can affect host defenses,
12 lung function, and the immune system. As summarized in Section 2.4 and fully
13 characterized in Chapter 5, key events in the toxicity pathway of O₃ have been identified
14 in humans and animal models. They include formation of secondary oxidation products,
15 activation of neural reflexes, initiation of inflammation, alteration of epithelial barrier
16 function, sensitization of bronchial smooth muscle, modification of innate/adaptive
17 immunity, airways remodeling, and systemic inflammation and oxidative/nitrosative
18 stress.

2.5.2 Summary of Causal Determinations

19 Recent studies support or build upon the strong body of evidence presented in the 1996
20 and 2006 O₃ AQCDs that *short-term O₃ exposure is causally associated with respiratory*
21 *health effects*. Recent controlled human exposure studies demonstrate statistically
22 significant group mean decreases in pulmonary function to exposures as low as
23 60-70 ppb O₃ in young, healthy adults, and are supported by the strong, cumulative
24 evidence from epidemiologic studies. Equally strong evidence demonstrated associations
25 of ambient O₃ with respiratory hospital admissions and ED visits across the U.S., Europe,
26 and Canada. Most effect estimates ranged from a 1.6 to 5.4% increase in daily all
27 respiratory-related ED visits or hospital admissions in all-year analyses for unit increases¹
28 in ambient O₃ concentrations. Several multicity studies and a multicontinent study
29 reported associations between short-term increases in ambient O₃ concentrations and
30 increases in respiratory mortality. This evidence is supported by a large body of
31 individual-level epidemiologic panel studies that demonstrate associations of ambient O₃
32 with respiratory symptoms in children with asthma. Further support is provided by recent
33 studies that found O₃-associated increases in indicators of airway inflammation and

¹ Effect estimates were standardized to a 40-, 30-, and 20-ppb unit increase for 1-h max, 8-h max, and 24-h avg O₃.

1 oxidative stress in children with asthma. Across respiratory endpoints, evidence indicates
2 antioxidant capacity may modify the risk of respiratory morbidity associated with O₃
3 exposure. The potentially elevated risk of populations with diminished antioxidant
4 capacity and the reduced risk of populations with enhanced antioxidant capacity
5 identified in epidemiologic studies is strongly supported by similar findings from
6 controlled human exposure studies and by evidence that characterizes O₃-induced
7 decreases in intracellular antioxidant levels as a mode of action for downstream effects.
8 By demonstrating O₃-induced airway hyperresponsiveness, decreased pulmonary
9 function, allergic responses, lung injury, impaired host defense, and airway inflammation,
10 toxicological studies have characterized O₃ modes of action and provided biological
11 plausibility for epidemiologic associations of ambient O₃ concentrations with lung
12 function and respiratory symptoms, hospital admissions, ED visits, and mortality.
13 Together, the evidence integrated across controlled human exposure, epidemiologic, and
14 toxicological studies and across the spectrum of respiratory health endpoints continues to
15 demonstrate that there **is a causal relationship between short-term O₃ exposure and**
16 **respiratory health effects.**

17 The strongest evidence for a relationship between *long-term O₃ exposure and respiratory*
18 *health effects* (including respiratory symptoms, new-onset asthma, and respiratory
19 mortality) is contributed by recent studies that demonstrated associations between long-
20 term measures of O₃ exposure and both new-onset asthma in children and increased
21 respiratory symptom effects in individuals with asthma. While the evidence is limited, a
22 U.S. multicomunity prospective cohort demonstrates that asthma risk is affected by
23 interactions among genetic variability, environmental O₃ exposure, and behavior. The
24 evidence relating new-onset asthma to long-term O₃ exposure is supported by
25 toxicological studies of asthma in monkeys. This nonhuman primate evidence of
26 O₃-induced changes supports the biologic plausibility of long-term exposure to O₃
27 contributing to the effects of asthma in children. Early life O₃ exposure may alter airway
28 development and lead to the development of asthma. Other recent epidemiologic studies
29 provide coherent evidence for long-term O₃ exposure and respiratory effects such as first
30 asthma hospitalization, respiratory symptoms in asthmatics, and respiratory mortality.
31 Generally, the epidemiologic and toxicological evidence provides a compelling case that
32 supports the hypothesis that a relationship exists between long-term exposure to ambient
33 O₃ and measures of respiratory health effects and mortality. The evidence for short-term
34 exposure to O₃ and effects on respiratory endpoints provides coherence and biological
35 plausibility for the effects of long-term exposure to O₃. Building upon that evidence, the
36 more recent epidemiologic evidence, combined with toxicological studies in rodents and
37 nonhuman primates, provides biologically plausible evidence that there **is likely to be a**
38 **causal relationship between long-term exposure to O₃ and respiratory health**
39 **effects.**

1 The 2006 O₃ AQCD concluded that the overall body of evidence was highly suggestive
2 that short-term exposure to O₃ directly or indirectly contributes to nonaccidental and
3 cardiopulmonary-related mortality, but additional research was needed to more fully
4 establish underlying mechanisms by which such effects occur. The evaluation of recent
5 multicity studies and a multicontinent study that examined the association between *short-*
6 *term increases in ambient O₃ concentration and mortality* found evidence that supports
7 the conclusions of the 2006 O₃ AQCD. These recent studies reported consistent positive
8 associations between short-term increases in ambient O₃ concentration and total
9 (nonaccidental) mortality, with associations being stronger during the warm season, as
10 well as provided additional support for associations between O₃ concentrations and
11 cardiovascular mortality being similar or larger in magnitude compared to respiratory
12 mortality. Additionally, these new studies examined previously identified areas of
13 uncertainty in the O₃-mortality relationship, and provide additional evidence supporting
14 an association between short-term O₃ exposure and mortality. Taken together, the body of
15 evidence indicates that there **is likely to be a causal relationship between short-term**
16 **O₃ exposures and total mortality.**

17 The 2006 O₃ AQCD concluded that an insufficient amount of evidence existed to suggest
18 a causal relationship between *long-term O₃ exposure and mortality* ([U.S. EPA, 2006b](#)).
19 A synthesis of the recent and earlier evidence reveals that the strongest evidence for an
20 association between long-term exposure to ambient O₃ concentrations and mortality is
21 derived from associations for respiratory mortality that remained robust after adjusting
22 for PM_{2.5} concentrations. There is inconsistent evidence for an association between long-
23 term exposure to ambient O₃ and cardiopulmonary mortality, with several analyses from
24 the ACS cohort reporting some positive associations, while other studies reported no
25 association. There is generally limited evidence for an association with long-term
26 exposure to ambient O₃ and total mortality. The findings for respiratory mortality are
27 consistent and coherent with the evidence from epidemiologic, controlled human
28 exposure, and animal toxicological studies for the effects of short- and long-term
29 exposure to O₃ on respiratory effects. Respiratory mortality is a relatively small portion
30 of total mortality [about 7.6% of all deaths in 2010 were due to respiratory causes
31 ([Murphy et al., 2012](#))], thus it is not surprising that the respiratory mortality signal may
32 be difficult to detect in studies of cardiopulmonary or total mortality. Based on the recent
33 evidence for respiratory mortality along with limited evidence for total and
34 cardiopulmonary mortality, the evidence **is suggestive of a causal relationship**
35 **between long-term O₃ exposures and total mortality.**

36 In past O₃ AQCDs the effects of *short- and long-term exposure to O₃ on the*
37 *cardiovascular system* could not be thoroughly evaluated due to the paucity of
38 information available. However, studies investigating O₃-induced cardiovascular events

1 have advanced in the last two decades. Animal toxicological studies provide evidence for
2 both short- and long-term O₃ exposure leading to cardiovascular morbidity. The
3 toxicological studies demonstrate O₃-induced cardiovascular effects, specifically
4 enhanced atherosclerosis and ischemia/reperfusion injury with or without the
5 corresponding development of a systemic oxidative, pro-inflammatory environment,
6 disrupted NO-induced vascular reactivity, decreased cardiac function, and increased heart
7 rate variability (HRV). The observed increase in HRV is supported by a recent controlled
8 human exposure study that also found increased high frequency HRV, but not altered
9 blood pressure, following O₃ exposure. It is still uncertain how O₃ inhalation may cause
10 systemic toxicity; however the cardiovascular effects of O₃ found in animals correspond
11 to the development and maintenance of an extrapulmonary oxidative, proinflammatory
12 environment that may result from pulmonary inflammation.

13 There is limited, inconsistent evidence for cardiovascular morbidity in epidemiologic
14 studies examining both short- and long-term exposure to O₃. This is highlighted by the
15 multiple studies that examined the association between short-term increases in ambient
16 O₃ concentration and cardiovascular-related hospital admissions and ED visits and other
17 various cardiovascular effects and found no evidence of a consistent relationship with O₃
18 exposure. Positive associations between short-term increases in O₃ concentration and
19 cardiovascular mortality have been consistently reported in multiple epidemiologic
20 studies. However, the lack of coherence between the results from studies that examined
21 associations between short-term increases in O₃ concentration and cardiovascular
22 morbidity and subsequently cardiovascular mortality, complicate the interpretation of the
23 evidence for O₃-induced cardiovascular mortality.

24 Overall, animal toxicological studies provide some evidence for O₃-induced
25 cardiovascular effects, but the effects observed were not consistently supported by
26 controlled human exposure studies or epidemiologic studies. Although the toxicological
27 evidence provides initial support to the relatively strong body of evidence indicating
28 O₃-induced cardiovascular mortality, there is a lack of coherence with controlled human
29 exposure and epidemiologic studies of cardiovascular morbidity which together do not
30 support O₃-induced cardiovascular effects. Thus, the overall body of evidence across
31 disciplines **is suggestive of a causal relationship for both relevant short- and long-**
32 **term exposures to O₃ and cardiovascular effects.**

33 In the 2006 O₃ AQCD, there were a number of health effects for which an insufficient
34 amount of evidence existed to adequately characterize the relationships with exposure to
35 O₃. However, recent evidence suggests that O₃ may impart health effects through
36 exposure durations and biological mechanisms not previously considered. For example,
37 recent toxicological studies add to earlier evidence that *short- and long-term exposures to*
38 *O₃ can produce a range of effects on the central nervous system and behavior.*

1 Additionally, an epidemiologic study demonstrated that long-term exposure to O₃ affects
 2 memory in humans as well. Together the evidence from studies of short- and long-term
 3 exposure to O₃ **is suggestive of a causal relationship between O₃ exposure and**
 4 **central nervous system effects.** There is also limited though positive toxicological
 5 evidence for *O₃-induced developmental effects*. Limited epidemiologic evidence exists
 6 for an association of O₃ concentration with decreased sperm concentration and
 7 associations with reduced birth weight and restricted fetal growth. Overall, the evidence
 8 **is suggestive of a causal relationship between long-term exposures to O₃ and**
 9 **reproductive and developmental effects.**

10 These causal determinations are summarized in Table 2-2, along with the conclusions
 11 from the previous NAAQS review. Special emphasis and additional details are provided
 12 in Table 2-2 for respiratory health outcomes, for which there is the strongest body of
 13 evidence.

Table 2-2 Summary of evidence from epidemiologic, controlled human exposure, and animal toxicological studies on the health effects associated with short- and long-term exposure to ozone.

| Health Outcome | Conclusions from 2006 O ₃ AQCD | Conclusions from 2012 3rd Draft ISA |
|---|---|---|
| Short-Term Exposure to O₃ | | |
| Respiratory effects | The overall evidence supports a causal relationship between acute ambient O ₃ exposures and increased respiratory morbidity outcomes. | Evidence integrated across controlled human exposure, epidemiologic, and toxicological studies and across the spectrum of respiratory health endpoints continues to demonstrate that there is a causal relationship between short-term O₃ exposure and respiratory health effects. |
| Lung function | Results from controlled human exposure studies and animal toxicological studies provide clear evidence of causality for the associations observed between acute (≤ 24 h) O ₃ exposure and relatively small, but statistically significant declines in lung function observed in numerous recent epidemiologic studies. Declines in lung function are particularly noted in children, asthmatics, and adults who work or exercise outdoors. | Recent controlled human exposure studies demonstrate group mean decreases in FEV ₁ in the range of 2 to 3% with 6.6 hour exposures to as low as 60 ppb O ₃ . The collective body of epidemiologic evidence demonstrates associations between short-term ambient O ₃ exposure and decrements in lung function, particularly in children with asthma, children, and adults who work or exercise outdoors. |
| Airway hyperresponsiveness | Evidence from human clinical and animal toxicological studies clearly indicate that acute exposure to O ₃ can induce airway hyperreactivity, thus likely placing atopic asthmatics at greater risk for more prolonged bouts of breathing difficulties due to airway constriction in response to various airborne allergens or other triggering stimuli. | A limited number of studies have observed airway hyperresponsiveness in rodents and guinea pigs after exposure to less than 300 ppb O ₃ . As previously reported in the 2006 O ₃ AQCD, increased airway responsiveness has been demonstrated at 80 ppb in young, healthy adults, and at 50 ppb in certain strains of rats. |

| Health Outcome | Conclusions from 2006 O ₃ AQCD | Conclusions from 2012 3rd Draft ISA |
|--|--|--|
| Pulmonary inflammation, injury and oxidative stress | The extensive human clinical and animal toxicological evidence, together with the limited available epidemiologic evidence, is clearly indicative of a causal role for O ₃ in inflammatory responses in the airways. | Epidemiologic studies provided new evidence for associations of ambient O ₃ with mediators of airway inflammation and oxidative stress and indicate that higher antioxidant levels may reduce pulmonary inflammation associated with O ₃ exposure. Generally, these studies had mean 8-h max O ₃ concentrations less than 73 ppb . Recent controlled human exposure studies show O ₃ -induced inflammatory responses at 60 ppb, the lowest concentration evaluated. |
| Respiratory symptoms and medication use | Young healthy adult subjects exposed in clinical studies to O ₃ concentrations ≥ 80 ppb for 6 to 8 h during moderate exercise exhibit symptoms of cough and pain on deep inspiration. The epidemiologic evidence shows significant associations between acute exposure to ambient O ₃ and increases in a wide variety of respiratory symptoms (e.g., cough, wheeze, production of phlegm, and shortness of breath) and medication use in asthmatic children. | The collective body of epidemiologic evidence demonstrates positive associations between short-term exposure to ambient O ₃ and respiratory symptoms (e.g., cough, wheeze, and shortness of breath) in children with asthma. Generally, these studies had mean 8-h max O ₃ concentrations less than 69 ppb . |
| Lung host defenses | Toxicological studies provided extensive evidence that acute O ₃ exposures as low as 80 to 500 ppb can cause increases in susceptibility to infectious diseases due to modulation of lung host defenses. A single controlled human exposure study found decrements in the ability of alveolar macrophages to phagocytize microorganisms upon exposure to 80 to 100 ppb O ₃ . | Recent controlled human exposure studies demonstrate the increased expression of cell surface markers and alterations in sputum leukocyte markers related to innate adaptive immunity with short-term O ₃ exposures of 80-400 ppb . Recent studies demonstrating altered immune responses and natural killer cell function build on prior evidence that O ₃ can affect multiple aspects of innate and acquired immunity with short-term O ₃ exposures as low as 80 ppb . |
| Allergic and asthma related responses | Previous toxicological evidence indicated that O ₃ exposure skews immune responses toward an allergic phenotype, and enhances the development and severity of asthma-related responses such as AHR. | Recent controlled human exposure studies demonstrate enhanced allergic cytokine production in atopic individuals and asthmatics, increased IgE receptors in atopic asthmatics, and enhanced markers of innate immunity and antigen presentation in health subjects or atopic asthmatics with short-term exposure to 80-400 ppb O ₃ , all of which may enhance allergy and/or asthma. Further evidence for O ₃ -induced allergic skewing is provided by a few recent studies in rodents using exposure concentrations as low as 200 ppb . |
| Respiratory Hospital admissions, ED visits, and physician visits | Aggregate population time-series studies observed that ambient O ₃ concentrations are positively and robustly associated with respiratory-related hospitalizations and asthma ED visits during the warm season. | Consistent, positive associations of ambient O ₃ with respiratory hospital admissions and ED visits in the U.S., Europe, and Canada with supporting evidence from single city studies. Generally, these studies had mean 8-h max O ₃ concentrations less than 60 ppb . |
| Respiratory Mortality | Aggregate population time-series studies specifically examining mortality from respiratory causes were limited in number and showed inconsistent associations between acute exposure to ambient O ₃ exposure and respiratory mortality. | Recent multicity time-series studies and a multicontinent study consistently demonstrated associations between ambient O ₃ and respiratory-related mortality visits across the U.S., Europe, and Canada with supporting evidence from single city studies. Generally, these studies had mean 8-h max O ₃ concentrations less than 63 ppb . |
| Cardiovascular effects | The limited evidence is highly suggestive that O ₃ directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association. | The overall body of evidence across disciplines is suggestive of a causal relationship for relevant short-term exposures to O₃ and cardiovascular effects . |

| Health Outcome | Conclusions from 2006 O ₃ AQCD | Conclusions from 2012 3rd Draft ISA |
|---|---|--|
| Central nervous system effects | Toxicological studies report that acute exposures to O ₃ are associated with alterations in neurotransmitters, motor activity, short- and long-term memory, sleep patterns, and histological signs of neurodegeneration. | Together the evidence from studies of short-term exposure to O ₃ is suggestive of a causal relationship between O₃ exposure and CNS effects. |
| Total Mortality | The evidence is highly suggestive that O ₃ directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality. | Taken together, the body of evidence indicates that there is likely to be a causal relationship between short-term exposures to O₃ and all-cause total mortality. |
| Long-term Exposure to O₃ | | |
| Respiratory effects | The current evidence is suggestive but inconclusive for respiratory health effects from long-term O ₃ exposure. | Recent epidemiologic evidence, combined with toxicological studies in rodents and non-human primates, provides biologically plausible evidence that there is likely to be a causal relationship between long-term exposure to O₃ and respiratory health effects. |
| New onset asthma | No studies examining this outcome were evaluated in the 2006 O ₃ AQCD. | Evidence that different genetic variants (HMOX, GST, ARG), in combination with O ₃ exposure, are related to new onset asthma. These associations were observed when subjects living in areas where the mean annual 8-h max O ₃ concentration was 55.2 ppb , compared to those who lived where it was 38.4 ppb . |
| Asthma hospital admissions | No studies examining this outcome were evaluated in the 2006 O ₃ AQCD. | Chronic O ₃ exposure was related to first childhood asthma hospital admissions in a positive concentration-response relationship. Generally, these studies had mean annual 8-h max O ₃ concentrations less than 41 ppb . |
| Pulmonary structure and function | Epidemiologic studies observed that reduced lung function growth in children was associated with seasonal exposure to O ₃ ; however, cohort studies of annual or multiyear O ₃ exposure observed little clear evidence for impacts of longer-term, relatively low-level O ₃ exposure on lung function development in children. Animal toxicological studies reported chronic O ₃ -induced structural alterations, some of which were irreversible, in several regions of the respiratory tract including the centriacinar region. Morphologic evidence from studies using exposure regimens that mimic seasonal exposure patterns report increased lung injury compared to conventional chronic stable exposures. | Evidence for pulmonary function effects is inconclusive, with some new epidemiologic studies observing positive associations (mean annual 8-h max O ₃ concentrations less than 65 ppb). Information from toxicological studies indicates that long-term maternal exposure during gestation (100 ppb) or development (500 ppb) can result in irreversible morphological changes in the lung, which in turn can influence pulmonary function. |
| Pulmonary inflammation, injury and oxidative stress | Extensive human clinical and animal toxicological evidence, together with limited epidemiologic evidence available, suggests a causal role for O ₃ in inflammatory responses in the airways. | Several epidemiologic studies (mean 8-h max O ₃ concentrations less than 69 ppb) and toxicology studies (as low as 500 ppb) add to observations of O ₃ -induced inflammation and injury. |
| Lung host defenses | Toxicological studies provided evidence that chronic O ₃ exposure as low as 100 ppb can cause increases in susceptibility to infectious diseases due to modulation of lung host defenses, but do not cause greater effects on infectivity than short exposures. | Consistent with decrements in host defenses observed in rodents exposed to 100 ppb O₃ , recent evidence demonstrates a decreased ability to respond to pathogenic signals in infant monkeys exposed to 500 ppb O₃ . |
| Allergic responses | Limited epidemiologic evidence supported an association between ambient O ₃ and allergic symptoms. Little if any information was available from toxicological studies. | Evidence relates positive outcomes of allergic response and O ₃ exposure but with variable strength for the effect estimates; exposure to O ₃ may increase total IgE in adult asthmatics. Allergic indicators in monkeys were increased by exposure to O ₃ concentrations of 500 ppb . |

| Health Outcome | Conclusions from 2006 O ₃ AQCD | Conclusions from 2012 3rd Draft ISA |
|---|---|---|
| Respiratory mortality | Studies of cardio-pulmonary mortality were insufficient to suggest a causal relationship between chronic O ₃ exposure and increased risk for mortality in humans. | A single study demonstrated that exposure to O ₃ (long-term mean O ₃ less than 104 ppb) elevated the risk of death from respiratory causes and this effect was robust to the inclusion of PM _{2.5} . |
| Cardiovascular Effects | No studies examining this outcome were evaluated in the 2006 O ₃ AQCD. | The overall body of evidence across disciplines is suggestive of a causal relationship for relevant long-term exposures to O₃ and cardiovascular effects. |
| Reproductive and developmental effects | Limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for O ₃ effects. | Overall, the evidence is suggestive of a causal relationship between long-term exposures to O₃ and reproductive and developmental effects. |
| Central nervous system effects | Toxicological studies reported that acute exposures to O ₃ are associated with alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration. Evidence regarding chronic exposure and neurobehavioral effects was not available. | Together the evidence from studies of long-term exposure to O ₃ is suggestive of a causal relationship between O₃ exposure and CNS effects. |
| Cancer | Little evidence for a relationship between chronic O ₃ exposure and increased risk of lung cancer. | Overall, the evidence is inadequate to determine if a causal relationship exists between ambient O₃ exposures and cancer. |
| Total Mortality | There is little evidence to suggest a causal relationship between chronic O ₃ exposure and increased risk for mortality in humans. | Collectively, the evidence is suggestive of a causal relationship between long-term O₃ exposures and total mortality. |

2.5.3 Integrated Synthesis of Evidence for Health Effects

1 Building off that evaluated in previous O₃ AQCDs, recent evidence demonstrates that O₃
2 is associated with a *broad range of respiratory effects, including altered development of*
3 *the respiratory tract*. Recent animal toxicological studies of long-term exposure to O₃
4 occurring throughout various lifestages in monkeys, beginning with prenatal and early
5 life exposures, provide novel evidence for effects on the development of the respiratory
6 system, including ultrastructural changes in bronchiole development, effects on the
7 developing immune system, and increased offspring airway hyper-reactivity
8 (Section [7.4.7](#)). The strongest evidence for O₃-induced effects on the developing lung
9 comes from a series of experiments using infant rhesus monkeys episodically exposed to
10 500 ppb O₃ for approximately 5 months, starting at one month of age. Functional changes
11 in the conducting airways of infant rhesus monkeys exposed to either O₃ alone or O₃ +
12 antigen were accompanied by a number of cellular and morphological changes. In
13 addition to these functional and cellular changes, substantial structural changes in the
14 respiratory tract were observed. Importantly, the O₃-induced structural pathway changes
15 persisted after recovery in filtered air for six months after cessation of the O₃ exposures.
16 Exposure to O₃ has also been associated with similar types of alterations in pulmonary
17 structure, including airways remodeling and pulmonary injury and increased

1 permeability, in all adult laboratory animal species studied, from rats to monkeys ([U.S.](#)
2 [EPA, 1996a](#)).

3 In addition to effects on the development and structure of the respiratory tract, there is
4 extensive evidence for the effects of *short-term exposure to O₃ on pulmonary*
5 *inflammation and oxidative stress*. Previous evidence from controlled human exposure
6 studies indicated that O₃ causes an inflammatory response in the lungs ([U.S. EPA,](#)
7 [1996a](#)). This inflammatory response to O₃ was detected after a single 1-h exposure with
8 exercise to O₃ concentrations of 300 ppb; the increased levels of some inflammatory cells
9 and mediators persisted for at least 18 hours. Toxicological studies provided additional
10 evidence for increases in permeability and inflammation in rabbits at levels as low as
11 100 ppb O₃. Evidence summarized in the 2006 O₃ AQCD demonstrated that
12 inflammatory responses were observed subsequent to 6.6 hours O₃ exposure to the lowest
13 tested level of 80 ppb in healthy human adults, while toxicological studies provided
14 extensive evidence that short-term (1-3 hours) O₃ exposure in the range of 100-500 ppb
15 could cause lung inflammatory responses. The limited epidemiologic evidence reviewed
16 in the 2006 O₃ AQCD demonstrated an association between short-term increases in
17 ambient O₃ concentration and airways inflammation in children (1-h max O₃ of
18 approximately 100 ppb). Recent studies in animals and in vitro models described
19 inflammatory and injury responses mediated by Toll-like receptors (e.g., TLR4, TLR2),
20 receptors for TNF or IL-1, multiple signaling pathways (e.g., p38, JNK, NFκB,
21 MAPK/AP-1), and oxidative stress (Section [6.2.3.3](#)). Recent epidemiologic studies
22 provide additional supporting evidence by demonstrating associations of ambient O₃ with
23 mediators of airways inflammation and oxidative stress.

24 The normal inflammatory response in lung tissue is part of host defense that aids in
25 removing microorganisms or particles that have reached the distal airways and alveolar
26 surface. The 1996 O₃ AQCD concluded that short-term exposure to elevated
27 concentrations of O₃ resulted in alterations in these host defense mechanisms in the
28 respiratory system. Specifically, toxicological studies of short-term exposures as low as
29 100 ppb O₃ for 2 hours were shown to decrease the ability of alveolar macrophages to
30 ingest particles, and short-term exposures as low as 80 ppb for 3 hours prevented mice
31 from resisting infection with streptococcal bacteria and resulted in infection-related
32 mortality. Similarly, alveolar macrophages removed from the lungs of human subjects
33 after 6.6 hours of exposure to 80 and 100 ppb O₃ had decreased ability to ingest
34 microorganisms, indicating some impairment of host defense capability. These altered
35 host defense mechanisms can lead to increased risk of respiratory infections, which can
36 often predispose individuals to developing asthma when occurring in early life. Despite
37 the strong toxicological evidence, in the limited body of epidemiologic evidence, ambient
38 O₃ concentrations have not been consistently associated with hospital admissions or ED

1 visits for respiratory infection, pneumonia, or influenza (Section [6.2.7.2](#) and
2 Section [6.2.7.3](#)).

3 The most commonly observed and strongest evidence for respiratory effects associated
4 with short-term exposure to O₃ is transient *decrements in pulmonary function*. Controlled
5 human exposure studies reviewed in previous assessments demonstrated O₃-induced
6 decrements in pulmonary function, characterized by alterations in lung volumes and flow
7 and airway resistance and responsiveness for multihour exposures (up to 8 hours) to O₃
8 concentrations as low as 80 ppb ([U.S. EPA, 1996a](#)). A series of mobile laboratory studies
9 of lung function and respiratory symptoms reported pulmonary function decrements at
10 mean ambient O₃ concentrations of 140 ppb in exercising healthy adolescents and
11 increased respiratory symptoms and pulmonary function decrements at 150 ppb in
12 heavily exercising athletes and at 170 ppb in lightly exercising healthy and asthmatic
13 subjects. Epidemiologic and animal toxicological evidence is coherent with the results of
14 the controlled human exposure studies, both indicating decrements in lung function upon
15 O₃ exposure. A combined statistical analysis of epidemiologic studies in children at
16 summer camp with particularly strong exposure assessment demonstrated decrements in
17 FEV₁ of 0.50 mL/ppb with an increase in previous hour O₃ concentration. For
18 preadolescent children exposed to 120 ppb ambient O₃, this estimated volume decrease
19 corresponded to an average decrement of 2.4-3.0% in FEV₁. Key studies of lung function
20 (FEV₁) measured before and after well-defined outdoor exercise events in adults yielded
21 concentration-response slopes of 0.40 and 1.35 mL/ppb ambient O₃ after exposure for up
22 to 1 hour. Animal toxicological studies reported similar respiratory effects in rats at
23 exposures as low as 200 ppb O₃ for 3 hours. The 2006 O₃ AQCD characterized the
24 controlled human exposure and animal toxicological studies as providing clear evidence
25 of causality for the associations observed between short-term (≤ 24 hours) increases in O₃
26 concentration and relatively small, but statistically significant declines in lung function
27 observed in numerous recent epidemiologic studies. In epidemiologic studies, declines in
28 lung function were particularly noted in children with and without asthma, and adults
29 who work or exercise outdoors.

30 Recent controlled human exposure studies examined lower concentration O₃ exposures
31 (40-80 ppb) and demonstrated that FEV₁, respiratory symptoms, and inflammatory
32 responses were affected by O₃ exposures of 6.6 hours as low as 60 to 70 ppb
33 (Section [6.2.1.1](#) and Section [6.2.3.1](#)). These studies demonstrated average O₃-induced
34 decreases in FEV₁ in the range of 2.8 to 3.6% with O₃ exposures to 60 ppb for 6.6 hours.
35 Further, in the controlled human exposure studies evaluating effects of 60 ppb O₃, on
36 average, 10% of the exposed individuals experienced >10% FEV₁ decrements following
37 6.6 hours of exposure. Considerable intersubject variability has also been reported in
38 studies at higher exposure concentrations (≥ 70 ppb) with some subjects experiencing

1 considerably greater decrements than average. Recent epidemiologic studies provide
2 greater insight into individual- and population-level factors that may increase for the risk
3 of O₃-associated respiratory morbidity. In addition to lung function decrements
4 consistently reported in healthy children at summer camp, O₃-associated decreases in
5 lung function were consistently observed in epidemiologic studies that included
6 potentially at-risk populations (e.g., individuals with asthma with concurrent respiratory
7 infection, older adults with AHR or elevated body mass index, or groups with diminished
8 antioxidant capacity).

9 Exposure to O₃ may also result in *respiratory symptoms* (e.g., coughing, wheezing,
10 shortness of breath). The 1996 O₃ AQCD identified an association between respiratory
11 symptoms and increasing ambient O₃, particularly among children with asthma. In the
12 2006 O₃ AQCD, symptoms of cough and pain on deep inspiration were well documented
13 in young healthy adult subjects after exposure of ≥ 80 ppb O₃ for 6-8 hours during
14 moderate exercise. Limited data suggested an increase in respiratory symptoms down to
15 60 ppb. More recently, these effects have been observed at 70 ppb in healthy adults.
16 Controlled human exposure studies of healthy adults, have also reported an increased
17 incidence of cough with O₃ exposures as low as 120 ppb and 1-3 hours in duration with
18 very heavy exercise. The controlled human exposure studies also demonstrated lesser
19 respiratory symptom responses in children and older adults relative to young healthy
20 adults. Cumulative epidemiologic evidence adds to the findings from controlled human
21 exposure studies for healthy adults by demonstrating the effects of ambient O₃ exposure
22 on respiratory symptoms in children with asthma. Increases in ambient O₃ concentration
23 were associated with a wide variety of respiratory symptoms (e.g., cough, wheeze, and
24 shortness of breath) in children with asthma. Epidemiologic studies also indicated that
25 short-term increases in O₃ concentration are likely associated with increased asthma
26 medication use in children with asthma. Additionally, epidemiologic studies provide
27 evidence for an association between long-term exposure to O₃ and respiratory symptoms
28 (Section [7.2.2](#)).

29 Ozone exposure has been shown to result in *both specific and non-specific airway*
30 *hyperresponsiveness (AHR)*. Increased AHR is an important consequence of exposure to
31 O₃ because its presence represents a change in airway smooth muscle reactivity and
32 implies that the airways are predisposed to narrowing on inhalation of a variety of stimuli
33 (e.g., specific allergens, SO₂, cold air). Specifically, short-term (2 or 3 hours) exposure to
34 250 or 400 ppb O₃ was found to cause increases in AHR in response to allergen
35 challenges among allergic asthmatic subjects who characteristically already had
36 somewhat increased AHR at baseline. Increased non-specific AHR has been
37 demonstrated in healthy young adults down to 80 ppb O₃ following 6.6 hours of exposure
38 during moderate exercise. While AHR has not been widely examined in epidemiologic

1 studies, findings for O₃-induced increases in AHR in controlled human exposure
2 (Section [6.2.2.1](#)) and toxicological (Section [6.2.2.2](#)) studies provide biological
3 plausibility for associations observed between increases in ambient O₃ concentration and
4 increases in respiratory symptoms in subjects with asthma.

5 In addition to asthma exacerbations, recent epidemiologic evidence has indicated that
6 *long-term ambient O₃ concentrations may contribute to new onset asthma* (Section [7.2.1](#),
7 [Table 7-2](#)). The new epidemiologic evidence base consists of studies using a variety of
8 designs and analysis methods evaluating the relationship between long-term annual
9 measures of exposure to ambient O₃ and measures of respiratory morbidity. Studies from
10 two California cohorts have provided evidence for different variants in genes related to
11 oxidative or nitrosative stress (e.g., *HMOX*, *GSTs*, *ARG*) that, depending on community
12 long-term O₃ concentrations, are related to new onset asthma. This is the first time that
13 evidence has extended beyond the association of short-term exposure to O₃ and asthma
14 exacerbations to suggest that long-term exposure to O₃ may play a role in the
15 development of the disease and contribute to incident cases of asthma.

16 The frequency of *ED visits and hospital admissions* due to respiratory symptoms, asthma
17 exacerbations and other respiratory diseases is associated with *short- and long-term*
18 *exposure to ambient O₃ concentrations*. Summertime daily hospital admissions for
19 respiratory causes in various locations of eastern North America were consistently
20 associated with ambient concentrations of O₃ in studies reviewed in the 1996 O₃ AQCD.
21 This association remained even with examination of only concentrations below 120 ppb
22 O₃. The 2006 O₃ AQCD concluded that aggregate population time-series studies
23 demonstrate a positive and robust association between ambient O₃ concentrations and
24 respiratory-related hospitalizations and asthma ED visits during the warm season. Recent
25 epidemiologic time-series studies that include additional multicity studies and a
26 multicontinent study further demonstrate that short-term exposures to ambient O₃
27 concentrations are consistently associated with increases in respiratory hospital
28 admissions and ED visits specifically during the warm/summer months across a range of
29 O₃ concentrations (Section [6.2.7](#)). There is also recent evidence for an association
30 between respiratory hospital admissions and long-term exposure to O₃ (Section [7.2.2](#)).

31 Finally, O₃ exposure may contribute to *death from respiratory causes*. Recent evidence
32 from several multicity studies and a multicontinent study demonstrate consistent positive
33 associations between short-term exposure to ambient O₃ concentrations and increases in
34 respiratory mortality (Section [6.6.2.5](#)). Similarly, a study of long-term exposure to
35 ambient O₃ concentrations also demonstrated an association between O₃ and increases in
36 respiratory mortality (Section [7.7.1](#)). Evidence from these recent mortality studies is
37 consistent and coherent with the evidence from epidemiologic, controlled human

1 exposure, and animal toxicological studies for the effects of short- and long-term
2 exposure to O₃ on respiratory effects. Additionally, the evidence for respiratory morbidity
3 after short- and long-term exposure provides biological plausibility for mortality due to
4 respiratory disease.

5 There is similar evidence for a positive association between short-term exposure to O₃
6 and mortality. This evidence has been substantiated by single-city studies reviewed in the
7 2006 O₃ AQCD and recent multicity and multicontinent studies. When examining
8 mortality due to cardiovascular disease, epidemiologic studies consistently observe
9 positive associations with short-term exposure to O₃. Additionally, there is some
10 evidence for an association between long-term exposure to O₃ and mortality. However,
11 the association between long-term ambient O₃ concentrations and cardiovascular
12 mortality may be confounded by other pollutants as evident by a study of cardiovascular
13 mortality that reported no association after adjustment for PM_{2.5} concentrations. The lack
14 of coherence between the results from studies that examined associations between short-
15 and long-term O₃ concentrations and cardiovascular morbidity, and results from studies of
16 cardiovascular mortality, complicate the interpretation of the evidence for O₃-induced
17 cardiovascular mortality.

18 Epidemiologic studies evaluating cardiovascular morbidity and short- and long-term
19 exposure to O₃ provide no consistent evidence for an association. This is highlighted by
20 the multiple studies that examined the association between short- and long-term O₃
21 concentrations and cardiovascular-related hospital admissions and ED visits and
22 cardiovascular disease-related biomarkers. Additionally, a single controlled human
23 exposure study reported no statistically significant O₃-induced differences in
24 electrocardiogram (ECG), heart rate, or blood pressure in normal or hypertensive subjects
25 (0.3 ppm for 3 h with intermittent exercise), however an overall increase in myocardial
26 work and impairment in pulmonary gas exchange was observed.

27 There is an emerging body of animal toxicological evidence suggesting that autonomic
28 nervous system alterations (in heart rate and/or heart rate variability) and
29 proinflammatory signals may mediate cardiovascular effects. Interactions of O₃ with ELF
30 components result in secondary oxidation products and inflammatory mediators that have
31 the potential to penetrate the epithelial barrier and to initiate toxic effects on the
32 cardiovascular system. Animal toxicological studies of long-term exposure to O₃ provide
33 evidence enhanced atherosclerosis and ischemia/reperfusion (I/R) injury, corresponding
34 with development of a systemic oxidative, proinflammatory environment.

35 Overall, animal toxicological studies provide some evidence for O₃-induced
36 cardiovascular effects, but the effects were not consistently supported by controlled
37 human exposure studies or epidemiologic evidence. Although the toxicological evidence

1 provides initial support to the body of evidence indicating an association between short-
2 term exposure to O₃ and cardiovascular mortality, there is a lack of coherence with
3 controlled human exposure and epidemiologic studies of cardiovascular morbidity.
4 Together, these findings are suggestive of O₃-induced cardiovascular effects.

2.5.4 Policy Relevant Considerations

2.5.4.1 Populations Potentially at Increased Risk

5 Studies were conducted to identify populations that are at increased risk for O₃-related
6 health effects. These studies have investigated factors that can cause populations to be at
7 increased risk for O₃-related health effects by conducting stratified epidemiologic
8 analyses; by examining individuals with an underlying health condition, genetic
9 polymorphism, or categorized by age, race, or sex in controlled human exposure studies;
10 or by developing animal models that mimic the pathophysiological conditions associated
11 with a health effect. These studies have identified a multitude of factors that could
12 potentially contribute to whether a population is at increased risk for O₃-related health
13 effects.

14 The populations identified in Chapter 8 that were examined for their potential for
15 increased risk of O₃-related health effects are listed in [Table 8-5](#) and are classified as
16 providing adequate, suggestive, inadequate, or no evidence of being an at-risk factor. The
17 factors that have adequate evidence to be classified as an at-risk factor for O₃-related
18 health effects are individuals with asthma, younger and older age groups, individuals with
19 reduced intake of certain nutrients (i.e., vitamins C and E), and outdoor workers, based
20 on consistency in findings across studies and evidence of coherence in results from
21 different scientific disciplines. Asthma as a factor affecting risk was supported by
22 controlled human exposure and toxicological studies, as well as some evidence from
23 epidemiologic studies. Generally, studies comparing age groups also reported greater
24 associations for respiratory hospital admissions and ED visits among children than for
25 adults. Biological plausibility for this increased risk is supported by toxicological and
26 controlled human exposure studies. Also, children have higher exposure and dose due to
27 increased time spent outdoors and ventilation rate, and childrens' respiratory systems are
28 also still undergrowing lung growth. Most studies comparing age groups reported greater
29 effects of short-term O₃ exposure on mortality among older adults, although studies of
30 other health outcomes had inconsistent findings regarding whether older adults were at
31 increased risk. Multiple epidemiologic, controlled human exposure, and toxicological
32 studies reported that diets lower in vitamins E and C are associated with increased risk of

1 O₃-related health effects. Previous studies have shown that increased exposure to O₃ due
2 to outdoor work leads to increased risk of O₃-related health effects and it is clear that
3 outdoor workers have higher exposures, and possibly greater internal doses, of O₃, which
4 may lead to increased risk of O₃-related health effects.

5 Other potential factors [genetic variants (such as those in *GSTM1*, *HMOX-1*, *NQO1*, and
6 *TNF-α*), obesity, sex, and SES] provided some suggestive evidence of increased risk, but
7 further investigation is needed. Similarly, many factors had inadequate evidence to
8 determine if they increased the risk of O₃-related health effects, including
9 influenza/infection, COPD, CVD, diabetes, hyperthyroidism, smoking, race/ethnicity,
10 and air conditioning use.

2.5.4.2 Exposure Metrics in Epidemiologic Studies

11 Some epidemiologic studies have conducted analyses between O₃ concentration and
12 health effects (i.e., mortality, respiratory or cardiovascular) using various exposure
13 metrics (i.e., 1-h max, 8-h max, and 24-h avg). No studies of long-term exposure
14 (i.e., months to years) to O₃ have compared the use of different exposure metrics on risk
15 estimation.

16 Among time-series studies, the limited evidence suggests comparable risk estimates
17 across exposure metrics with some evidence for smaller O₃ risk estimates when using a
18 24-hour average exposure metric. Several panel studies examined whether associations of
19 lung function and respiratory symptoms varied depending on the O₃ exposure metric
20 used. Although differences in effect estimates across exposure metrics were found within
21 some studies, collectively, there was no indication that the consistency or magnitude of
22 the observed association was stronger for a particular O₃ exposure metric. Comparisons
23 of lung function decrements among O₃ exposure metrics were similarly inconsistent in
24 populations without increased outdoor exposures. It is important to note in these studies,
25 the degree of exposure measurement error associated with use of central site ambient O₃
26 concentrations may vary among O₃ averaging times, depending on time spent outdoors.
27 Among studies that examined associations of multiple respiratory symptoms in children
28 with multiple O₃ exposure metrics, most did not find higher odds ratios for any particular
29 exposure metric. Overall, the evidence from time-series and panel epidemiologic studies
30 does not indicate that one exposure metric is more consistently or strongly associated
31 with mortality or respiratory-related health effects.

2.5.4.3 Lag Structure in Epidemiologic Studies

1 Epidemiologic studies have attempted to identify the time-frame in which exposure to O₃
2 can impart a health effect. The time period between O₃ exposure and health effects can
3 potentially be influenced by a multitude of factors, such as age or existence of
4 pre-existing diseases. Different lag times have been evaluated for specific health
5 outcomes.

6 The epidemiologic evidence evaluated in the 2006 O₃ AQCD indicated that one of the
7 remaining uncertainties in characterizing the O₃-mortality relationship was identifying
8 the appropriate lag structure (e.g., single-day lags versus distributed lag model). An
9 examination of lag times used in the epidemiologic studies evaluated in this assessment
10 can provide further insight on the characterization of the relationship between O₃
11 exposure and morbidity and mortality outcomes from epidemiologic studies.

12 The majority of epidemiologic studies that focused on the association between short-term
13 O₃ exposure and mortality (i.e., all-cause, respiratory and cardiovascular) examined the
14 average of multiday lags with some studies examining single-day lags. Across a range of
15 multiday lags (i.e., average of 0-1 to 0-6 days), the studies evaluated consistently
16 demonstrate that the O₃ effects on mortality occur within a few days of exposure
17 ([Figure 6-28](#)).

18 Epidemiologic studies of lung function, respiratory symptoms, and biological markers of
19 airway inflammation and oxidative stress examined associations with single-day ambient
20 O₃ concentrations (using various averaging times) lagged from 0 to 7 days as well as
21 concentrations averaged over 2 to 19 days. Lags of 0 and 1 day ambient O₃
22 concentrations were associated with decreases in lung function and increases in
23 respiratory symptoms, airway inflammation, and oxidative stress. Additionally, several
24 studies found that multiday averages of O₃ concentration were associated with these
25 endpoints, indicating that not only single day, but exposures accumulated over several
26 days led to a respiratory health effect. In studies of respiratory hospital admissions and
27 ED visits, investigators either examined the lag structure of associations by including
28 both single-day and the average of multiday lags, or selecting lags a priori. The collective
29 evidence indicates a rather immediate response within the first few days of O₃ exposure
30 (i.e., for lags days averaged at 0-1, 0-2, and 0-3 days) for hospital admissions and ED
31 visits for all respiratory outcomes, asthma, and chronic obstructive pulmonary disease in
32 all-year and seasonal analyses.

2.5.4.4 Ozone Concentration-Response Relationship

1 An important consideration in characterizing the O₃-morbidity and mortality association
2 is whether the concentration-response (C-R) relationship is linear across the full
3 concentration range that is encountered or if there are concentration ranges where there
4 are departures from linearity (i.e., nonlinearity). In this ISA studies have been identified
5 that attempt to characterize the shape of the O₃ C-R curve along with possible O₃
6 “thresholds” (i.e., O₃ concentrations which must be exceeded in order to elicit an
7 observable health response). The controlled human exposure and epidemiologic studies
8 that examined the shape of the C-R curve and the potential presence of a threshold have
9 indicated a generally linear C-R function with no indication of a threshold in analyses
10 that have examined 8-h max and 24-h avg O₃ concentrations. However, there is less
11 certainty in the shape of the C-R curve at the lower end of the distribution of O₃
12 concentrations due to the low density of data in this range.

13 Controlled human exposure studies have provided strong and quantifiable C-R data on
14 the human health effects of O₃. The magnitude of respiratory effects in these studies is
15 generally a function of O₃ exposure, i.e., the product of concentration (C), minute
16 ventilation (\dot{V}_E), and exposure duration. Several studies provide evidence for a smooth
17 C-R curve without indication of a threshold in young healthy adults exposed during
18 moderate exercise for 6.6 hours to O₃ concentrations between 40 and 120 ppb
19 ([Figure 6-1](#)). It is difficult to characterize the C-R relationship below 40 ppb due to
20 uncertainty associated with the sparse data at these lower concentrations.

21 Although relatively few epidemiologic studies have examined the O₃-health effects C-R
22 relationship, the C-R relationship has been examined across multiple health endpoints
23 and exposure durations. Some studies of populations engaged in outdoor activity found
24 that associations between O₃ and lung function decrements persisted at lower O₃
25 concentrations with some studies showing larger negative associations in analyses limited
26 to lower O₃ concentrations (e.g., 60-80 ppb; [Table 6-6](#)) and shorter exposure durations
27 (i.e., in the range of 30 minutes to less than 8 hours; [Table 6-6](#)). A study examining the
28 C-R relationship between short-term O₃ exposure and pediatric asthma ED visits found
29 no evidence of a threshold with a linear relationship evident down to 8-h max O₃
30 concentrations as low as 30 ppb ([Figure 6-17](#)). In an additional study, authors used a
31 smooth function while also accounting for the potential confounding effects of PM_{2.5}, to
32 examine whether the shape of the C-R curve for short-term exposure to O₃ and asthma
33 hospital admissions is linear. When comparing the curve to a linear fit, the authors found
34 that the linear fit is a reasonable approximation of the C-R relationship between O₃ and
35 asthma hospital admissions in the mid-range of the data though it can be seen that there is

1 greater uncertainty at the lower end of the distribution of ambient O₃ concentrations,
2 generally below 20 ppb ([Figure 6-15](#)) due to sparse data at these lower concentrations.

3 Several recent studies applied a variety of statistical approaches to examine the shape of
4 the O₃-mortality C-R relationship and existence of a threshold (Section [6.6.2.4](#)). These
5 studies suggest that the shape of the O₃-mortality C-R curve is linear across the range of
6 O₃ concentrations though uncertainty in the relationship increases at the lower end of the
7 distribution ([Figure 6-35](#)). Generally, the epidemiologic studies that examined the
8 O₃-mortality C-R relationship do not provide evidence for the existence of a threshold
9 within the range of 24-h average (24-h avg) O₃ concentrations most commonly observed
10 in the U.S. during the O₃ season (i.e., above 20 ppb). It should be noted that the
11 evaluation of the C-R relationship for short-term exposure to O₃ and mortality is difficult
12 due to the evidence from multicity studies indicating highly heterogeneous O₃-mortality
13 associations across regions of the U.S. In addition, there are numerous issues that may
14 influence the shape of the O₃-mortality C-R relationship that need to be taken into
15 consideration including: multiday effects (distributed lags), and potential adaptation and
16 mortality displacement (i.e., hastening of death by a short period). Additionally, given the
17 effect modifiers identified in mortality analyses that are also expected to vary regionally
18 (e.g., temperature, air conditioning prevalence), a national or combined analysis may not
19 be appropriate to identify whether a threshold exists in the O₃-mortality C-R relationship.

20 In addition, the C-R relationship of long-term exposure to O₃ and birth outcomes has
21 been evaluated. Evidence from the southern California Children's Health Study identified
22 a C-R relationship of birth weight with 24-h avg O₃ concentrations averaged over the
23 entire pregnancy that was clearest above the 30 ppb level ([Figure 7-4](#)).

24 Generally, both short- and long-term exposure studies indicate a linear, no threshold C-R
25 relationship when examining the association between O₃ exposure and multiple health
26 effects across the range of 8-h max and 24-h avg O₃ concentrations most commonly
27 observed in the U.S. during the O₃ season (i.e., greater than 20 ppb). However, evidence
28 from studies of respiratory health effects and mortality indicates less certainty in the
29 shape of the C-R curve at the lower end of the distribution of O₃ data, which corresponds
30 to 8-h max and 24-h avg O₃ concentrations generally below 20 ppb.

2.5.4.5 Regional Heterogeneity in Risk Estimates

31 Multicity epidemiologic studies that have examined the relationship between short-term
32 O₃ exposures and mortality have provided evidence of city-to-city and regional
33 heterogeneity in O₃-mortality risk estimates. A possible explanation for this heterogeneity
34 may be differences in community characteristics (individual- or community-level) across

1 cities that could modify the O₃ effect. Another possible explanation for the observed
2 heterogeneity could be effect modification by concentrations of other air pollutants or
3 interactions with temperature or other meteorological factors that vary regionally in the
4 U.S.

5 An examination of community characteristics measured at the individual level that may
6 contribute to the observed heterogeneity in O₃-mortality risk estimates indicates increased
7 risk in older adults (i.e., ≥ 65 years of age), women, African American individuals,
8 individuals with pre-existing diseases/conditions (e.g., diabetes, atrial fibrillation), and
9 lower SES. Furthermore, studies have examined community characteristics measured at
10 the community level and found that higher O₃-mortality risk estimates were associated
11 with higher: percent unemployment, fraction of the population Black/African-American,
12 percent of the population that take public transportation to work; and with lower:
13 temperatures and percent of households with central air conditioning. There is also
14 evidence of greater effects in cities with lower mean O₃ concentrations. Additionally,
15 there is evidence of increased risk of O₃-related mortality as percentage unemployed
16 increases and a reduction in O₃-related mortality as mean temperature increased (i.e., a
17 surrogate for air conditioning rate) in the U.S. The lack of a consistent reduction in
18 O₃-risk estimates in cities with a higher percentage of central air conditioning across
19 health outcomes complicates the interpretation of the potential modifying effects of air
20 conditioning use.

21 Overall, the epidemiologic studies that have examined the city-to-city and regional
22 heterogeneity observed in multicity studies have identified a variety of factors that may
23 modify the O₃-mortality or -respiratory hospital admission relationship. Some studies
24 have also examined the correlation with other air pollutants or the potential interactive
25 effects between O₃ and temperature to explain city-to-city heterogeneity in O₃-mortality
26 risk estimates. This includes evidence that O₃-mortality risk estimates in the U.S. varied
27 by mean SO₂ concentrations, the ratio between mean NO₂/PM₁₀ concentrations, and
28 temperatures. However, studies have not consistently identified specific community
29 characteristics that explain the observed heterogeneity.

2.6 Integration of Effects on Vegetation and Ecosystems

30 Chapter 9 presents the most policy-relevant information related to this review of the
31 NAAQS for the welfare effects of O₃ on vegetation and ecosystems. This section
32 integrates the key findings from the disciplines evaluated in this assessment of the O₃
33 scientific literature, which includes plant physiology, whole plant biology, ecosystems,
34 and exposure-response.

1 Overall, exposure to O₃ is causally related or likely to be causally related to effects
2 observed on vegetation and ecosystems. These effects are observed across the entire
3 continuum of biological organization; from the cellular and subcellular level to the whole
4 plant level, and up to ecosystem-level processes. Furthermore, there is evidence that the
5 effects observed across this continuum are related to one another; effects of O₃ at lower
6 levels of organization, such as the leaf of an individual plant, can result in effects at
7 higher levels. Ozone enters leaves through stomata, and can alter stomatal conductance
8 and disrupt CO₂ fixation (Section 9.3). These effects can change rates of leaf gas
9 exchange, growth and reproduction at the individual plant level and result in changes in
10 ecosystems, such as productivity, C storage, water cycling, nutrient cycling, and
11 community composition (Section 9.4). [Figure 2-3](#) is a simplified illustrative diagram of
12 the major pathway through which O₃ enters leaves and the major endpoints O₃ may affect
13 in vegetation and ecosystems.

14 The framework for causal determinations (see Preamble) has been applied to the body of
15 scientific evidence to examine effects attributed to O₃ exposure ([Table 2-3](#)). The
16 summary below provides brief integrated summaries of the evidence that supports the
17 causal determinations. The detailed discussion of the underlying evidence used to
18 formulate each causal determination can be found in Chapter 9. This summary ends with
19 a short discussion of policy relevant considerations.

2.6.1 Visible Foliar Injury

20 Visible foliar injury resulting from exposure to O₃ has been well characterized and
21 documented over several decades of research on many tree, shrub, herbaceous, and crop
22 species ([U.S. EPA, 2006b, 1996b, 1984, 1978a](#)) (Section 9.4.2). Ozone-induced visible
23 foliar injury symptoms on certain bioindicator plant species are considered diagnostic as
24 they have been verified experimentally in exposure-response studies, using exposure
25 methodologies such as continuous stirred tank reactors (CSTRs), open-top chambers
26 (OTCs), and free-air fumigation. Experimental evidence has clearly established a
27 consistent association of visible injury with O₃ exposure, with greater exposure often
28 resulting in greater and more prevalent injury. Since publication of the 2006 O₃ AQCD,
29 the results of several multiple-year field surveys of O₃-induced visible foliar injury at
30 National Wildlife Refuges in Maine, Michigan, New Jersey, and South Carolina have
31 been published. New sensitive species showing visible foliar injury continue to be
32 identified from field surveys and verified in controlled exposure studies.

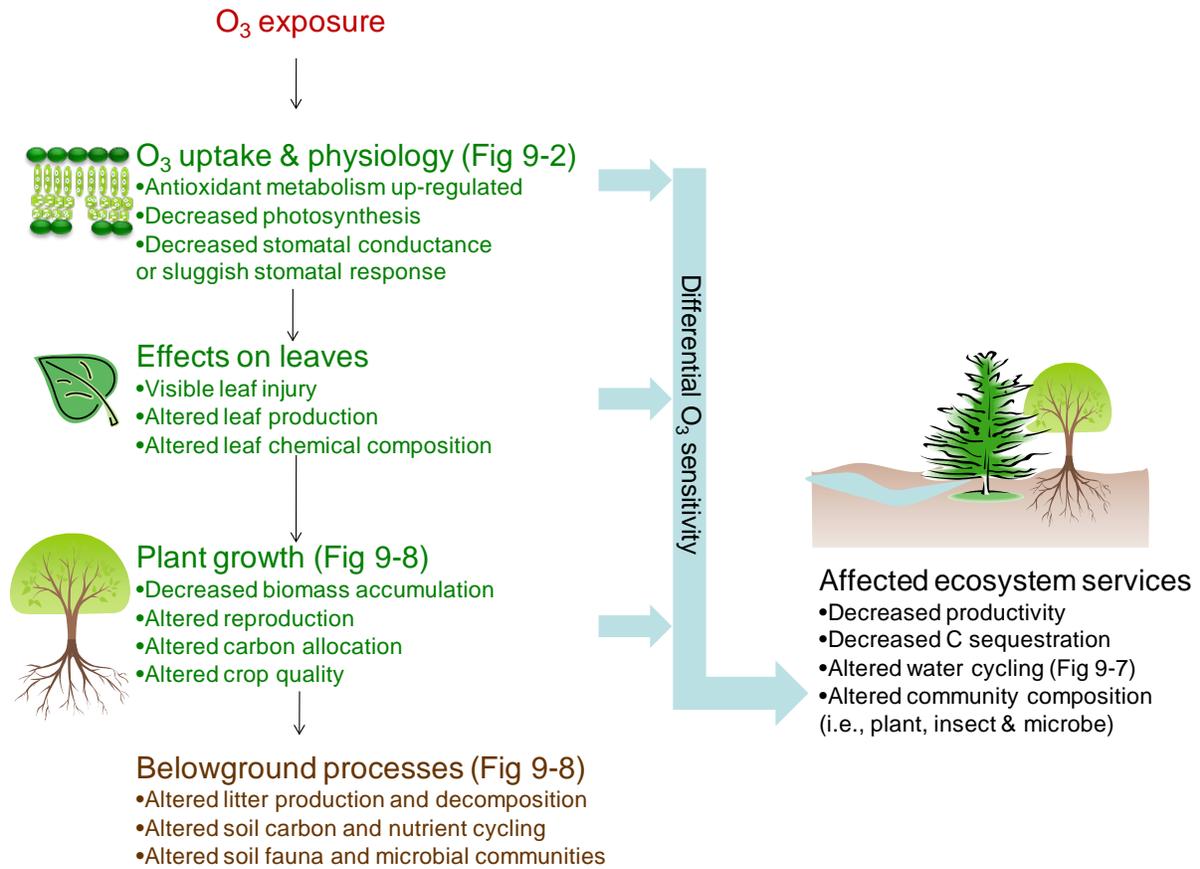


Figure 2-3 An illustrative diagram of the major pathway through which ozone enters leaves and the major endpoints that ozone may affect in plants and ecosystems.

Table 2-3 Summary of ozone causal determinations for vegetation and ecosystem effects.

| Vegetation and Ecosystem Effects | Conclusions from 2006 O₃ AQCD | Conclusions from 2011 2nd Draft ISA |
|--|--|--|
| Visible Foliar Injury Effects on Vegetation | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause impaired aesthetic quality of many native plants and trees by increasing foliar injury. | Causal Relationship |
| Reduced Vegetation Growth | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause decreased growth and biomass accumulation in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees. | Causal Relationship |
| Reduced Productivity in Terrestrial Ecosystems | There is evidence that O ₃ is an important stressor of ecosystems and that the effects of O ₃ on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity. | Causal Relationship |
| Reduced Carbon (C) Sequestration in Terrestrial Ecosystems | Limited studies from previous review | Likely to be a Causal Relationship |
| Reduced Yield and Quality of Agricultural Crops | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause decreased yield and/or nutritive quality in a large number of agronomic and forage crops. | Causal Relationship |
| Alteration of Terrestrial Ecosystem Water Cycling | Ecosystem water quantity may be affected by O ₃ exposure at the landscape level. | Likely to be a Causal Relationship |
| Alteration of Below-ground Biogeochemical Cycles | Ozone-sensitive species have well known responses to O ₃ exposure, including altered C allocation to below-ground tissues, and altered rates of leaf and root production, turnover, and decomposition. These shifts can affect overall C and N loss from the ecosystem in terms of respired C, and leached aqueous dissolved organic and inorganic C and N. | Causal Relationship |
| Alteration of Terrestrial Community Composition | Ozone may be affecting above- and below-ground community composition through impacts on both growth and reproduction. Significant changes in plant community composition resulting directly from O ₃ exposure have been demonstrated. | Likely to be a Causal Relationship |

1 The use of biological indicators in field surveys to detect phytotoxic levels of O₃ is a
2 longstanding and effective methodology. The USDA Forest Service through the Forest
3 Health Monitoring (FHM) Program (1990-2001) and currently the Forest Inventory and
4 Analysis (FIA) Program has been collecting data regarding the incidence and severity of
5 visible foliar injury on a variety of O₃ sensitive plant species throughout the U.S. The
6 network has provided evidence that O₃ concentrations were high enough to induce visible
7 symptoms on sensitive vegetation. From repeated observations and measurements made
8 over a number of years, specific geographical patterns of visible O₃ injury symptoms can
9 be identified. In addition, a study assessed the risk of O₃-induced visible foliar injury on
10 bioindicator plants in 244 national parks in support of the National Park Service's Vital
11 Signs Monitoring Network. The results of the study demonstrated that the estimated risk
12 of visible foliar injury was high in 65 parks (27%), moderate in 46 parks (19%), and low
13 in 131 parks (54%). Some of the well-known parks with a high risk of O₃-induced visible
14 foliar injury include Gettysburg, Valley Forge, Delaware Water Gap, Cape Cod, Fire

1 Island, Antietam, Harpers Ferry, Manassas, Wolf Trap Farm Park, Mammoth Cave,
2 Shiloh, Sleeping Bear Dunes, Great Smoky Mountains, Joshua Tree, Sequoia and Kings
3 Canyon, and Yosemite. Overall, evidence is sufficient to conclude that there **is a causal**
4 **relationship between ambient O₃ exposure and the occurrence of O₃-induced**
5 **visible foliar injury on sensitive vegetation across the U.S.**

2.6.2 Growth, Productivity, Carbon Storage and Agriculture

6 Ambient O₃ concentrations have long been known to cause decreases in photosynthetic
7 rates and plant growth. The O₃-induced damages at the plant scale may translate to
8 damages at the stand, then ecosystem scales, and cause changes in productivity and C
9 storage. The effects of O₃ exposure on photosynthesis, growth, biomass allocation,
10 ecosystem production, and ecosystem C sequestration were reviewed for the natural
11 ecosystems, and crop productivity and crop quality were reviewed for the agricultural
12 ecosystems.

2.6.2.1 Natural Ecosystems

13 The previous O₃ AQCDs concluded that there is strong and consistent evidence that
14 ambient concentrations of O₃ decrease plant photosynthesis and growth in numerous
15 plant species across the U.S. Studies published since the last review continue to support
16 that conclusion (Section [9.4.3.1](#)). Recent studies, based on the Aspen free-air carbon-
17 dioxide/ozone enrichment (FACE) experiment, found that O₃ caused reductions in total
18 biomass relative to the control in aspen, paper birch, and sugar maple communities
19 during the first seven years of stand development. Overall, the studies at the Aspen FACE
20 experiment were consistent with the open-top chamber (OTC) studies that were the
21 foundation of previous O₃ NAAQS reviews. These results strengthen the understanding
22 of O₃ effects on forests and demonstrate the relevance of the knowledge gained from
23 trees grown in OTC studies.

24 A set of meta-analyses assessed the effects of O₃ on plant photosynthesis and growth
25 across different species and fumigation methods (such as OTC and FACE). Those studies
26 reported that current O₃ concentrations in the northern hemisphere are decreasing
27 photosynthesis (~11%) across tree species, and the decreases in photosynthesis are
28 consistent with cumulative uptake of O₃ into the leaf. The current ambient O₃
29 concentrations (~40 ppb averaged across all hours of exposure) decreased annual total
30 biomass growth of forest species by an average of 7%, with potentially greater decreases
31 (11-17%) with elevated O₃ exposures (Section [9.4.3.1](#)). The meta-analyses further

1 confirmed that reduction of plant photosynthesis and growth under O₃ exposure are
2 coherent across numerous species and various experimental techniques.

3 Studies during recent decades have also demonstrated O₃ alters biomass allocation and
4 plant reproduction (Section [9.4.3](#)). Recent meta-analyses have generally indicated that O₃
5 reduced C allocated to roots. Several recent studies published since the 2006 O₃ AQCD
6 further demonstrate that O₃ altered reproductive processes, such as timing of flowering,
7 number of flowers, fruits and seeds, in herbaceous and woody plant species. However, a
8 knowledge gap still exists pertaining to the exact mechanism of the responses of
9 reproductive processes to O₃ exposure (Section [9.4.3.3](#)).

10 Studies at the leaf and plant scales show that O₃ decreased photosynthesis and plant
11 growth, providing coherence and biological plausibility for the reported decreases in
12 ecosystem productivity. During the previous NAAQS reviews, there were very few
13 studies that investigated the effect of O₃ exposure on ecosystem productivity and
14 C sequestration. Recent studies from long-term FACE experiments and ecosystem
15 models provided evidence of the association of O₃ exposure and reduced productivity at
16 the ecosystem scale. Elevated O₃ reduced stand biomass at Aspen FACE after 7 years of
17 O₃ exposure, and annual volume growth at the Kranzberg Forest in Germany. Results
18 across different ecosystem models were consistent with the FACE experimental
19 evidence, which showed that O₃ reduced ecosystem productivity (Section [9.4.3.4](#)). In
20 addition to primary productivity, other indicators such as net ecosystem productivity
21 (NEP), net ecosystem CO₂ exchange (NEE) and C sequestration were often assessed by
22 model studies. Model simulations consistently found that O₃ exposure caused negative
23 impacts on these indicators (Section [9.4.3.4](#), [Table 9-3](#)), but the severity of these impacts
24 was influenced by multiple interactions of biological and environmental factors. The
25 suppression of ecosystem C sinks results in more CO₂ accumulation in the atmosphere. A
26 recent study suggested that the indirect radiative forcing caused by O₃ exposure through
27 lowering the ecosystem C sink could have an even greater impact on global warming than
28 the direct radiative forcing of O₃.

29 Although O₃ generally causes negative effects on ecosystem productivity, the magnitude
30 of the response varies among plant communities (Section [9.4.3.4](#)). For example, O₃ had
31 little impact on white fir, but greatly reduced growth of ponderosa pine in southern
32 California. Ozone decreased net primary production (NPP) of most forest types in the
33 Mid-Atlantic region, but had small impacts on spruce-fir forest. Ozone could also affect
34 regional C budgets through interacting with multiple factors, such as N deposition,
35 elevated CO₂ and land use history. Model simulations suggested that O₃ partially offset
36 the growth stimulation caused by elevated CO₂ and N deposition in both Northeast- and
37 Mid-Atlantic-region forest ecosystems of the U.S.

1 Overall, evidence is sufficient to conclude that there **is a causal relationship between**
2 **ambient O₃ exposure and reduced native plant growth and productivity**, and a **likely**
3 **causal relationship between O₃ exposure and reduced carbon sequestration in**
4 **terrestrial ecosystems.**

2.6.2.2 Agricultural Crops

5 The detrimental effect of O₃ on crop production has been recognized since the 1960's and
6 a large body of research has subsequently stemmed from those initial findings. Previous
7 O₃ AQCDs have extensively reviewed this body of literature. Current O₃ concentrations
8 across the U.S. are high enough to cause yield loss for a variety of agricultural crops
9 including, but not limited to, soybean, wheat, potato, watermelon, beans, turnip, onion,
10 lettuce, and tomato (Section [9.4.4.1](#)). Continued increases in O₃ concentration may
11 further decrease yield in these sensitive crops. Despite the well-documented yield losses
12 due to increasing O₃ concentration, there is still a knowledge gap pertaining to the exact
13 mechanism of O₃-induced yield loss. Research has linked increasing O₃ concentration to
14 decreased photosynthetic rates and accelerated senescence, which are related to yield.

15 In addition, recent research has highlighted the effects of O₃ on crop quality. Increasing
16 O₃ concentration decreases nutritive quality of grasses, decreases macro- and micro-
17 nutrient concentrations in fruits and vegetable crops, and decreases cotton fiber quality.
18 These areas of research require further investigation to determine the mechanism and
19 dose-responses (Section [9.4.4.2](#)).

20 During the previous NAAQS reviews, there were very few studies that estimated O₃
21 impacts on crop yields at large geographical scales (i.e., regional, national or global).
22 Recent modeling studies found that O₃ generally reduced crop yield, but the impacts
23 varied across regions and crop species (Section [9.4.4.1](#)). For example, the largest
24 O₃-induced crop yield losses occurred in high-production areas exposed to high O₃
25 concentrations, such as the Midwest and the Mississippi Valley regions of the U.S.
26 Among crop species, the estimated yield loss for wheat and soybean were higher than
27 rice and maize. Satellite and ground-based O₃ measurements have been used to assess
28 yield loss caused by O₃ over the continuous tri-state area of Illinois, Iowa, and
29 Wisconsin. The results showed that O₃ concentrations reduced soybean yield, which
30 correlates well with the previous results from FACE- and OTC-type experiments
31 (Section [9.4.4.1](#)).

32 Evidence is sufficient to conclude that there **is a causal relationship between O₃**
33 **exposure and reduced yield and quality of agricultural crops.**

2.6.3 Water Cycling

1 Ozone can affect water use in plants and ecosystems through several mechanisms
2 including damage to stomatal functioning and loss of leaf area. Section [9.3.6](#) reviewed
3 possible mechanisms for O₃ exposure effects on stomatal functioning. Regardless of the
4 mechanism, O₃ exposure has been shown to alter stomatal performance, which may affect
5 plant and stand transpiration and therefore possibly affecting hydrological cycling.

6 Although the evidence was from a limited number of field and modeling studies, these
7 findings showed an association of O₃ exposure and the alteration of water use and cycling
8 in vegetation and ecosystems (Section [9.4.5](#)). There is not a clear consensus on the nature
9 of leaf-level stomatal conductance response to O₃ exposure. When measured at steady-
10 state high light conditions, leaf-level stomatal conductance is often found to be reduced
11 when exposed to O₃. However, measurements of stomatal conductance under dynamic
12 light and vapor pressure deficit conditions indicate sluggish responses under elevated O₃
13 exposure which could potentially lead to increased water loss from vegetation. In
14 situations where stomata fail to close under low light or water stressed conditions water
15 loss may be greater over time. In other situations it is possible that sluggish stomata may
16 fail to completely open in response to environmental stimuli and result in decreased water
17 loss. Field studies suggested that peak hourly O₃ exposure increased the rate of water loss
18 from several tree species, and led to a reduction in the late-season modeled stream flow in
19 three forested watersheds in eastern Tennessee. Sluggish stomatal responses during O₃
20 exposure was suggested as a possible mechanism for increased water loss during peak O₃
21 exposure. Currently, the O₃-induced reduction in stomatal aperture is the biological
22 assumption for most process-based models. Therefore, results of those models normally
23 found that O₃ reduced water loss. For example, one study found that O₃ damage and
24 N limitation together reduced evapotranspiration and increase runoff.

25 Although the direction of the response differed among studies, the evidence is sufficient
26 to conclude that there **is likely to be a causal relationship between O₃ exposure and**
27 **the alteration of ecosystem water cycling.**

2.6.4 Below-Ground Processes

28 Below-ground processes are tightly linked with aboveground processes. The responses of
29 aboveground process to O₃ exposure, such as reduced photosynthetic rates, increased
30 metabolic cost, and reduced root C allocation, have provided biologically plausible
31 mechanisms for the alteration of below-ground processes. Since the 2006 O₃ AQCD,
32 more evidence has shown that although the responses are often species specific, O₃

1 altered the quality and quantity of C input to soil, microbial community composition, and
2 C and nutrient cycling.

3 Results from Aspen FACE and other experimental studies consistently found that O₃
4 reduced litter production and altered C chemistry, such as soluble sugars, soluble
5 phenolics, condensed tannins, lignin, and macro/micro nutrient concentration in litter
6 (Section [9.4.6.1](#)). Under elevated O₃, the changes in substrate quality and quantity could
7 alter microbial metabolism, and therefore soil C and nutrient cycling. Several studies
8 indicated that O₃ generally suppressed soil enzyme activities (Section [9.4.6.2](#)). However,
9 the impact of O₃ on litter decomposition was inconsistent and varied among species,
10 sites, and exposure length. Similarly, O₃ had inconsistent impacts on dynamics of micro
11 and macro nutrients (Section [9.4.6.4](#)).

12 Studies from the Aspen FACE experiment suggested that the response of below-ground
13 C cycle to O₃ exposure, such as litter decomposition, soil respiration, and soil C content,
14 changed over time. For example, in the early part of the experiment (1998-2003), O₃ had
15 no impact on soil respiration but reduced the formation rates of total soil C under
16 elevated CO₂. However, after 10 to 11 years of exposure, O₃ was found to increase soil
17 respiration but have no substantial impact on soil C formation under elevated CO₂
18 (Section [9.4.6.3](#)).

19 The evidence is sufficient to infer that there **is a causal relationship between O₃**
20 **exposure and the alteration of below-ground biogeochemical cycles.**

2.6.5 Community Composition

21 In the 2006 O₃ AQCD, the impact of O₃ exposure on species competition and community
22 composition was assessed. Ozone was found to be one of the dominant factors causing a
23 decline in ponderosa and Jeffrey pine in the San Bernardino Mountains in southern
24 California. Ozone exposure also tended to shift the grass-legume mixtures in favor of
25 grass species. Since the 2006 O₃ AQCD, more evidence has shown that O₃ exposure
26 changed the competitive interactions and led to loss of O₃ sensitive species or genotypes.
27 Studies found that the severity of O₃ damage on growth, reproduction and foliar injury
28 varied among species (Section [9.4.3](#)), which provided the biological plausibility for the
29 alteration of community composition. Additionally, research since the last review has
30 shown that O₃ can alter community composition and diversity of soil microbial
31 communities.

32 The decline of conifer forests under O₃ exposure was continually observed in several
33 regions. Ozone damage was believed to be an important causal factor in the dramatic

1 decline of sacred fir in the valley of Mexico, as well as cembran pine in southern France
2 and the Carpathian Mountains, although several factors, such as drought, insect outbreak
3 and forest management, may also contribute to or even be the dominant factors causing
4 the mortality of the conifer trees. Results from the Aspen FACE site indicated that O₃
5 could alter community composition of broadleaf forests as well. At the Aspen FACE site,
6 O₃ reduced growth and increased mortality of a sensitive aspen clone, while the O₃
7 tolerant clone emerged as the dominant clone in the pure aspen community. In the mixed
8 aspen-birch and aspen-maple communities, O₃ reduced the competitive capacity of aspen
9 compared to birch and maple (Section [9.4.7.1](#)).

10 The tendency for O₃-exposure to shift the biomass of grass-legume mixtures in favor of
11 grass species was reported in the 2006 O₃ AQCD and has been generally confirmed by
12 recent studies. However, in a high elevation mature/species-rich grass-legume pasture, O₃
13 fumigation showed no substantial impact on community composition (Section [9.4.7.2](#)).

14 Ozone exposure not only altered community composition of plant species, but also
15 microorganisms. The shift in community composition of bacteria and fungi has been
16 observed in both natural and agricultural ecosystems, although no general patterns could
17 be identified (Section [9.4.7.3](#)).

18 The evidence is sufficient to conclude that there **is likely to be a causal relationship**
19 **between O₃ exposure and the alteration of community composition of some**
20 **ecosystems.**

2.6.6 Policy Relevant Considerations

2.6.6.1 Air Quality Indices

21 Exposure indices are metrics that quantify exposure as it relates to measured plant injury
22 (e.g., reduced growth). They are summary measures of monitored ambient O₃
23 concentrations over time intended to provide a consistent metric for reviewing and
24 comparing exposure-response effects obtained from various studies. No recent
25 information is available since 2006 that alters the basic conclusions put forth in the 2006
26 and 1996 O₃ AQCDs. These AQCDs focused on the research used to develop various
27 exposure indices to help quantify effects on growth and yield in crops, perennials, and
28 trees (primarily seedlings). The performance of indices was compared through regression
29 analyses of earlier studies designed to support the estimation of predictive O₃ exposure-
30 response models for growth and/or yield of crops and tree (seedling) species.

1 Another approach for improving risk assessment of vegetation response to ambient O₃ is
2 based on determining the O₃ concentration from the atmosphere that enters the leaf
3 (i.e., flux or deposition). Interest has been increasing in recent years, particularly in
4 Europe, in using mathematically tractable flux models for O₃ assessments at the regional,
5 national, and European scale. While some efforts have been made in the U.S. to calculate
6 O₃ flux into leaves and canopies, little information has been published relating these
7 fluxes to effects on vegetation. There is also concern that not all O₃ stomatal uptake
8 results in a yield reduction, which depends to some degree on the amount of internal
9 detoxification occurring with each particular species. Species having high detoxification
10 capacity may show little relationship between O₃ stomatal uptake and plant response. The
11 lack of data in the U.S. and the lack of understanding of detoxification processes have
12 made this technique less viable for vulnerability and risk assessments in the U.S.

13 The main conclusions from the 1996 and 2006 O₃ AQCDs regarding indices based on
14 ambient exposure remain valid. These key conclusions can be restated as follows:

- 15 ■ O₃ effects in plants are cumulative;
- 16 ■ higher O₃ concentrations appear to be more important than lower
17 concentrations in eliciting a response;
- 18 ■ plant sensitivity to O₃ varies with time of day and plant development stage;
19 and
- 20 ■ quantifying exposure with indices that cumulate hourly O₃ concentrations and
21 preferentially weight the higher concentrations improves the explanatory
22 power of exposure/response models for growth and yield, over using indices
23 based on mean and peak exposure values.

24 Various weighting functions have been used, including threshold-weighted
25 (e.g., SUM06) and continuous sigmoid-weighted (e.g., W126) functions. Based on
26 statistical goodness-of-fit tests, these cumulative, concentration-weighted indices could
27 not be differentiated from one another using data from previous exposure studies.
28 Additional statistical forms for O₃ exposure indices are summarized in Section [9.5](#) of this
29 ISA. The majority of studies published since the 2006 O₃ AQCD do not change earlier
30 conclusions, including the importance of peak concentrations, and the duration and
31 occurrence of O₃ exposures in altering plant growth and yield.

32 Given the current state of knowledge and the best available data, exposure indices that
33 cumulate and differentially weight the higher hourly average concentrations and also
34 include the mid-level values continue to offer the most defensible approach for use in
35 developing response functions and comparing studies, as well as for defining future
36 indices for vegetation protection.

2.6.6.2 Exposure-Response

1 None of the information on effects of O₃ on vegetation published since the 2006 O₃
2 AQCD has modified the assessment of quantitative exposure-response relationships that
3 was presented in that document ([U.S. EPA, 2006b](#)). This assessment updates the 2006
4 exposure-response models by computing them using the W126 metric, cumulated over
5 90 days. Almost all of the experimental research on the effects of O₃ on growth or yield
6 of plants published since 2006 used only two levels of exposure. In addition, hourly O₃
7 concentration data that would allow calculations of exposure using the W126 metric are
8 generally unavailable. However, two long-term experiments, one with a crop species
9 (soybean), one with a tree species (aspen), have produced data that are used in
10 Section [9.6](#) to validate the exposure-response models presented in the 2006 O₃ AQCD,
11 and the methodology used to derive them. EPA compared predictions from the models
12 presented in the 2006 O₃ AQCD, updated to use the 90 day 12hr W126 metric, with more
13 recent observations for yield of soybean and biomass growth of trembling aspen. The
14 models were parameterized using data from the National Crop Loss Assessment Network
15 (NCLAN) and EPA's National Health and Environmental Effects Research Laboratory –
16 Western Ecology Division (NHEERL-WED) projects, which were conducted in OTCs.
17 The more recent observations were from experiments using FACE technology, which is
18 intended to provide conditions closer to natural environments than OTC. Observations
19 from these new experiments were exceptionally close to predictions from the models.
20 The accuracy of model predictions for two widely different plant species, grown under
21 very different conditions, provides support for the validity of the models for crops and
22 trees developed using the same methodology and data for other species. However,
23 variability observed among species in the NCLAN and NHEERL-WED projects indicates
24 that the range of sensitivity between and among species is likely quite wide.

25 Results from several meta-analyses have provided approximate values for responses of
26 yield of soybean, wheat, rice and other crops under broad categories of exposure, relative
27 to charcoal-filtered air. Additional reports have summarized yield data for six crop
28 species under various broad comparative exposure categories, and reviewed 263 studies
29 that reported effects on tree biomass. However, these analyses have proved difficult to
30 compare with exposure-response models, especially given that exposure was not
31 expressed using a common metric (i.e., W126).

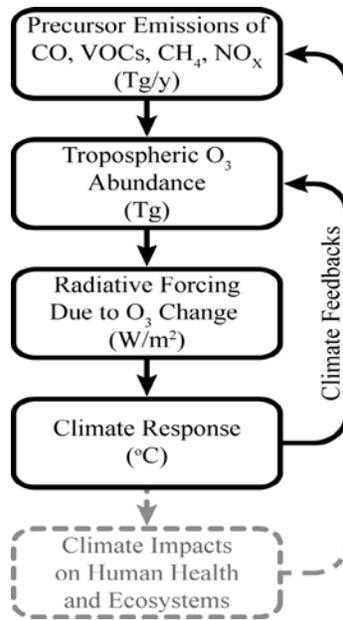
2.7 The Role of Tropospheric Ozone in Climate Change and UV-B Effects

1 Atmospheric O₃ plays an important role in the Earth's energy budget by interacting with
2 incoming solar radiation and outgoing infrared radiation. Tropospheric O₃ makes up only
3 a small portion of the total column of O₃, but it has important incremental effects on the
4 overall radiation budget. Chapter [10](#) assesses the specific role of tropospheric O₃ in the
5 earth's radiation budget and how perturbations in tropospheric O₃ might affect (1) climate
6 through its role as a greenhouse gas, and (2) health, ecology and welfare through its role
7 in shielding the earth's surface from solar ultraviolet (UV) radiation.

2.7.1 Tropospheric Ozone as a Greenhouse Gas

8 Ozone is an important greenhouse gas, and increases in its abundance in the troposphere
9 may contribute to climate change according to the 2007 climate assessment by the
10 Intergovernmental Panel on Climate Change (IPCC). Models calculate that the global
11 burden of tropospheric O₃ has doubled since the pre-industrial era, while observations
12 indicate that in some regions O₃ may have increased by factors as great as 4 or 5. These
13 increases are tied to the rise in emissions of O₃ precursors from human activity, mainly
14 fossil fuel consumption and agricultural processes.

15 [Figure 2-4](#) shows the main steps involved in the influence of tropospheric O₃ on climate.
16 Emissions of O₃ precursors including CO, VOCs, CH₄, and NO_x lead to production of
17 tropospheric O₃. A change in the abundance of tropospheric O₃ perturbs the radiative
18 balance of the atmosphere, an effect quantified by the radiative forcing (RF) metric. The
19 earth-atmosphere-ocean system responds to the forcing with a climate response, typically
20 expressed as a change in surface temperature. Finally, the climate response causes
21 downstream climate-related health and ecosystem impacts, such as redistribution of
22 diseases or ecosystem characteristics due to temperature changes. Feedbacks from both
23 the climate response and downstream impacts can, in turn, affect the abundance of
24 tropospheric O₃ and O₃ precursors through multiple feedback mechanisms as indicated in
25 [Figure 2-4](#). Direct feedbacks are discussed in Section [10.3.2.4](#) while downstream climate
26 impacts and their feedbacks are extremely complex and outside the scope of this
27 assessment.



Note: Units shown are those typical for each quantity illustrated. Feedbacks from both the climate response and climate impacts can, in turn, affect the abundance of tropospheric O₃ and O₃ precursors through multiple feedback mechanisms. Climate impacts are deemphasized in the figure since these downstream effects are extremely complex and outside the scope of this assessment.

Figure 2-4 Schematic illustrating the effects of tropospheric ozone on climate; including the relationship between precursor emissions, tropospheric ozone abundance, radiative forcing, climate response, and climate impacts. Tropospheric Ozone and UV-B related effects

1 The impact of the tropospheric O₃ change since pre-industrial times on climate has been
 2 estimated to be about 25-40% of the anthropogenic CO₂ impact and about 75% of the
 3 anthropogenic CH₄ impact according to the IPCC, ranking it third in importance among
 4 the greenhouse gases. There are large uncertainties in the RF estimate attributed to
 5 tropospheric O₃, making the impact of tropospheric O₃ on climate more uncertain than
 6 the impact of the long-lived greenhouse gases. Overall, the evidence supports **a causal**
 7 **relationship between changes in tropospheric O₃ concentrations and radiative**
 8 **forcing.**

9 RF does not take into account the climate feedbacks that could amplify or dampen the
 10 actual surface temperature response. Quantifying the change in surface temperature
 11 requires a complex climate simulation in which all important feedbacks and interactions
 12 are accounted for. As these processes are not well understood or easily modeled, the
 13 surface temperature response to a given RF is highly uncertain and can vary greatly
 14 among models and from region to region within the same model. In light of these
 15 uncertainties, the evidence indicates that there **is likely to be a causal relationship**
 16 **between changes in tropospheric O₃ concentrations and effects on climate.**

2.7.3 Tropospheric Ozone and UV-B Related Effects

1 UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to
2 break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on
3 living organisms and materials. Atmospheric O₃ plays a crucial role in reducing exposure
4 to solar UV radiation at the Earth's surface. Ozone in the stratosphere is responsible for
5 the majority of this shielding effect, as approximately 90% of total atmospheric O₃ is
6 located there over mid-latitudes. Ozone in the troposphere provides supplemental
7 shielding of radiation in the wavelength band from 280-315 nm, referred to as UV-B
8 radiation. UV-B radiation has important effects on human health and ecosystems, and is
9 associated with materials damage.

10 Human health effects associated with solar UV-B radiation exposure include erythema,
11 skin cancer, ocular damage, and immune system suppression. A potential human health
12 benefit of increased UV-B exposure involves the UV-induced production of vitamin D
13 which may help reduce the risk of metabolic bone disease, type I diabetes, mellitus, and
14 rheumatoid arthritis, and may provide beneficial immunomodulatory effects on multiple
15 sclerosis, insulin-dependent diabetes mellitus, and rheumatoid arthritis. Ecosystem and
16 materials damage effects associated with solar UV-B radiation exposure include
17 terrestrial and aquatic ecosystem impacts, alteration of biogeochemical cycles, and
18 degradation of man-made materials.

19 There is a lack of published studies that critically examine the incremental health or
20 welfare effects (adverse or beneficial) attributable specifically to changes in UV-B
21 exposure resulting from perturbations in tropospheric O₃ concentrations. The effects are
22 expected to be small and they cannot yet be critically assessed within reasonable
23 uncertainty. Overall, the evidence **is inadequate to determine if a causal relationship**
24 **exists between changes in tropospheric O₃ concentrations and effects on health**
25 **and welfare related to UV-B shielding.**

2.8 Summary of Causal Determinations for Health Effects and Welfare Effects

26 This chapter has provided an overview of the underlying evidence used in making the
27 causal determinations for the health and welfare effects of O₃. This review builds upon
28 the conclusions of the previous AQCDs for O₃.

29 The evaluation of the epidemiologic, toxicological, and controlled human exposure
30 studies published since the completion of the 2006 O₃ AQCD have provided additional
31 evidence for O₃-related health outcomes. [Table 2-4](#) provides an overview of the causal

1 determinations for all of the health outcomes evaluated. Causal determinations for O₃ and
 2 welfare effects are included in [Table 2-5](#), while causal determinations for climate change
 3 and UV-B effects are in [Table 2-6](#). Detailed discussions of the scientific evidence and
 4 rationale for these causal determinations are provided in subsequent chapters of this ISA.

Table 2-4 Summary of ozone causal determinations by exposure duration and health outcome.

| Health Outcome | Conclusions from 2006 O ₃ AQCD | Conclusions from 2012 3rd Draft ISA |
|---|--|---|
| Short-Term Exposure to O₃ | | |
| Respiratory effects | The overall evidence supports a causal relationship between acute ambient O ₃ exposures and increased respiratory morbidity outcomes. | Causal Relationship |
| Cardiovascular effects | The limited evidence is highly suggestive that O ₃ directly and/or indirectly contributes to cardiovascular-related morbidity, but much remains to be done to more fully substantiate the association. | Suggestive of a Causal Relationship |
| Central nervous system effects | Toxicological studies report that acute exposures to O ₃ are associated with alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration. | Suggestive of a Causal Relationship |
| Total Mortality | The evidence is highly suggestive that O ₃ directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality. | Likely to be a Causal Relationship |
| Long-term Exposure to O₃ | | |
| Respiratory effects | The current evidence is suggestive but inconclusive for respiratory health effects from long-term O ₃ exposure. | Likely to be a Causal Relationship |
| Cardiovascular Effects | No studies from previous review | Suggestive of a Causal Relationship |
| Reproductive and developmental effects | Limited evidence for a relationship between air pollution and birth-related health outcomes, including mortality, premature births, low birth weights, and birth defects, with little evidence being found for O ₃ effects. | Suggestive of a Causal Relationship |
| Central nervous system effects | Evidence regarding chronic exposure and neurobehavioral effects was not available. | Suggestive of a Causal Relationship |
| Cancer | Little evidence for a relationship between chronic O ₃ exposure and increased risk of lung cancer. | Inadequate to infer a Causal Relationship |
| Total Mortality | There is little evidence to suggest a causal relationship between chronic O ₃ exposure and increased risk for mortality in humans. | Suggestive of a Causal Relationship |

Table 2-5 Summary of ozone causal determination for welfare effects.

| Vegetation and Ecosystem Effects | Conclusions from 2006 O₃ AQCD | Conclusions from 2012 3rd Draft ISA |
|--|--|--|
| Visible Foliar Injury Effects on Vegetation | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause impaired aesthetic quality of many native plants and trees by increasing foliar injury. | Causal Relationship |
| Reduced Vegetation Growth | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause decreased growth and biomass accumulation in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees. | Causal Relationship |
| Reduced Productivity in Terrestrial Ecosystems | There is evidence that O ₃ is an important stressor of ecosystems and that the effects of O ₃ on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity. | Causal Relationship |
| Reduced Carbon (C) Sequestration in Terrestrial Ecosystems | Limited studies from previous review | Likely to be a Causal Relationship |
| Reduced Yield and Quality of Agricultural Crops | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause decreased yield and/or nutritive quality in a large number of agronomic and forage crops. | Causal Relationship |
| Alteration of Terrestrial Ecosystem Water Cycling | Ecosystem water quantity may be affected by O ₃ exposure at the landscape level. | Likely to be a Causal Relationship |
| Alteration of Below-ground Biogeochemical Cycles | Ozone-sensitive species have well known responses to O ₃ exposure, including altered C allocation to below-ground tissues, and altered rates of leaf and root production, turnover, and decomposition. These shifts can affect overall C and N loss from the ecosystem in terms of respired C, and leached aqueous dissolved organic and inorganic C and N. | Causal Relationship |
| Alteration of Terrestrial Community Composition | Ozone may be affecting above- and below -ground community composition through impacts on both growth and reproduction. Significant changes in plant community composition resulting directly from O ₃ exposure have been demonstrated. | Likely to be a Causal Relationship |

Table 2-6 Summary of ozone causal determination for climate and UV-B effects.

| Effects | Conclusions from 2006 O₃ AQCD | Conclusions from 2012 3rd Draft ISA |
|--|---|---|
| Radiative Forcing | Climate forcing by O ₃ at the regional scale may be its most important impact on climate. | Causal Relationship |
| Climate Change | While more certain estimates of the overall importance of global-scale forcing due to tropospheric O ₃ await further advances in monitoring and chemical transport modeling, the overall body of scientific evidence suggests that high concentrations of O ₃ on the regional scale could have a discernible influence on climate, leading to surface temperature and hydrological cycle changes. | Likely to be a Causal Relationship |
| Health and Welfare Effects Related to UV-B Shielding | UV-B has not been studied in sufficient detail to allow for a credible health benefits assessment. In conclusion, the effect of changes in surface-level O ₃ concentrations on UV-induced health outcomes cannot yet be critically assessed within reasonable uncertainty. | Inadequate to Determine if a Causal Relationship Exists |

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3 ATMOSPHERIC CHEMISTRY AND AMBIENT CONCENTRATIONS

3.1 Introduction

1 In the stratosphere, O₃ serves the beneficial role of absorbing the Sun's harmful
2 ultraviolet radiation and preventing the majority of this radiation from reaching the
3 Earth's surface. In the troposphere, however, O₃ and other photochemical oxidants are air
4 pollutants that can exert harmful effects on humans, animals, and vegetation. This chapter
5 discusses the atmospheric chemistry associated with tropospheric O₃ and other related
6 photochemical oxidants and provides a detailed description of their surface-level
7 concentrations. The focus of this chapter is on O₃ since it is the NAAQS indicator for all
8 photochemical oxidants. To the extent possible, other photochemical oxidants are
9 discussed, but limited information is currently available. Although O₃ is involved in
10 reactions in indoor air, the focus in this chapter will be on chemistry occurring in
11 outdoor, ambient air.

12 The material in this chapter is organized as follows. Section [3.2](#) outlines the physical and
13 chemical processes involved in O₃ formation and removal. Section [3.3](#) describes the latest
14 methods used to model global O₃ concentrations, and Section [3.4](#) describes the
15 application of these methods for estimating background concentrations of O₃ that are
16 useful for risk and policy assessments informing decisions about the NAAQS. Section [3.5](#)
17 includes a comprehensive description of available O₃ monitoring techniques and
18 monitoring networks, while Section [3.6](#) presents information on the spatial and temporal
19 variability of O₃ concentrations across the U.S. and their associations with other
20 pollutants using available monitoring data. Section [3.7](#) summarizes the main conclusions
21 from Chapter [3](#). Finally, Section [3.8](#) provides supplemental material on atmospheric
22 model simulations of background O₃ concentrations (referenced in Section [3.4](#)) and
23 Section [3.9](#) contains supplemental material on observed ambient O₃ concentrations
24 (referenced in Section [3.6](#)).

3.2 Physical and Chemical Processes

25 Ozone in the troposphere is a secondary pollutant formed by photochemical reactions of
26 precursor gases and is not directly emitted from specific sources. Ozone and other
27 oxidants, such as peroxyacetyl nitrate (PAN) and H₂O₂ form in polluted areas by
28 atmospheric reactions involving two main classes of precursor pollutants: VOCs and

1 NO_x.¹ Carbon monoxide (CO) is also important for O₃ formation in polluted areas and in
2 the remote troposphere. The formation of O₃, other oxidants and oxidation products from
3 these precursors is a complex, nonlinear function of many factors including (1) the
4 intensity and spectral distribution of sunlight; (2) atmospheric mixing; (3) concentrations
5 of precursors in the ambient air and the rates of chemical reactions of these precursors;
6 and (4) processing on cloud and aerosol particles.

7 Ozone is present not only in polluted urban atmospheres, but throughout the troposphere,
8 even in remote areas of the globe. The same basic processes involving sunlight-driven
9 reactions of NO_x, VOCs and CO contribute to O₃ formation throughout the troposphere.
10 These processes also lead to the formation of other photochemical products, such as
11 PAN, HNO₃, and H₂SO₄, and to other compounds, such as HCHO and other carbonyl
12 compounds, and to secondary components of particulate matter.

13 A schematic overview of the major photochemical cycles influencing O₃ in the
14 troposphere and the stratosphere is given in [Figure 3-1](#). The processes responsible for
15 producing summertime O₃ episodes are fairly well understood, and were covered in detail
16 in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). This section focuses on topics that form the
17 basis for discussions in later chapters and for which there is substantial new information
18 since the previous O₃ review.

¹ The term VOCs refers to all organic gas-phase compounds in the atmosphere, both biogenic and anthropogenic in origin. This definition excludes CO and CO₂. NO_x, also referred to as nitrogen oxides, is equal to the sum of NO and NO₂.

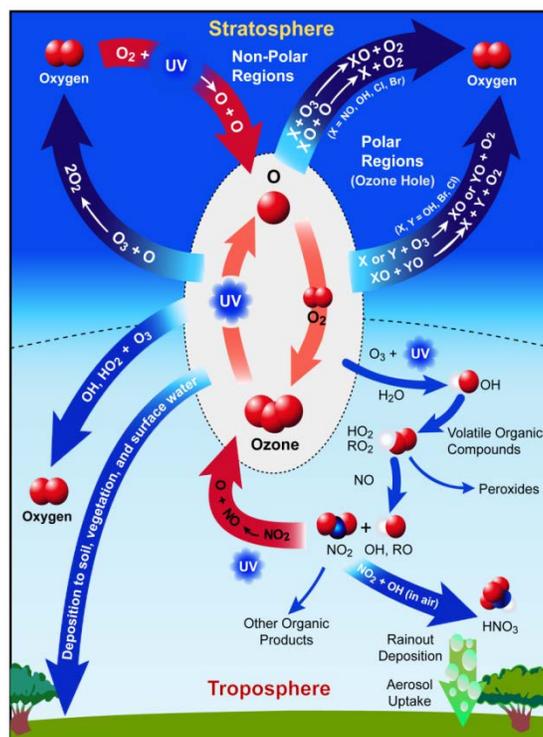


Figure 3-1 Schematic overview of photochemical processes influencing stratospheric and tropospheric ozone.

1 Major episodes of high O₃ concentrations in the eastern U.S. and in Europe are associated
 2 with slow moving high pressure systems. High pressure systems during the warmer
 3 seasons are associated with the sinking of air, resulting in warm, generally cloudless
 4 skies, with light winds. The sinking of air results in the development of stable conditions
 5 near the surface which inhibit or reduce the vertical mixing of O₃ precursors.
 6 Photochemical activity involving these precursors is enhanced because of higher
 7 temperatures and the availability of sunlight during the warmer seasons. In the eastern
 8 U.S., concentrations of O₃ and other secondary pollutants are determined by
 9 meteorological and chemical processes extending typically over areas of several hundred
 10 thousand square kilometers ([Civerolo et al., 2003](#); [Rao et al., 2003](#)). Ozone episodes are
 11 thus best regarded as regional in nature. The conditions conducive to formation of high
 12 O₃ can persist for several days. These conditions have been described in greater detail in
 13 the 1996 and 2006 O₃ AQCDs ([U.S. EPA, 2006b, 1996a](#)). The transport of pollutants
 14 downwind of major urban centers is characterized by the development of urban plumes.
 15 Mountain barriers limit mixing (as in Los Angeles and Mexico City) and result in a
 16 higher frequency and duration of days with high O₃ concentrations. However, orographic
 17 lifting over the San Gabriel Mountains results in O₃ transport from Los Angeles to areas

1 hundreds of kilometers downwind (e.g., in Colorado and Utah) ([Langford et al., 2009](#)).
2 Ozone concentrations in southern urban areas (such as Houston, TX and Atlanta, GA)
3 tend to decrease with increasing wind speed. In northern U.S. cities (such as Chicago, IL;
4 New York, NY; Boston, MA; and Portland, ME), the average O₃ concentrations over the
5 metropolitan areas increase with wind speed, indicating that transport of O₃ and its
6 precursors from upwind areas is important ([Schichtel and Husar, 2001](#); [Husar and
7 Renard, 1998](#)).

8 Aircraft observations indicate that there can be substantial differences in mixing ratios of
9 key species between the surface and the overlying atmosphere ([Berkowitz and Shaw,
10 1997](#); [Fehsenfeld et al., 1996](#)). In particular, mixing ratios of O₃ can (depending on time
11 and location) be higher in the lower free troposphere (aloft) than in the planetary
12 boundary layer (PBL) during multiday O₃ episodes ([Taubman et al., 2006](#); [Taubman et
13 al., 2004](#)). Convective processes and turbulence transport O₃ and other pollutants both
14 upward and downward throughout the planetary boundary layer and the free troposphere.
15 During the day, convection is driven by heating of the earth's surface results in a deeper
16 PBL with vertically well mixed O₃ and precursors. As solar heating of the surface
17 decreases going into night, the daytime boundary layer collapses leaving behind O₃ and
18 its precursors in a residual layer above a shallow nighttime boundary layer. Pollutants in
19 the residual layer have now become essentially part of the free troposphere, as described
20 in Annex AX2.3.2 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). Winds in the free
21 troposphere tend to be stronger than those closer to the surface and so are capable of
22 transporting pollutants over long distances. Thus, O₃ and its precursors can be transported
23 vertically by convection into the upper part of the mixed layer on one day, then
24 transported overnight as a layer of elevated mixing ratios, and then entrained into a
25 growing convective boundary layer downwind and brought back down to the surface.

26 High O₃ concentrations showing large diurnal variations at the surface in southern New
27 England were associated with the presence of such layers ([Berkowitz et al., 1998](#)). Winds
28 several hundred meters above the ground can bring pollutants from the west, even though
29 surface winds are from the southwest during periods of high O₃ in the eastern U.S.
30 ([Blumenthal et al., 1997](#)). These considerations suggest that in many areas of the U.S., O₃
31 and its precursors can be transported over hundreds if not thousands of kilometers.

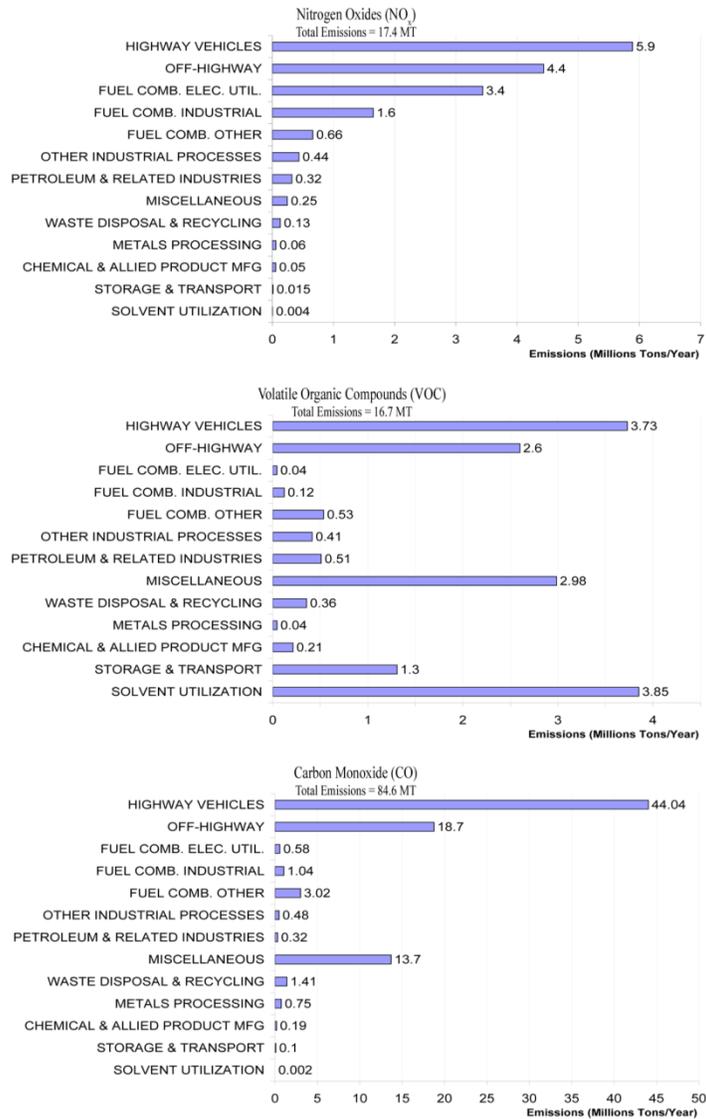
32 Nocturnal low level jets (LLJs) are an efficient means for transporting pollutants that
33 have been entrained into the residual boundary layer over hundreds of kilometers. LLJs
34 are most prevalent in the central U.S. extending northward from eastern Texas, and along
35 the Atlantic states extending southwest to northeast. LLJs have also been observed off the
36 coast of California. Turbulence induced by wind shear associated with LLJs brings
37 pollutants to the surface and results in secondary O₃ maxima during the night and early

1 morning in many locations ([Corsmeier et al., 1997](#)). Comparison of observations at
2 low-elevation surface sites with those at nearby high-elevation sites at night can be used
3 to discern the effects of LLJs. For example, [Fischer \(2004\)](#) found occasions when O₃ at
4 the base of Mt. Washington during the night was much higher than typically observed,
5 and closer to those observed at the summit of Mt. Washington. They suggested that
6 mechanically driven turbulence due to wind shear caused O₃ from aloft to penetrate the
7 stable nocturnal inversion thus causing O₃ to increase near the base of Mt. Washington.
8 The high wind speeds causing this mechanically driven turbulence could have resulted
9 from the development of a LLJ. Stratospheric intrusions and intercontinental transport of
10 O₃ are also important and are covered in Section [3.4](#) in relation to background
11 concentrations.

3.2.1 Sources of Precursors Involved in Ozone Formation

12 Emissions of O₃ precursor compounds (NO_x, VOCs, and CO) can be divided into natural
13 and anthropogenic source categories. Natural sources can be further divided into biogenic
14 from vegetation, microbes, and animals, and abiotic from biomass combustion, lightning,
15 and geogenic sources. However, the distinction between natural and anthropogenic
16 sources is often difficult to make in practice, as human activities directly or indirectly
17 affect emissions from what would have been considered natural sources during the
18 preindustrial era. Thus, emissions from plants and animals used in agriculture have been
19 referred to as anthropogenic or biogenic in different applications. Wildfire emissions can
20 be considered natural, except that forest management practices can lead to buildup of
21 fuels on the forest floor, thereby altering the frequency and severity of forest fires.

22 Estimates of emissions for NO_x, VOCs, and CO from the 2005 National Emissions
23 Inventory (NEI) ([U.S. EPA, 2008a](#)) are shown in [Figure 3-2](#) to provide a general
24 indication of the relative importance of the different sources in the U.S. as a whole. The
25 magnitudes of the sources are strongly location and time dependent and so should not be
26 used to apportion sources of exposure. Shown in [Figure 3-2](#) are Tier 1 categories. The
27 miscellaneous category can be quite large compared to total emissions, especially for CO
28 and VOCs. The miscellaneous category includes agriculture and forestry, wildfires,
29 prescribed burns, and a much more modest contribution from structural fires.



Note: NO_x (top), VOCs (middle), and CO (bottom) in the U.S. in million metric tons (MT) per year.
Source: [U.S. EPA \(2008a\)](#).

Figure 3-2 Estimated anthropogenic emissions of ozone precursors for 2005.

1 Anthropogenic NO_x emissions are associated with combustion processes. Most emissions
 2 are in the form of NO, which is formed at high combustion temperatures from
 3 atmospheric nitrogen (N₂) and oxygen (O₂) and from fuel nitrogen (N). According to the
 4 2005 NEI, the largest sources of NO_x are on- and off-road (such as construction
 5 equipment, agricultural equipment, railroad trains, ships, and aircraft) mobile sources and
 6 electric power generation plants. Emissions of NO_x therefore are highest in areas having
 7 a high density of power plants and in urban regions having high traffic density. [Dallmann](#)

1 [and Harley \(2010\)](#) compared NO_x emissions estimates from the 2005 NEI mobile sector
2 data with an alternative method based on fuel consumption and found reasonable
3 agreement in total U.S. anthropogenic emissions between the two techniques (to within
4 about 5%). However, emissions from on-road diesel engines in the fuel based inventory
5 constituted 46% of total mobile source NO_x compared to 35% in the EPA inventory. As a
6 result, emissions from on-road diesel engines in the fuel based approach are even larger
7 than electric power generation as estimated in the 2005 NEI, and on-road diesel engines
8 might represent the largest single NO_x source category. Differences between the two
9 techniques are largely accounted for by differences in emissions from on-road gasoline
10 engines. Uncertainties in the fuel consumption inventory ranged from 3% for on-road
11 gasoline engines to 20% for marine sources, and in the EPA inventory uncertainties
12 ranged from 16% for locomotives to 30% for off-road diesel engines. It should be noted
13 that the on-road diesel engine emissions estimate by [Dallmann and Harley \(2010\)](#) is still
14 within the uncertainty of the EPA estimate (22%). Because of rapid changes to heavy
15 duty diesel NO_x controls, emissions are likely to also rapidly change.

16 Satellite-based techniques have been used to obtain tropospheric concentrations of O₃
17 precursors (e.g., NO₂, VOCs and CO). Such satellite-based measurements provide a
18 large-scale picture of spatial and temporal distribution of NO₂, VOCs and CO that can be
19 used to evaluate emissions inventories produced using the bottom-up approach and to
20 produce top-down emissions inventories of these species. Although there are
21 uncertainties associated with satellite-based measurements, several studies have shown
22 the utility of top-down constraints on the emissions of O₃ precursors ([McDonald-Buller et](#)
23 [al., 2011 and references therein](#)). Following mobile sources, power plants are considered
24 the second largest anthropogenic source of NO_x. Over the past decade, satellite
25 measurements have shown appreciable reductions in NO_x power plant emissions across
26 the U.S. as a result of emission abatement strategies ([Stavrou et al., 2008](#); [Kim et al.,](#)
27 [2006](#)). For instance, [Kim et al. \(2006\)](#) observed a 34% reduction in NO_x emission over
28 the Ohio River Valley from 1999-2006 due to such strategies. Based on these results, less
29 than 25% of anthropogenic NO_x emissions were expected to originate from power plants
30 in this region. Uncertainty in NO_x satellite measurements are impacted by several factors,
31 such as cloud and aerosol properties, surface albedo, stratospheric NO_x concentration,
32 and solar zenith angle. [Boersma et al. \(2004\)](#) estimated an overall uncertainty between
33 35-60% for satellite-retrieved NO_x measurements in urban, polluted regions. Although
34 trends in satellite-retrieved NO_x power plant emissions reported by [Kim et al. \(2006\)](#) are
35 uncertain to some extent, similar reductions were reported by region-wide power plant
36 measurements (e.g., Continuous Emission Monitoring System observations, CEMS).

37 Major natural sources of NO_x in the U.S. include lightning, soils, and wildfires.

38 Uncertainties in natural NO_x emissions are much larger than for anthropogenic NO_x

1 emissions. [Fang et al. \(2010\)](#) estimated lightning generated NO_x of ~0.6 MT for July
2 2004. This value is ~40% of the anthropogenic emissions for the same period, but the
3 authors estimated that ~98% is formed in the free troposphere and so contributions to the
4 surface NO_x burden are low because most of this NO_x is oxidized to nitrate containing
5 species during downward transport into the planetary boundary layer. The remaining 2%
6 is formed within the planetary boundary layer. Both nitrifying and denitrifying organisms
7 in the soil can produce NO_x, mainly in the form of NO. Emission rates depend mainly on
8 fertilization amount and soil temperature and moisture. Nationwide, about 60% of the
9 total NO_x emitted by soils is estimated to occur in the central corn belt of the U.S. Spatial
10 and temporal variability in soil NO_x emissions leads to considerable uncertainty in
11 emissions estimates. However, these emissions are relatively low, only ~0.97 MT/year, or
12 about 6% of anthropogenic NO_x emissions. However, these emissions occur mainly
13 during summer when O₃ is of most concern and occur across the entire country including
14 areas where anthropogenic emissions are low.

15 Hundreds of VOCs, containing mainly 2 to ~12 carbon (C) atoms, are emitted by
16 evaporation and combustion processes from a large number of anthropogenic sources.
17 The two largest anthropogenic source categories in the U.S. EPA's emissions inventories
18 are industrial processes and transportation. Emissions of VOCs from highway vehicles
19 account for roughly two-thirds of the transportation-related emissions. The accuracy of
20 VOC emission estimates is difficult to determine, both for stationary and mobile sources.
21 Evaporative emissions, which depend on temperature and other environmental factors,
22 compound the difficulties of assigning accurate emission factors. In assigning VOC
23 emission estimates to the mobile source category, models are used that incorporate
24 numerous input parameters (e.g., type of fuel used, type of emission controls, and age of
25 vehicle), each of which has some degree of uncertainty.

26 On the U.S. and global scales, emissions of VOCs from vegetation are much larger than
27 those from anthropogenic sources. Emissions of VOCs from anthropogenic sources in the
28 2005 NEI were ~17 MT/year (wildfires constitute ~1/6 of that total and were included in
29 the 2005 NEI under the anthropogenic category, but see Section [3.4](#) for how wildfires are
30 treated for background O₃ considerations), but were 29 MT/year from biogenic sources.
31 Uncertainties in both biogenic and anthropogenic VOC emission inventories prevent
32 determination of the relative contributions of these two categories, at least in many areas.
33 Vegetation emits substantial quantities of VOCs, such as terpenoid compounds (isoprene,
34 2-methyl-3-buten-2-ol, monoterpenes), compounds in the hexanal family, alkenes,
35 aldehydes, organic acids, alcohols, ketones, and alkanes. The major chemicals emitted by
36 plants are isoprene (40%), other terpenoid and sesqui-terpenoid compounds (25%) and
37 the remainder consists of assorted oxygenated compounds and hydrocarbons according to
38 the 2005 NEI. Most biogenic emissions occur during the summer because of their

1 dependence on temperature and incident sunlight. Biogenic emissions are also higher in
2 southern states than in northern states for these reasons and because of species variations.
3 The uncertainty in natural emissions is about 50% for isoprene under midday summer
4 conditions and could be as much as a factor of ten higher for some compounds ([Guenther
5 et al., 2000](#)). In EPA's regional modeling efforts, biogenic emissions of VOCs are
6 estimated using the Biogenic Emissions Inventory System (BEIS) model ([U.S. EPA,
7 2010b](#)) with data from the Biogenic Emissions Landcover Database (BELD) and annual
8 meteorological data. However, other emissions models are used such as Model of
9 Emissions of Gases and Aerosols from Nature (MEGAN) ([Guenther et al., 2006](#)),
10 especially in global modeling efforts.

11 Satellite measurements of HCHO, produced by the oxidation of isoprene and other
12 VOCs, have also been used to estimate biogenic VOC emissions attributed to isoprene
13 ([Millet et al., 2008](#); [Millet et al., 2006](#)). [Millet et al. \(2008\)](#) demonstrated that both
14 satellite-based and model techniques capture the spatial variability of biogenic isoprene
15 emissions in the U.S. reasonably well (satellite vs. MEGAN isoprene estimates, $R^2 = 0.48$
16 or 0.68 depending on vegetation data base used). However, MEGAN tends to
17 overestimate emissions compared to satellite-based measurements. The uncertainty in
18 satellite derived isoprene emissions is roughly 40%, based on combined uncertainty in
19 satellite retrieval and isoprene yield from isoprene oxidation ([Millet et al., 2006](#)), which
20 is similar to the error associated with model-based techniques (~50%) (e.g., [Millet et al.,
21 2006](#); [Guenther et al., 2000](#)).

22 Anthropogenic CO is emitted primarily by incomplete combustion of carbon-containing
23 fuels. In general, any increase in fuel oxygen content, burn temperature, or mixing time in
24 the combustion zone will tend to decrease production of CO relative to CO₂. However, it
25 should be noted that controls mute the response of CO formation to fuel-oxygen. CO
26 emissions from large fossil-fueled power plants are typically very low since the boilers at
27 these plants are tuned for highly efficient combustion with the lowest possible fuel
28 consumption. Additionally, the CO-to-CO₂ ratio in these emissions is shifted toward CO₂
29 by allowing time for the furnace flue gases to mix with air and be oxidized by OH to CO₂
30 in the hot gas stream before the OH concentrations drop as the flue gases cool.

31 Nationally, on-road mobile sources constituted about half of total CO emissions in the
32 2005 NEI. When emissions from non-road vehicles are included, it can be seen from
33 [Figure 3-2](#) that all mobile sources accounted for about three-quarters of total
34 anthropogenic CO emissions in the U.S.

35 Analyses by [Harley et al. \(2005\)](#) and [Parrish \(2006\)](#) are consistent with the suggestion in
36 [Pollack et al. \(2004\)](#) that the EPA MOBILE6 vehicle emissions model ([U.S. EPA, 2010d](#))
37 overestimates vehicle CO emissions by a factor of ~2. Field measurements by [Bishop and](#)

1 [Stedman \(2008\)](#) were in accord with the [Parrish \(2006\)](#) findings that the measured trends
2 of CO and NO_x concentrations from mobile sources in the U.S. indicated that modeled
3 CO emission estimates were substantially too high. [Hudman et al. \(2008\)](#) found that the
4 NEI overestimated anthropogenic CO emissions by 60% for the eastern U.S. during the
5 period July 1-August 15, 2004 based on comparison of aircraft observations of CO from
6 the International Consortium for Atmospheric Research on Transport and Transformation
7 (ICARTT) campaign ([Fehsenfeld et al., 2006](#)) and results from a tropospheric chemistry
8 model (GEOS-Chem). Improvements in emissions technologies not correctly represented
9 in MOBILE emission models have been suggested as one cause for this discrepancy. For
10 example, [Pokharel et al. \(2003, 2002\)](#) demonstrated substantial decrements in the CO
11 fraction of tailpipe exhaust in several U.S. cities and [Burgard et al. \(2006\)](#) documented
12 improvements in emission from heavy-duty on-road diesel engines. Some of the largest
13 errors in the MOBILE models are addressed in the successor model, MOVES ([U.S. EPA,
14 2011e](#)).

15 Estimates of biogenic CO emissions in the 2005 NEI are made in a manner similar to that
16 for VOCs. National biogenic emissions, excluding fires, were estimated to contribute
17 ~7% and wildfires added another ~16% to the national CO emissions total.

18 Photodecomposition of organic matter in oceans, rivers, lakes, and other surface waters,
19 and from soil surfaces also releases CO ([Goldstein and Galbally, 2007](#)). However, soils
20 can act as a CO source or a sink depending on soil moisture, UV flux reaching the soil
21 surface, and soil temperature ([Conrad and Seiler, 1985](#)). Soil uptake of CO is driven by
22 anaerobic bacteria ([Inman et al., 1971](#)). Emissions of CO from soils appear to occur by
23 abiotic processes, such as thermodecomposition or photodecomposition of organic
24 matter. In general, warm and moist conditions found in most soils favor CO uptake,
25 whereas hot and dry conditions found in deserts and some savannas favor the release of
26 CO ([King, 1999](#)).

3.2.2 Gas Phase Reactions Leading to Ozone Formation

27 Photochemical processes involved in O₃ formation have been extensively reviewed in a
28 number of books ([Jacobson, 2002](#); [Jacob, 1999](#); [Seinfeld and Pandis, 1998](#); [Finlayson-
29 Pitts and Pitts, 1986](#)) and in the 1996 and 2006 O₃ AQCDs ([U.S. EPA, 2006b, 1996a](#)).
30 The photochemical formation of O₃ in the troposphere proceeds through the oxidation of
31 NO to nitrogen dioxide (NO₂) by organic-peroxy (RO₂) or hydro-peroxy (HO₂) radicals.
32 The peroxy radicals oxidizing NO to NO₂ are formed during the oxidation of VOCs as
33 presented in Annex AX2.2.2 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). The photolysis of
34 NO₂ yields NO and a ground-state oxygen atom, O(³P), which then reacts with molecular
35 oxygen to form O₃.

1 VOCs important for the photochemical formation of O₃ include alkanes, alkenes,
2 aromatic hydrocarbons, carbonyl compounds (e.g., aldehydes and ketones), alcohols,
3 organic peroxides, and halogenated organic compounds (e.g., alkyl halides). This array of
4 compounds encompasses a wide range of chemical properties and lifetimes: isoprene has
5 an atmospheric lifetime of approximately an hour, whereas methane has an atmospheric
6 lifetime of about a decade.

7 In urban areas, compounds representing all classes of VOCs and CO are important for O₃
8 formation. In non-urban vegetated areas, biogenic VOCs emitted from vegetation tend to
9 be the most important. In the remote troposphere, methane (CH₄) and CO are the main
10 carbon-containing precursors to O₃ formation. The oxidation of VOCs is initiated mainly
11 by reaction with hydroxyl (OH) radicals. The primary source of OH radicals in the
12 atmosphere is the reaction of electronically excited oxygen atoms, O(¹D), with water
13 vapor. O(¹D) is produced by the photolysis of O₃ in the Hartley bands. In polluted areas,
14 the photolysis of aldehydes (e.g., HCHO), HONO and H₂O₂ can also be appreciable
15 sources of OH, or HO₂ radicals that can rapidly be converted to OH ([Eisele et al., 1997](#)).
16 Ozone can oxidize alkenes, as can NO₃ radicals. NO₃ radicals are most effective at night
17 when they are most abundant. In coastal environments and other selected environments,
18 atomic Cl and Br radicals can also initiate the oxidation of VOCs as discussed in Annex
19 AX2.2.3 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). It was also emphasized in Annex
20 AX2.2.9 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) that the reactions of oxygenated
21 VOCs are important components of O₃ formation. They may be present in ambient air not
22 only as the result of the atmospheric oxidation of hydrocarbons but also by direct
23 emissions. For example, motor vehicles (including compressed natural gas vehicles) and
24 some industrial processes emit formaldehyde ([Rappenglück et al., 2009](#)) and vegetation
25 emits methanol.

26 There are a large number of oxidized N-containing compounds in the atmosphere
27 including NO, NO₂, NO₃, HNO₂, HNO₃, N₂O₅, HNO₄, PAN and its homologues, other
28 organic nitrates, such as alkyl nitrates, isoprene nitrates, and particulate nitrate.
29 Collectively these species are referred to as NO_Y. Oxidized nitrogen compounds are
30 emitted to the atmosphere mainly as NO which rapidly interconverts with NO₂ and so NO
31 and NO₂ are often “lumped” together into their own group or family, which is referred to
32 as NO_X. All the other species mentioned above in the definition of NO_Y are products of
33 NO_X reactions are referred to as NO_Z, such that NO_Y = NO_X + NO_Z. The major reactions
34 involving interconversions of oxidized N species were covered in Annex AX2.2.4 of the
35 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). [Mollner et al. \(2010\)](#) identified pernitrous acid
36 (HOONO), an unstable isomer of nitric acid, as a product of the major gas phase reaction
37 forming HNO₃. However, since pernitrous acid is unstable, it is not a substantial reservoir

1 for NO_x. This finding stresses the importance of identifying products in addition to
2 measuring the rate of disappearance of reactants in kinetic studies.

3 The photochemical cycles by which the oxidation of hydrocarbons leads to O₃ production
4 are best understood by considering the oxidation of methane, structurally the simplest
5 VOC. The CH₄ oxidation cycle serves as a model for the chemistry of the relatively clean
6 or unpolluted troposphere (although this is a simplification because vegetation releases
7 large quantities of complex VOCs, such as isoprene, into the atmosphere). In the polluted
8 atmosphere, the underlying chemical principles are the same, as discussed in Annex
9 AX2.2.5 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). The conversion of NO to NO₂
10 occurring with the oxidation of VOCs is accompanied by the production of O₃ and the
11 efficient regeneration of the OH radical, which in turn can react with other VOCs as
12 shown in [Figure 3-1](#).

13 The oxidation of alkanes and alkenes in the atmosphere has been treated in depth in the
14 1996 O₃ AQCD ([U.S. EPA, 1996a](#)) and was updated in Annexes AX2.2.6 and AX2.2.7
15 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). In contrast to simple hydrocarbons containing
16 one or two C atoms, detailed kinetic information about the gas phase oxidation pathways
17 of many anthropogenic hydrocarbons (e.g., aromatic compounds such as benzene and
18 toluene), biogenic hydrocarbons (e.g., isoprene, the monoterpenes), and their
19 intermediate oxidation products (e.g., peroxides, nitrates, carbonyls and epoxides) is
20 lacking. This information is crucial even for compounds formed in low yields, such as
21 isoprene epoxides, as they are major precursors to secondary organic aerosol formation
22 ([see, e.g., Surratt et al., 2010](#)). Reaction with OH radicals represents the major loss
23 process for alkanes. Reaction with chlorine (Cl) atoms is an additional sink for alkanes.
24 Stable products of alkane photooxidation are known to include a wide range of
25 compounds and concentrations including carbonyl compounds, alkyl nitrates, and
26 d-hydroxycarbonyls. Major uncertainties in the atmospheric chemistry of the alkanes
27 concern the chemistry of alkyl nitrate formation; these uncertainties affect the amount of
28 NO-to-NO₂ conversion occurring and, hence, the amounts of O₃ formed during
29 photochemical degradation of the alkanes.

30 The reaction of OH radicals with aldehydes produced during the oxidation of alkanes
31 forms acyl (R'CO) radicals, and acyl peroxy radicals (R'C(O)-O₂) are formed by the
32 further addition of O₂. As an example, the oxidation of ethane (C₂H₅-H) yields
33 acetaldehyde (CH₃-CHO). The reaction of CH₃-CHO with OH radicals yields acetyl
34 radicals (CH₃-CO). The acetyl radicals will then participate with O₂ in a termolecular
35 recombination reaction to form acetyl peroxy radicals, which can then react with NO to
36 form CH₃ + CO₂ or they can react with NO₂ to form PAN. PAN acts as a temporary

1 reservoir for NO₂. Upon the thermal decomposition of PAN, either locally or elsewhere,
2 NO₂ is released to participate in the O₃ formation process again.

3 Alkenes react in ambient air with OH, NO₃, and Cl radicals and with O₃. All of these
4 reactions are important atmospheric transformation processes, and all proceed by initial
5 addition to the carbon double bonds. Major products of alkene photooxidation include
6 carbonyl compounds. Hydroxynitrates and nitratocarboxyls, and decomposition products
7 from the energy-rich biradicals formed in alkene-O₃ reactions are also produced. Major
8 uncertainties in the atmospheric chemistry of the alkenes concern the products and
9 mechanisms of their reactions with O₃, especially the yields of radicals that participate in
10 O₃ formation. Examples of oxidation mechanisms of complex alkanes and alkenes can be
11 found in comprehensive texts such as [Seinfeld and Pandis \(1998\)](#).

12 Although the photochemistry of isoprene is crucial for understanding O₃ formation, there
13 are major uncertainties in its oxidation pathways that still need to be addressed. Apart
14 from the effects of the oxidation of isoprene on production of radicals and O₃ formation,
15 isoprene nitrates (RONO₂) appear to play an important role as NO_x reservoirs over the
16 eastern U.S. (e.g., [Perring et al., 2009](#)). Their decomposition leads to the recycling of
17 NO_x, which can participate in the O₃ formation process. Laboratory and field-based
18 approaches support yields for RONO₂ formation from isoprene oxidation ranging from 4
19 to 12% (see summaries in, [Lockwood et al., 2010](#); [Perring et al., 2009](#); [Horowitz et al.,](#)
20 [2007](#); [von Kuhlmann et al., 2004](#)). The rate at which RONO₂ reacts to recycle NO_x is
21 poorly understood ([Archibald et al., 2010](#); [Paulot et al., 2009](#)) with ranges from 0 to
22 100% in global chemical transport models. This range affects the sign of the O₃ response
23 to changes in biogenic VOC emissions as well as the sensitivity of O₃ to changes in NO_x
24 emissions ([Archibald et al., 2011](#); [Ito et al., 2009](#); [Weaver et al., 2009](#); [Horowitz et al.,](#)
25 [2007](#); [Fiore et al., 2005](#)). In models that assume zero RONO₂ recycling ([Zhang et al.,](#)
26 [2011](#); [Wu et al., 2007](#); [Fiore et al., 2003](#)) O₃ production is suppressed relative to a model
27 that recycles NO_x from RONO₂ ([Kang et al., 2003](#)). A related issue concerns the lack of
28 regeneration of OH + HO₂ radicals especially in low NO_x (<~1 ppb) environments. The
29 isomerization of the isoprene peroxy radicals that are formed after initial OH attack and
30 subsequent reactions could help resolve this problem ([Peeters and Müller, 2010](#); [Peeters](#)
31 [et al., 2009](#)) and result in increases in OH concentrations from 20 to 40% over the
32 southeastern U.S. ([Archibald et al., 2011](#)). However, the effectiveness of this pathway is
33 uncertain and depends on the fraction of isoprene-peroxy radicals reacting by
34 isomerization. [Crouse et al. \(2011\)](#) estimated that only 8-11% of the isoprene-peroxy
35 radicals isomerizes to reform HO₂ radicals. [Hofzumahaus et al. \(2009\)](#) also found under
36 predictions of OH in the Pearl River Delta and they also note that the sequence of
37 reactions beginning with OH attack on VOCs introduces enormous complexity which is
38 far from being fully understood.

1 The oxidation of aromatic hydrocarbons constitutes an important component of the
2 chemistry of O₃ formation in urban atmospheres as discussed in Annex AX2.2.8 of the
3 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). Virtually all of the important aromatic hydrocarbon
4 precursors emitted in urban atmospheres are lost through reaction with the hydroxyl
5 radical. Loss rates for these compounds vary from slow (e.g., benzene) to moderate
6 (e.g., toluene), to very rapid (e.g., xylene and trimethylbenzene isomers). However, the
7 mechanism for the oxidation of aromatic hydrocarbons following reaction with OH is
8 poorly understood, as is evident from the poor mass balance of the reaction products. The
9 mechanism for the oxidation of toluene has been studied most thoroughly, and there is
10 general agreement on the initial steps in the mechanism. However, at present there is no
11 promising approach for resolving the remaining issues concerning the later steps. The
12 oxidation of aromatic hydrocarbons also leads to particle formation that could remove
13 gas-phase constituents that participate in O₃ formation.

14 Adequate analytical techniques needed to identify and quantify key intermediate species
15 are not available for many compounds. In addition, methods to synthesize many of the
16 suspected intermediate compounds are not available so that laboratory studies of their
17 reaction kinetics cannot be performed. Similar considerations apply to the oxidation of
18 biogenic hydrocarbons besides isoprene. These considerations are important because
19 oxidants, other than O₃, that are formed from the chemistry described above could exert
20 effects on human health and perhaps also on vegetation ([Doyle et al., 2007](#); [Doyle et al.,
21 2004](#); [Sexton et al., 2004](#)). Gas phase oxidants include PAN, H₂O₂, CH₃OOH, and other
22 organic hydroperoxides.

23 Ozone is lost through a number of gas phase reactions and deposition to surfaces. The
24 reaction of O₃ with NO to produce NO₂, for example in urban centers near roads, mainly
25 results in the recycling of O₃ downwind via the recombination of O(³P) with O₂ to re-
26 form O₃. By itself, this reaction does not lead to a net loss of O₃ unless the NO₂ is
27 converted to stable end products such as HNO₃. Ozone reacts with unsaturated
28 hydrocarbons and with OH and HO₂ radicals.

29 Perhaps the most recent field study aimed at obtaining a better understanding of
30 atmospheric chemical processes was the Second Texas Air Quality Field Study
31 (TexAQS-II) conducted in Houston in August and September 2006 ([Olague et al., 2009](#)).
32 The TexAQS-II Radical and Aerosol Measurement Project (TRAMP) found evidence for
33 the importance of short-lived radical sources such as HCHO and HONO in increasing O₃
34 productivity. During TRAMP, daytime HCHO pulses as large as 32 ppb were observed
35 and attributed to industrial activities upwind in the Houston Ship Channel (HSC) and
36 HCHO peaks as large as 52 ppb were detected by in situ surface monitors in the HSC.
37 Primary HCHO produced in flares from local refineries and petrochemical facilities could

1 increase peak O₃ by ~30 ppb ([Webster et al., 2007](#)). Other findings from TexAQS-II
2 included substantial concentrations of HONO during the day, with peak concentrations
3 approaching 1 ppb at local noon. These concentrations are well in excess of current air
4 quality model predictions using gas phase mechanisms alone ([Sarwar et al., 2008](#)) and
5 multiphase processes are needed to account for these observations. [Olague et al. \(2009\)](#)
6 also noted that using measured HONO brings modeled O₃ concentrations into much
7 better agreement with observations and could result in the production of an additional
8 10 ppb O₃. Large nocturnal vertical gradients indicating a surface or near-surface source
9 of HONO, and large concentrations of night-time radicals (~30 ppt HO₂) were also found
10 during TRAMP.

3.2.3 Multiphase Processes

11 In addition to the gas phase, chemical reactions also occur on the surfaces of or within
12 cloud droplets and airborne particles. Their collective surface area is huge, implying that
13 collisions with gas phase species occur on very short time scales. In addition to
14 hydrometeors (e.g., cloud and fog droplets and snow and ice crystals) there are also
15 potential reactions involving atmospheric particles of varying composition (e.g., wet
16 [deliquesced] inorganic particles, mineral dust, carbon chain agglomerates and organic
17 carbon particles). Multiphase reactions are involved in the formation of a number of
18 species such as particulate nitrate, and gas phase HONO that can act to both increase and
19 reduce the rate of O₃ formation in the polluted troposphere. Data collected in Houston as
20 part of TexAQS-II summarized by [Olague et al. \(2009\)](#) indicate that concentrations of
21 HONO are much higher than can be explained by gas phase chemistry and by tailpipe
22 emissions. Photolysis of HONO formed in multiphase reactions in addition to the other
23 sources can help to reduce the model underestimate of simulated O₃ in Houston.

24 Multiphase processes have been associated with the release of gaseous halogen
25 compounds from marine aerosol, mainly in marine and coastal environments. However,
26 [Thornton et al. \(2010\)](#) found production rates of gaseous nitryl chloride near Boulder, CO
27 from reaction of N₂O₅ with particulate Cl⁻, similar to those found in coastal and marine
28 environments. ClNO₂ readily photolyzes to yield Cl. They also found that substantial
29 quantities of N₂O₅ are recycled through ClNO₂ back into NO_x instead of forming HNO₃
30 (a stable reservoir for reactive nitrogen compounds). The oxidation of hydrocarbons by
31 Cl radicals released from the marine aerosol could lead to the rapid formation of peroxy
32 radicals and higher rates of O₃ production. It should be noted that in addition to
33 production from marine aerosol, reactive halogen species are also produced by the
34 oxidation of halogenated organic compounds (e.g., CH₃Cl, CH₃Br, and CH₃I). The
35 atmospheric chemistry of halogens is complex because Cl, Br and I containing species

1 can react among themselves and with hydrocarbons and other species and could also be
2 important for O₃ destruction, as has been noted for the lower stratosphere ([McElroy et al.,](#)
3 [1986](#); [Yung et al., 1980](#)). For example, the reactions of Br and Cl containing radicals
4 deplete O₃ in selected environments such as the Arctic during the spring ([Barrie et al.,](#)
5 [1988](#)), the tropical marine boundary layer ([Dickerson et al., 1999](#)), and inland salt flats
6 and salt lakes ([Stutz et al., 2002](#)). [Mahajan et al. \(2010\)](#) found that I and Br species acting
7 together resulted in O₃ depletion that was much larger than would have been expected if
8 they acted individually and did not interact with each other; see Annex AX2.2.10.3 of the
9 2006 O₃ AQCD ([U.S. EPA, 2006b](#)).

10 Multiphase processes have also been associated with the uptake of reactive gas phase
11 species affecting global budgets of O₃ and nitrogen oxides among others. The uptake of
12 N₂O₅ on aerosols or cloud droplets leads to the loss of O₃ and NO_x and the production of
13 aqueous phase nitric acid, aerosol nitrate, and gaseous halogen nitrites. In addition to loss
14 of HO₂, the uptake of HO₂ radicals on aerosol surfaces potentially reduces O₃
15 concentrations and increases formation of sulfate (if H₂O₂ is formed after uptake).
16 [Macintyre and Evans \(2011\)](#) developed a parameterization for uptake of HO₂ based on
17 laboratory studies, which were about a factor of seven lower than previously estimated.
18 However they note that some of the earlier studies reporting higher values might have
19 been influenced by transition metal ions (e.g., Cu(II), Fe(II)), which are highly spatially
20 variable and could be important catalysts in areas with high concentrations of these ions.
21 Although the global change in O₃ was small (~-0.3%) much larger regional changes were
22 found (e.g., up to -27% at the surface over China).

23 Uptake coefficients for these species vary widely among laboratory studies. [Macintyre](#)
24 [and Evans \(2010\)](#) showed that the sensitivity of key tropospheric species such as O₃
25 varies from very small to significant over the range of uptake coefficients for N₂O₅
26 obtained in laboratory studies. For example, global O₃ loss ranges from 0 to over 10%,
27 with large regional variability over the range of N₂O₅ uptake coefficients reported. In this
28 regard, it should be stressed that knowledge of multiphase processes is still evolving and
29 there are still many questions that remain to be answered. However, it is becoming clear
30 that multiphase processes are important for O₃ chemistry.

31 Reactions of O₃ with monoterpenes have been shown to produce oxidants in the aerosol
32 phase, principally as components of ultrafine particles. [Docherty et al. \(2005\)](#) found
33 evidence for the substantial production of organic hydroperoxides in secondary organic
34 aerosol (SOA) resulting from the reaction of monoterpenes with O₃. Analysis of the SOA
35 formed in their environmental chamber indicated that the SOA consisted mainly of
36 organic hydroperoxides. In particular, they obtained yields of 47% and 85% of organic
37 peroxides from the oxidation of α - and β -pinene. The hydroperoxides then react with

1 aldehydes in particles to form peroxyhemiacetals, which can either rearrange to form
2 other compounds such as alcohols and acids or revert back to the hydroperoxides. The
3 aldehydes are also produced in large measure during the ozonolysis of the monoterpenes.
4 Monoterpenes also react with OH radicals resulting in the production of more
5 lower-molecular-weight products than in the reaction with monoterpenes and O₃. [Bonn et
6 al. \(2004\)](#) estimated that hydroperoxides lead to 63% of global SOA formation from the
7 oxidation of terpenes. The oxidation of anthropogenic aromatic hydrocarbons by OH
8 radicals could also produce organic hydroperoxides in SOA ([Johnson et al., 2004](#)).
9 Recent measurements show that the abundance of oxidized SOA exceeds that of more
10 reduced hydrocarbon like organic aerosol in Pittsburgh ([Zhang et al., 2005](#)) and in about
11 30 other cities across the Northern Hemisphere ([Zhang et al., 2007b](#)). Based on aircraft
12 and ship-based sampling of organic aerosols over coastal waters downwind of
13 northeastern U.S. cities, [de Gouw et al. \(2008\)](#) reported that 40-70% of measured organic
14 mass was water soluble and estimated that approximately 37% of SOA is attributable to
15 aromatic precursors, using PM yields estimated for NO_x-limited conditions. Uncertainties
16 still exist as to the pathways by which the oxidation of isoprene leads to the formation of
17 SOA. [Nozière et al. \(2011\)](#) found that a substantial fraction of 2-methyltetrols are
18 primary in origin, although these species have been widely viewed solely as products of
19 the atmospheric oxidation of isoprene. This finding points to lingering uncertainty in
20 reaction pathways in the oxidation of isoprene and in estimates of the yield of SOA from
21 isoprene oxidation.

22 Reactions of O₃ on the surfaces of particles, in particular those with humic acid like
23 composition, are instrumental in the processing of SOA and the release of
24 low-molecular-weight products such as HCHO ([D'Anna et al., 2009](#)). However, direct
25 reactions of O₃ and atmospheric particles appear to be too slow to represent a major O₃
26 sink in the troposphere ([D'Anna et al., 2009](#)).

3.2.3.1 Indoor Air

27 Except when activities such as photocopying or welding are occurring, the major source
28 of O₃ to indoor air is through infiltration of outdoor air. Reactions involving ambient O₃
29 with NO either from exhaled breath or from gas-fired appliances, surfaces of furnishings
30 and terpenoid compounds from cleaning products, air fresheners and wood products also
31 occur in indoor air as was discussed in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). The
32 previous O₃ review also noted that the ozonolysis of terpenoid compounds could be a
33 substantial source of secondary organic aerosol in the ultrafine size fraction. [Chen et al.
34 \(2011\)](#) examined the formation of secondary organic aerosol from the reaction of O₃ that
35 has infiltrated indoors with terpenoid components of commonly used air fresheners. They

1 focused on the formation and decay of particle bound reactive oxygen species (ROS) and
2 on their chemical properties. They found that the ROS content of samples can be
3 decomposed into fractions that differ in terms of reactivity and volatility; however, the
4 overall ROS content of samples decays and over 90% is lost within a day at room
5 temperature. This result also suggests loss of ROS during sampling periods longer than a
6 couple of hours.

3.2.4 Temperature and Chemical Precursor Relationships

7 As might be expected based on the temperature dependence of many reactions involved
8 in the production and destruction of O₃ and the temperature dependence of emissions
9 processes such as evaporation of hydrocarbon precursors and the emissions of
10 biogenically important precursors such as isoprene, ambient concentrations of O₃ also
11 show temperature dependence. [Bloomer et al. \(2009\)](#) determined the sensitivity of O₃ to
12 temperature at rural sites in the eastern U.S. They found that O₃ increased on average at
13 rural Clean Air Status and Trends Network (CASTNET) sites by ~3.2 ppbv/°C before
14 2002, and after 2002 by ~2.2 ppbv/°C. This change in sensitivity was largely the result of
15 reductions in NO_x emissions from power plants. These results are in accord with model
16 predictions by [Wu et al. \(2008b\)](#) showing that the sensitivity of O₃ to temperature
17 decreases with decreases in precursor emissions. [Rasmussen et al. \(2012\)](#) recently
18 extended the work of [Bloomer et al. \(2009\)](#) to quantify seasonal changes in the sensitivity
19 of O₃ to temperature as well as regional variability (3-6 ppb/°C over the Northeast and
20 mid-Atlantic; 3-4 ppb/°C over the Great Lakes region) and to evaluate the capability of a
21 chemistry-climate model to capture O₃ sensitivity to temperature. However, the
22 associations of O₃ with temperature are not as clear in the West as they might be in the
23 East. For example, sites downwind of Phoenix, AZ showed basically no sensitivity of O₃
24 to temperature ($R^2 = 0.02$) ([U.S. EPA, 2006b](#)). However, [Wise and Comrie \(2005\)](#) did
25 find that meteorological parameters (mixing height and temperature) typically accounts
26 for 40 to 70% of the variability in O₃ in the five southwestern cities (including Phoenix)
27 they examined. It is likely that differences in the nature of sites chosen (urban vs. rural)
28 accounted for this difference and are at least partially responsible for the difference in
29 results. [Jaffe et al. \(2008\)](#) regressed O₃ on temperature at Yellowstone and Rocky
30 Mountain NP and found weak associations ($R^2 = 0.09$ and 0.16). They found that
31 associations with area burned by wildfires are much stronger. Other sources as discussed
32 in Section [3.4](#) might also be more important in the West than in the East.

33 The warmer months of the year are generally regarded as being the most conducive to
34 higher O₃ concentrations. However, [Schnell et al. \(2009\)](#) reported observations of high O₃
35 concentrations (maximum 1-h avg of 140 ppb; maximum 8-h avg of 120 ppb) in the

1 Jonah-Pinedale gas fields in Wyoming during winter at temperatures of -17°C . Potential
2 factors contributing to these anomalously high concentrations include a highly reflective
3 snow surface, emissions of NO_x , hydrocarbons and short-lived radical reservoirs
4 (e.g., HONO and HCHO) and a very shallow, stable boundary layer trapping these
5 emissions close to the surface ([Schnell et al., 2009](#)). Multiphase processes might also be
6 involved in the production of these short-lived reservoirs. At a temperature of -17°C , the
7 production of hydroxyl radicals (by the photolysis of O_3 yielding O^1D followed by the
8 reaction, $\text{O}^1\text{D} + \text{H}_2\text{O}$, needed to initiate hydrocarbon oxidation) is severely limited,
9 suggesting that another source of radicals is needed. Radicals can be produced by the
10 photolysis of molecules such as HONO and HCHO which photolyze in optically thin
11 regions of the solar spectrum. A similar issue, in part due to the under-prediction of
12 radicals, has arisen in the Houston airshed where chemistry-transport models (CTMs;
13 discussed further in Section [3.3](#)) under-predict O_3 ([Olague et al., 2009](#)). [Carter and](#)
14 [Seinfeld \(2012\)](#) modeled several of the events using the SAPRC-07 chemical mechanism
15 and found that the release of HONO from the snow surface aids in the formation of O_3 .
16 The chemical mechanism they used—including the temperature dependence of rate
17 coefficients—was developed for application at higher temperatures. They also note that
18 temperature changes will also affect the distribution of products and radicals formed
19 when individual VOCs react, but the current version of the mechanism represents these
20 by lumped overall processes in which the product and radical distributions are treated as
21 if they are temperature independent. It is not clear how this treatment of radical
22 production might affect their results.

23 Rather than varying directly with emissions of its precursors, O_3 changes in a nonlinear
24 fashion with the concentrations of its precursors. At the low NO_x concentrations found in
25 remote continental areas to rural and suburban areas downwind of urban centers (low-
26 NO_x regime), the net production of O_3 typically increases with increasing NO_x . In the
27 low- NO_x regime, the overall effect of the oxidation of VOCs is to generate (or at least
28 not consume) free radicals, and O_3 production varies directly with NO_x . In the high- NO_x
29 regime, NO_2 scavenges OH radicals which would otherwise oxidize VOCs to produce
30 peroxy radicals, which in turn would oxidize NO to NO_2 . In this regime, O_3 production is
31 limited by the availability of free radicals and O_3 shows only a weak dependence on NO_x
32 concentrations. The production of free radicals is in turn limited by the availability of
33 solar UV radiation capable of photolyzing O_3 (in the Hartley bands) or aldehydes and/or
34 by the abundance of VOCs whose oxidation produce more radicals than they consume.
35 At even higher NO_x concentrations, as found in downtown metropolitan areas, especially
36 near busy streets and roads, and in power plant plumes, there is scavenging (titration) of
37 O_3 by reaction with NO.

1 There are a number of ways to refer to the chemistry in these chemical regimes.
2 Sometimes the terms VOC-limited and NO_x-limited are used. However, there are
3 difficulties with this usage because (1) VOC measurements are not as abundant as they
4 are for nitrogen oxides; (2) rate coefficients for reaction of individual VOCs with radicals
5 (e.g., OH, Cl) vary over an extremely wide range; and (3) consideration is not given to
6 CO nor to reactions that can produce radicals without involving VOCs. The terms NO_x-
7 limited and NO_x-saturated ([Jaegle et al., 2001](#)) will be used wherever possible to more
8 adequately describe these two regimes. However, the terminology used in original
9 articles will also be used here. In addition to these two regimes, there is also a “very low
10 NO_x regime” in the remote marine troposphere in which NO_x concentrations are ~20 ppt
11 or less. Under these very low NO_x conditions, which are not likely to be found in the
12 continental U.S, HO₂ and CH₃O₂ radicals react with each other and HO₂ radicals undergo
13 self-reaction (to form H₂O₂), and OH and HO₂ react with O₃, leading to net destruction of
14 O₃ and inefficient OH radical regeneration by comparison with much higher NO_x
15 concentrations found in polluted areas. In polluted areas, HO₂ and CH₃O₂ radicals react
16 with NO to convert NO to NO₂, regenerate the OH radical, and, through the photolysis of
17 NO₂, produce O₃ as noted in Annex AX2.2.5 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)).
18 There are no sharp transitions between these regimes. For example, in the “low NO_x
19 regime” there still may be appreciable peroxy-peroxy radical reactions depending on the
20 local NO_x concentration. In any case, in all of these NO_x regimes, O₃ production is also
21 limited by the abundance of HO_x radicals.

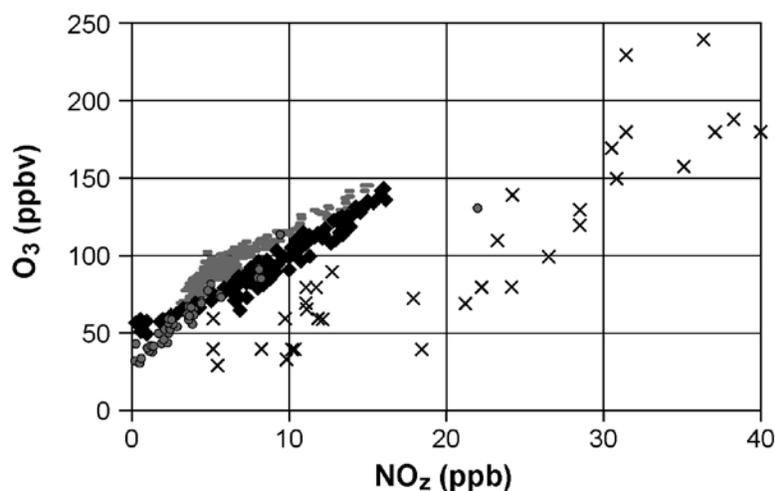
22 The chemistry of OH radicals, which are responsible for initiating the oxidation of
23 hydrocarbons, shows behavior similar to that for O₃ with respect to NO_x concentrations
24 ([Poppe et al., 1993](#); [Zimmermann and Poppe, 1993](#); [Hameed et al., 1979](#)). These
25 considerations introduce a high degree of uncertainty into attempts to relate changes in
26 O₃ concentrations to emissions of precursors. There are no definitive rules governing the
27 concentrations of NO_x at which the transition from NO_x-limited to NO_x-saturated
28 conditions occurs. The transition between these two regimes is highly spatially and
29 temporally dependent and depends also on the nature and abundance of the hydrocarbons
30 that are present.

31 [Trainer et al. \(1993\)](#) and [Olszyna et al. \(1994\)](#) have shown that O₃ and NO_y are highly
32 correlated in rural areas in the eastern U.S. [Trainer et al. \(1993\)](#) also showed that O₃
33 concentrations correlate even better with NO_z than with NO_y, as may be expected
34 because NO_z represents the amount of NO_x that has been oxidized, forming O₃ in the
35 process. NO_z is equal to the difference between measured total reactive nitrogen (NO_y)
36 and NO_x and represents the summed products of the oxidation of NO_x. NO_z is composed
37 mainly of HNO₃, PAN and other organic nitrates, particulate nitrate, and HNO₄. [Trainer](#)
38 [et al. \(1993\)](#) also suggested that the slope of the regression line between O₃ and NO_z can

1 be used to estimate the rate of O₃ production per NO_x oxidized (also known as the O₃
2 production efficiency [OPE]). [Ryerson et al. \(2001\)](#); [Ryerson et al. \(1998\)](#) used measured
3 correlations between O₃ and NO_z to identify different rates of O₃ production in plumes
4 from large point sources. A number of studies in the planetary boundary layer over the
5 continental U.S. have found that the OPE ranges typically from 1 to nearly 10. However,
6 it may be higher in the upper troposphere and in certain areas, such as the Houston-
7 Galveston area in Texas. Observations indicate that the OPE depends mainly on the
8 abundance of NO_x and also on availability of solar UV radiation, VOCs and O₃ itself.

9 Various techniques have been proposed to use ambient NO_x and VOC measurements to
10 derive information about the dependence of O₃ production on their concentrations. For
11 example, it has been suggested that O₃ formation in individual urban areas could be
12 understood in terms of measurements of ambient NO_x and VOC concentrations during
13 the early morning ([NRC, 1991](#)). In this approach, the ratio of summed (unweighted) VOC
14 to NO_x is used to determine whether conditions were NO_x-limited or VOC-limited. This
15 procedure is inadequate because it omits many factors that are important for O₃
16 production such as the impact of biogenic VOCs (which are typically not present in urban
17 centers during early morning); important differences in the ability of individual VOCs to
18 generate radicals (rather than just total VOC) and other differences in O₃ forming
19 potential for individual VOCs ([Carter, 1995](#)); and changes in the VOC to NO_x ratio due
20 to photochemical reactions and deposition as air moves downwind from urban areas
21 ([Milford et al., 1994](#)).

22 Photochemical production of O₃ generally occurs simultaneously with the production of
23 various other species such as HNO₃, organic nitrates, and other oxidants such as
24 hydrogen peroxide. The relative rate of production of O₃ and other species varies
25 depending on photochemical conditions, and can be used to provide information about
26 O₃-precursor sensitivity. [Sillman \(1995\)](#) and [Sillman and He \(2002\)](#) identified several
27 secondary reaction products that show different correlation patterns for NO_x-limited and
28 NO_x-saturated conditions. The most important correlations are for O₃ versus NO_y, O₃
29 versus NO_z, O₃ versus HNO₃, and H₂O₂ versus HNO₃. The correlations between O₃ and
30 NO_y, and O₃ and NO_z are especially important because measurements of NO_y and NO_x
31 are more widely available than for VOCs. Measured O₃ versus NO_z ([Figure 3-3](#)) shows
32 distinctly different patterns in different locations. In rural areas and in urban areas such as
33 Nashville, TN, O₃ is highly correlated with NO_z. By contrast, in Los Angeles, CA, O₃ is
34 not as highly correlated with NO_z, and the rate of increase of O₃ with NO_z is lower and
35 the O₃ concentrations for a given NO_z value are generally lower. The different O₃ versus
36 NO_z relations in Nashville, TN and Los Angeles, CA reflects the difference between
37 NO_x-limited conditions in Nashville versus an approach to NO_x-saturated conditions in
38 Los Angeles.



Note: ($\text{NO}_y - \text{NO}_x$) during the afternoon at rural sites in the eastern U.S. (grey circles) and in urban areas and urban plumes associated with Nashville, TN (gray dashes); Paris, France (black diamonds); and Los Angeles, CA (Xs).
 Source: Adapted with permission of American Geophysical Union, ([Sillman and He, 2002](#); [Sillman et al., 1998](#); [Trainer et al., 1993](#)).

Figure 3-3 Measured concentrations of ozone and NO_z .

1 The difference between NO_x -limited and NO_x -saturated regimes is also reflected in
 2 measurements of H_2O_2 . H_2O_2 production is highly sensitive to the abundance of radicals
 3 and is thus favored in the NO_x -limited regime. Measurements in the rural eastern U.S.
 4 ([Jacob et al., 1995](#)), Nashville, TN ([Sillman et al., 1998](#)), and Los Angeles, CA
 5 ([Sakugawa and Kaplan, 1989](#)), show large differences in H_2O_2 concentrations between
 6 likely NO_x -limited and NO_x -saturated locations.

7 The applications of indicator species mentioned above are limited to individual urban
 8 areas either because they are based on point measurements or by the range of the aircraft
 9 carrying the measurement instruments. Satellites provide a platform for greatly extending
 10 the range of applicability of the indicator technique and also have the resolution
 11 necessary to examine urban to rural differences. [Duncan et al. \(2010\)](#) used satellite data
 12 from Ozone Monitoring Instrument (OMI) for HCHO to NO_2 column ratios to diagnose
 13 NO_x -limited and radical-limited (NO_x -saturated) regimes. HCHO can be used as an
 14 indicator of VOCs as it is a common, short-lived, oxidation product of many VOCs that
 15 is a source of HO_x ([Sillman, 1995](#)). In adopting the satellite approach, CTMs are used to
 16 estimate the fractional abundance of the indicator species in the planetary boundary layer.
 17 [Duncan et al. \(2010\)](#) found that O_3 formation over most of the U.S. became more
 18 sensitive to NO_x over most of the U.S. from 2005 to 2007 largely because of decreases in
 19 NO_x emissions. They also found that surface temperature is correlated with the ratio of

1 HCHO to NO₂ especially in cities in the Southeast where emissions of isoprene (a major
2 source of HCHO) are high due to high temperatures in summer.

3.3 Atmospheric Modeling

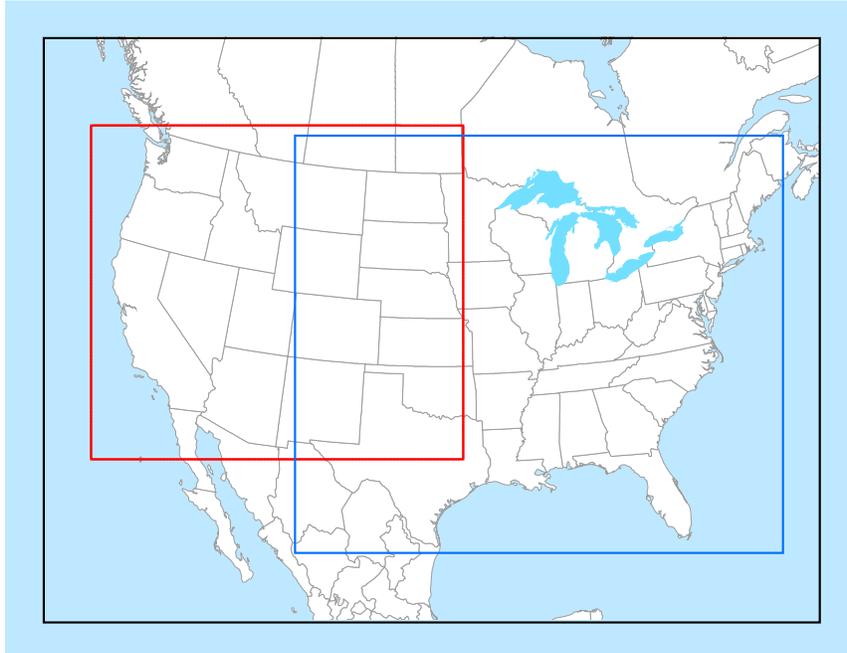
3 CTMs have been widely used to compute the interactions among atmospheric pollutants
4 and their transformation products, and the transport and deposition of pollutants. They
5 have also been widely used to improve basic understanding of atmospheric chemical
6 processes and to develop control strategies. The spatial scales over which pollutant fields
7 are calculated range from intra-urban to regional to global. Generally, these models are
8 applied to problems on different spatial scales but efforts are underway to link across
9 spatial scales for dealing with global scale environmental issues that affect population
10 health within cities. Many features are common to all of these models and hence they
11 share many of the same problems. On the other hand, there are appreciable differences in
12 approaches to parameterizing physical and chemical processes that must be addressed in
13 applying these models across spatial scales.

14 CTMs solve a set of coupled, non-linear partial differential equations, or continuity
15 equations, for relevant chemical species. [Jacobson \(2005\)](#) described the governing partial
16 differential equations, and the methods that are used to solve them. Because of limitations
17 imposed by the complexity and spatial-temporal scales of relevant physical and chemical
18 processes, the CTMs must include parameterizations of these processes, which include
19 atmospheric transport; the transfer of solar radiation through the atmosphere; chemical
20 reactions; and removal to the surface by turbulent motions and precipitation.

21 Development of parameterizations for use in CTMs requires data for three dimensional
22 wind fields, temperatures, humidity, cloudiness, and solar radiation; emissions data for
23 primary (i.e., directly emitted from sources) species such as NO_x, SO₂, NH₃, VOCs, and
24 primary PM; and chemical reactions.

25 The domains of CTMs extend from a few hundred kilometers on a side to the entire
26 globe. Most major regional (i.e., sub-continental) scale air-related modeling efforts at
27 EPA rely on the Community Multi-scale Air Quality (CMAQ) modeling system ([Byun
28 and Schere, 2006](#); [Byun and Ching, 1999](#)). CMAQ's horizontal domain typically extends
29 over North America with efforts underway to extend it over the entire Northern
30 Hemisphere. Note that CTMs can be 'nested' within each other as shown in [Figure 3-4](#)
31 which shows domains for CMAQ (Version 4.6.1); additional details on the model
32 configuration and application are found elsewhere ([U.S. EPA, 2009e](#)). The figure shows
33 the outer domain (36 km horizontal grid spacing) and two 12 km spatial resolution (east
34 and west) sub-domains. The upper boundary for CMAQ is typically set at about 100 hPa,

1 or at about 16 km altitude on average, although in some recent applications the upper
2 boundary has been set at 50 hPa. These domains and grid spacings are quite common and
3 can also be found in a number of other models.



Note: Figure depicts a 36 km grid-spacing outer parent domain in black; 12 km western U.S. domain in red; 12 km eastern U.S. domain in blue.

Figure 3-4 Sample Community Multi-scale Air Quality (CMAQ) modeling domains.

4 The main components of a CTM such as EPA’s CMAQ are summarized in [Figure 3-5](#).
5 The capabilities of a number of CTMs designed to study local- and regional-scale air
6 pollution problems were summarized by [Russell and Dennis \(2000\)](#) and in the 2006 O₃
7 AQCD ([U.S. EPA, 2006b](#)). Historically, CMAQ has been driven most often by the MM5
8 mesoscale meteorological model ([Seaman, 2000](#)), though it could be driven by other
9 meteorological models including the Weather Research and Forecasting (WRF) model
10 and the Regional Atmospheric Modeling System (RAMS) ([ATMET, 2011](#)).

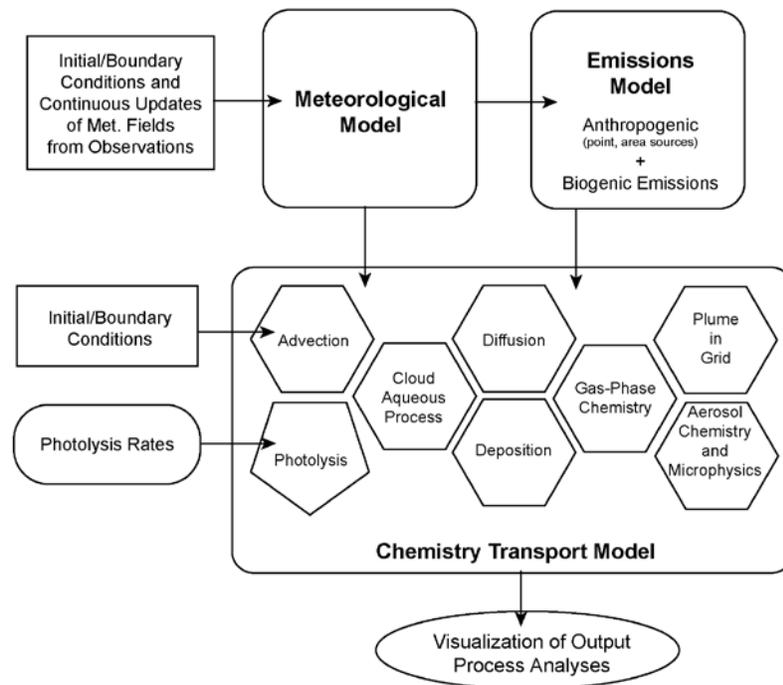


Figure 3-5 Main components of a comprehensive atmospheric chemistry modeling system, such as the U.S. EPA’s Community Multi-scale Air Quality (CMAQ) modeling system.

1 Simulations of pollution episodes over regional domains have been performed with a
 2 horizontal resolution down to 1 km; see the application and general survey results
 3 reported in [Ching et al. \(2006\)](#). However, simulations at such high resolution require
 4 better parameterizations of meteorological processes such as boundary layer fluxes, deep
 5 convection, and clouds ([Seaman, 2000](#)). Finer spatial resolution is necessary to resolve
 6 features such as urban heat island circulation; sea, bay, and land breezes; mountain and
 7 valley breezes; and the nocturnal low-level jet; all of which can affect pollutant
 8 concentrations. Other major air quality systems used for regional scale applications
 9 include the Comprehensive Air Quality Model with extensions (CAMx) ([ENVIRON,](#)
 10 [2005](#)) and the Weather Research and Forecast model with Chemistry (WRF/Chem)
 11 ([NOAA, 2010](#)).

12 CMAQ and other grid-based or Eulerian air quality models subdivide the modeling
 13 domain into a three-dimensional array of grid cells. The most common approach to
 14 setting up the horizontal domain is to nest a finer grid within a larger domain of coarser
 15 resolution. The use of finer horizontal resolution in CTMs will necessitate finer-scale
 16 inventories of land use and better knowledge of the exact paths of roads, locations of
 17 factories, and, in general, better methods for locating sources and estimating their

1 emissions. The vertical resolution of CTMs is variable and usually configured to have
2 more layers in the PBL and fewer in the free troposphere.

3 The meteorological fields are produced either by other numerical prediction models such
4 as those used for weather forecasting (e.g., MM5, WRF), and/or by assimilation of
5 satellite data. The flow of information shown in [Figure 3-5](#) has most often been
6 unidirectional in the sense that information flows into the CTM (large box) from outside;
7 feedbacks on the meteorological fields and on boundary conditions (i.e., out of the box)
8 have not been included. However, CTMs now have the capability to consider these
9 feedbacks as well; see, for example, [Binkowski et al. \(2007\)](#) and WRF/Chem ([NOAA,](#)
10 [2010](#)).

11 Because of the large number of chemical species and reactions that are involved in the
12 oxidation of realistic mixtures of anthropogenic and biogenic hydrocarbons, condensed
13 mechanisms must be used in atmospheric models. These mechanisms can be tested by
14 comparison with smog chamber data. However, the existing chemical mechanisms often
15 neglect many important processes such as the formation and subsequent reactions of
16 long-lived carbonyl compounds, the incorporation of the most recent information about
17 intermediate compounds, and heterogeneous reactions involving cloud droplets and
18 aerosol particles. To the extent that information is available, models like CMAQ and
19 CAMx do include state-of-the-science parameterization for some of these processes such
20 as heterogeneous N₂O₅ chemistry.

21 The initial conditions, or starting concentration fields of all species computed by a model,
22 and the boundary conditions, or concentrations of species along the horizontal and upper
23 boundaries of the model domain throughout the simulation, must be specified at the
24 beginning of the simulation. Both initial and boundary conditions can be estimated from
25 models or data or, more generally, model plus data hybrids. Because data for vertical
26 profiles of most species of interest are very sparse, results of model simulations over
27 larger, usually global, domains are often used.

28 Chemical kinetics mechanisms representing the important reactions occurring in the
29 atmosphere are used in CTMs to estimate the rates of chemical formation and destruction
30 of each pollutant simulated as a function of time. The Master Chemical Mechanism
31 (MCM) ([Univ of Leeds, 2010](#)) is a comprehensive reaction database providing as near an
32 explicit treatment of chemical reactions in the troposphere as is possible. The MCM
33 currently includes over 12,600 reactions and 4,500 species. However, mechanisms that
34 are this comprehensive are still computationally too demanding to be incorporated into
35 CTMs for regulatory use. Simpler treatments of tropospheric chemistry have been
36 assembled by combining chemical species into mechanisms that group together
37 compounds with similar chemistry. It should be noted that because of different

1 approaches to the lumping of organic compounds into surrogate groups for computational
2 efficiency, chemical mechanisms can produce different results under similar conditions.
3 [Jimenez et al. \(2003\)](#) briefly described the features of the seven main chemical
4 mechanisms in use and compared concentrations of several key species predicted by
5 these mechanisms in a box-model simulation over 24 hours. Several of these mechanisms
6 have been incorporated into CMAQ including extensions of the Carbon Bond (CB)
7 mechanism ([Luecken et al., 2008](#)), SAPRC ([Luecken et al., 2008](#)), and the Regional
8 Atmospheric Chemistry Mechanism, version 2 (RACM2) ([Fuentes et al., 2007](#)). The CB
9 mechanism is currently undergoing extension (CB06) to include, among other things,
10 longer lived species to better simulate chemistry in the remote and upper troposphere.
11 These mechanisms were developed primarily for homogeneous gas phase reactions and
12 treat multiphase chemical reactions in a very cursory manner, if at all. As a consequence
13 of neglecting multiphase chemical reactions, models such as CMAQ could have
14 difficulties capturing the regional nature of O₃ episodes, in part because of uncertainty in
15 the chemical pathways converting NO_x to HNO₃ and recycling of NO_x ([Godowitch et al.,
16 2008](#); [Hains et al., 2008](#)). Much of this uncertainty also involves multiphase processes as
17 described in Section [3.2.3](#).

18 CMAQ and other CTMs incorporate processes and interactions of aerosol-phase
19 chemistry ([Zhang and Wexler, 2008](#); [Gaydos et al., 2007](#); [Binkowski and Roselle, 2003](#)).
20 There have also been several attempts to study the feedbacks of chemistry on
21 atmospheric dynamics using meteorological models like MM5 and WRF ([Liu et al.,
22 2001](#); [Park et al., 2001](#); [Grell et al., 2000](#); [Lu et al., 1997](#)). This coupling is necessary to
23 accurately simulate feedbacks from PM ([Park et al., 2001](#); [Lu et al., 1997](#)) over areas
24 such as Los Angeles or the Mid-Atlantic region. Photolysis rates in CMAQ can now be
25 calculated interactively with model produced O₃, NO₂, and aerosol fields ([Binkowski et
26 al., 2007](#)).

27 Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions
28 can be specified as inputs to a CTM or these emissions can be calculated in-line in
29 CMAQ. Emissions inventories have been compiled on grids of varying resolution for
30 many hydrocarbons, aldehydes, ketones, CO, NH₃, and NO_x. Preprocessing of emissions
31 data for CMAQ is done by the Spare-Matrix Operator Kernel Emissions (SMOKE)
32 system ([UNC, 2011](#)). For many species, information on temporal variability of emissions
33 is lacking, so long-term annual averages are used in short-term, episodic simulations.
34 Annual emissions estimates can be modified by the model to produce emissions more
35 characteristic of the time of day and season. Appreciable errors in emissions can occur if
36 inappropriate time dependence is applied.

1 Each of the model components described above has associated uncertainties; and the
2 relative importance of these uncertainties varies with the modeling application. Large
3 errors in photochemical modeling arise from the meteorological, chemical and emissions
4 inputs to the model ([Russell and Dennis, 2000](#)). While the effects of poorly specified
5 boundary conditions propagate through the model's domain, the effects of these errors
6 remain undetermined. Because many meteorological processes occur on spatial scales
7 smaller than the model's vertical or horizontal grid spacing and thus are not calculated
8 explicitly, parameterizations of these processes must be used. These parameterizations
9 introduce additional uncertainty.

10 The performance of CTMs must be evaluated by comparison with field data as part of a
11 cycle of model evaluations and subsequent improvements ([NRC, 2007](#)). However, they
12 are too computationally demanding to have the full range of their sensitivities examined
13 using Monte Carlo techniques ([NRC, 2007](#)). Models of this complexity are evaluated by
14 comparison with field observations for O₃ and other species. Evaluations of the
15 performance of CMAQ are given in [Arnold et al. \(2003\)](#), [Eder and Yu \(2005\)](#), [Appel et
16 al. \(2005\)](#), and [Fuentes and Raftery \(2005\)](#). Discrepancies between model predictions and
17 observations can be used to point out gaps in current understanding of atmospheric
18 chemistry and to spur improvements in parameterizations of atmospheric chemical and
19 physical processes. Model evaluation does not merely involve a straightforward
20 comparison between model predictions and the concentration field of the pollutant of
21 interest. Such comparisons may not be meaningful because it is difficult to determine if
22 agreement between model predictions and observations truly represents an accurate
23 treatment of physical and chemical processes in the CTM or the effects of compensating
24 errors in complex model routines (in other words, it is important to know if the right
25 answer is obtained for the right reasons). Each of the model components (emissions
26 inventories, chemical mechanism, and meteorological driver) should be evaluated
27 individually as has been done to large extent in some major field studies such as TexAQ
28 I and II and CalNex. Comparisons of correlations between measured and modeled VOCs
29 and NO_x are useful for evaluating results from CTMs and can provide information about
30 the chemical state of the atmosphere. A CTM that accurately computes both VOC and
31 NO_x along with the spatial and temporal relations among the critical secondary species
32 associated with O₃ has a higher probability of representing O₃-precursor relations
33 correctly than one that does not.

34 The above evaluation techniques are sometimes referred to as "static" in the sense that
35 individual model variables are compared to observations. It is also crucial to understand
36 the dynamic response to changes in inputs and to compare the model responses to those
37 that are observed. These tests might involve changes in some natural forcing or in
38 emissions from an anthropogenic source. As an example, techniques such as the direct

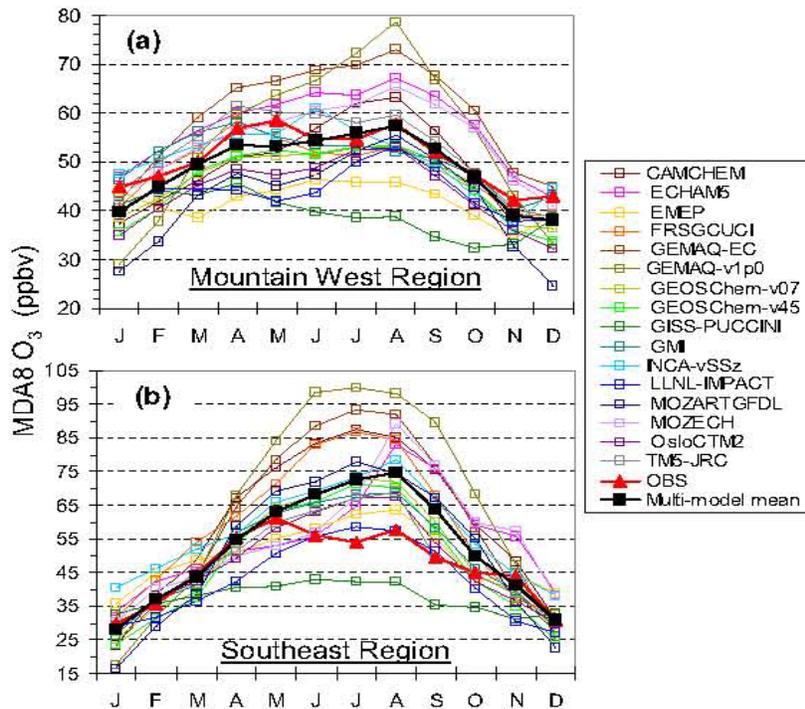
1 decoupled method (DDM) ([Dunker et al., 2002](#); [Dunker, 1981](#)) could be used. However,
2 the observational basis for comparing a model's response is largely unavailable for many
3 problems of interest, in large part because meteorological conditions are also changing
4 while the emissions are changing. As a result, methods such as DDM are used mainly to
5 address the effectiveness of emissions controls.

3.3.1 Global Scale CTMs

6 With recognition of the global nature of many air pollution problems, global scale CTMs
7 have been applied to regional scale pollution problems ([NRC, 2009](#)). Global-scale CTMs
8 are used to address issues associated with global change, to characterize long-range
9 transport of air pollutants, and to provide boundary conditions for the regional-scale
10 models. The upper boundaries of global scale CTMs extend anywhere from the
11 tropopause (~8 km at the poles to ~16 km in the tropics) to the mesopause at ~80 km, in
12 order to obtain more realistic boundary conditions for problems involving stratospheric
13 dynamics and chemistry. The global-scale CTMs consider the same processes shown in
14 [Figure 3-5](#) for the regional scale models. In addition, many of the same issues that have
15 arisen for the regional models have also arisen for the global scale models ([Emmerson
16 and Evans, 2009](#)). For example, after adjusting lightning NO_x to better match observed
17 constraints in the MOZART-4 model, simulated HNO₃ was too low and PAN too high in
18 the mid-troposphere, though observations were captured in the upper troposphere, over
19 the U.S. during summer 2004 in the MOZART-4 model ([Fang et al., 2010](#)). In contrast,
20 summer 2004 simulations with improved lightning NO_x in GEOS-Chem indicate that
21 PAN is too low but HNO₃ is overestimated throughout the mid- and upper troposphere
22 ([Hudman et al., 2007](#)). Predictions of HNO₃ were too high and PAN too low over the
23 U.S. during summer in the MOZART model ([Fang et al., 2010](#)). Similar findings were
24 obtained in a box model of upper tropospheric chemistry ([Henderson et al., 2011](#)),
25 indicating a need for improved constraints on processes controlling NO_y distributions in
26 the free troposphere.

27 The GEOS-Chem model is a community-owned, global scale CTM that has been widely
28 used to study issues associated with the hemispheric transport of pollution and global
29 change ([Harvard University, 2010a](#)). Comparisons of the capabilities of GEOS-Chem and
30 several other models to simulate intra-hemispheric transport of pollutants are given in a
31 number of articles ([Fiore et al., 2009](#); [Reidmiller et al., 2009](#)). [Reidmiller et al. \(2009\)](#)
32 compared 18 global models and their ensemble average to spatially and monthly
33 averaged observations of O₃ at CASTNET sites in the U.S. (see [Figure 3-6](#)). These results
34 show that the multi-model ensemble agrees much better with observations than do most
35 of the individual models. The GEOS-Chem model was run for two grid spacings

1 (4° × 4.5° and 2° × 2.5°) over the U.S. with very similar results that lie close to the
2 ensemble average. In general, the model ensemble mean and the two GEOS-Chem
3 simulations are much closer to observations in the Intermountain West than in the
4 Southeast during summer, when most major O₃ episodes occur (Note, though, that more
5 current versions of GEOS-Chem are now in use.) However, there are also sizable over-
6 predictions by many models in both regions during summer.



Source: Reprinted with permission of Copernicus Publications, ([Reidmiller et al., 2009](#)).

Figure 3-6 Comparison of global chemical-transport model (CTM) predictions of maximum daily 8-h avg ozone concentrations and multi-model mean with monthly averaged CASTNET observations in the Intermountain West and Southeast regions of the U.S.

7 In their review, [McDonald-Buller et al. \(2011\)](#) noted that global scale chemical transport
8 models exhibit biases in monthly mean daily maximum 8-h avg (MDA8) O₃ in some
9 regions of the U.S., including the Gulf Coast, regions affected by fires, and regions with
10 complex topography, which have implications for model estimates of background O₃; and
11 they also have difficulty representing the fine structures of O₃ events at sub-grid scales at

1 relatively remote monitoring sites that include contributions to O₃ from background
2 sources.

3 Global models are not alone in overestimating O₃ in the Southeast. [Godowitch et al.](#)
4 [\(2008\)](#), [Gilliland et al. \(2008\)](#) and [Nolte et al. \(2008\)](#) found positive O₃ biases in regional
5 models over the eastern U.S., as well, which they largely attributed to uncertainties in
6 temperature, relative humidity and planetary boundary layer height. Agreement between
7 monthly average values is expected to be better than with daily values because of a
8 number of factors including the increasing uncertainty of emissions at finer time
9 resolution. [Kasibhatla and Chameides \(2000\)](#) found that the accuracy of simulations
10 improved as the averaging time of both the simulation and the observations increased.

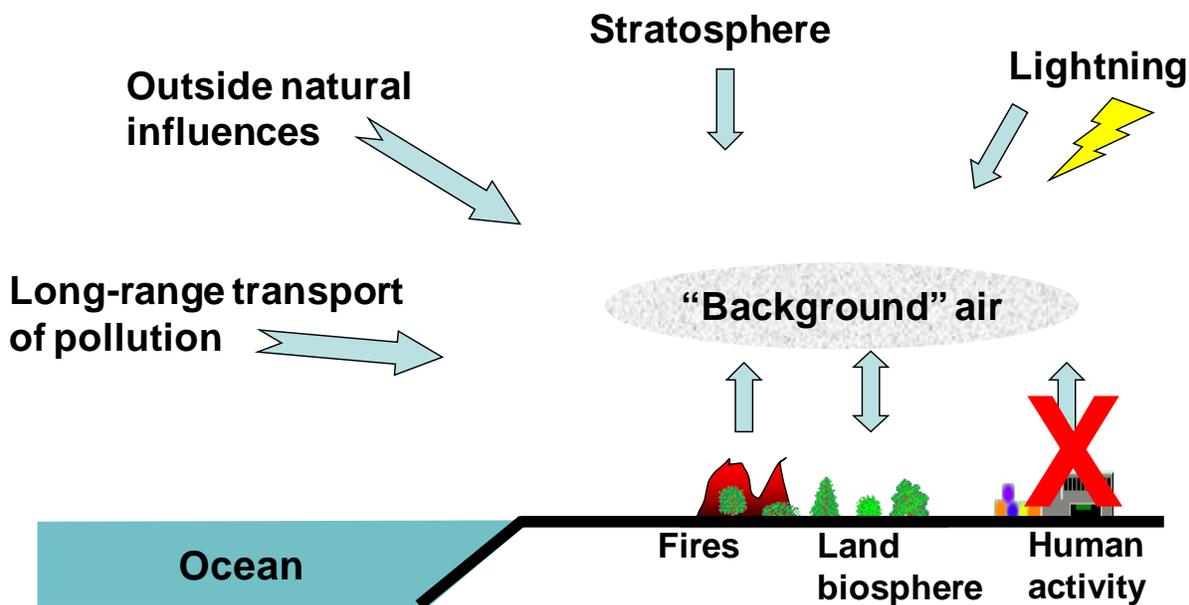
11 Simulations of the effects of long-range transport at particular locations must be able to
12 link multiple horizontal resolutions from the global to the local scale. Because of
13 computational limitations, global simulations are not made at the same horizontal
14 resolutions found in the regional scale models, i.e., down to 1-4 km² horizontal
15 resolution. They are typically conducted with a horizontal grid spacing of 1°-2° of latitude
16 and longitude (or roughly 100-200 km at mid-latitudes). Some models such as GEOS-
17 Chem have the capability to include nested models at a resolution of 0.5° × 0.667° ([Wang](#)
18 [et al., 2009a](#)) and efforts are underway to achieve even higher spatial resolution. Another
19 approach is to nest regional models within GEOS-Chem. Caution must be exercised with
20 nesting different models because of differences in chemical mechanisms and numerical
21 schemes, and in boundary conditions between the outer and inner models. As an example
22 of these issues, surface O₃ concentrations that are too high have been observed in models
23 in which CMAQ was nested inside of GEOS-Chem. The high O₃ results in large measure
24 from stratospheric O₃ intruding into the CMAQ domain (see [Lam and Fu, 2010](#)) for one
25 way to address this issue). Large vertical O₃ gradients in the upper troposphere must be
26 preserved to accurately represent downward transport of stratospheric O₃. This
27 complicates efforts to link global and regional models with different vertical grid spacing.
28 Efforts are also underway to extend the domain of CMAQ over the entire Northern
29 Hemisphere. In this approach, the same numerical schemes are used for transporting
30 species and the same chemistry is used throughout all spatial scales. Finer resolution in
31 models of any scale can only improve scientific understanding to the extent that the
32 governing processes are accurately described. Consequently, there is a crucial need for
33 observations at the appropriate scales to evaluate the scientific understanding represented
34 by the models.

3.4 Background Ozone Concentrations

1 Background concentrations of O₃ have been given various definitions in the literature
2 over time. An understanding of the sources and contributions of background O₃ to
3 O₃ concentrations in the U.S. is potentially useful in reviewing the O₃ NAAQS,
4 especially related to days at the upper end of the distribution of O₃ concentrations. In the
5 context of a review of the NAAQS, it is useful to define background O₃ concentrations in
6 a way that distinguishes between concentrations that result from precursor emissions that
7 are relatively less controllable from those that are relatively more controllable through
8 U.S. policies. In previous NAAQS reviews, a specific definition of background
9 concentrations was used and referred to as policy relevant background (PRB). In those
10 previous reviews, PRB concentrations were defined by EPA as those concentrations that
11 would occur in the U.S. in the absence of anthropogenic emissions in continental North
12 America (CNA), defined here as the U.S., Canada, and Mexico. There is no chemical
13 difference between background O₃ and O₃ attributable to CNA anthropogenic sources.
14 However, to inform policy considerations regarding the current or potential alternative
15 standards, it is useful to understand how total O₃ concentrations can be attributed to
16 different sources.

17 For this document, EPA has considered background O₃ concentrations more broadly by
18 considering three different definitions of background. The first is natural background
19 which includes contributions resulting from emissions from natural sources
20 (e.g., stratospheric intrusion, wildfires, biogenic methane and more short-lived VOC
21 emissions) throughout the globe simulated in the absence of all anthropogenic emissions.
22 The second is North American background (NA background) which includes
23 contributions from natural background throughout the globe and emissions of
24 anthropogenic pollutants contributing to global concentrations of O₃ (e.g., anthropogenic
25 methane) from countries outside North America. The third is United States background
26 (U.S. background) which includes contributions from natural background throughout the
27 globe and emissions from anthropogenic pollutants contributing to global concentrations
28 of O₃ from countries outside the U.S. U.S. background differs from NA background in
29 that it includes anthropogenic emissions from neighboring Canada and Mexico. These
30 three definitions have been explored in recent literature and are discussed further below.

31 Sources included in the definitions of NA background and U.S. background O₃ are shown
32 schematically in [Figure 3-7](#). Definitions of background and approaches to derive
33 background concentrations were reviewed in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) and
34 in [Reid et al. \(2008\)](#). Further detail about the processes involved in these sources is given
35 in Section [3.4.1](#) and Section [3.4.2](#) and application to models calculating background
36 concentrations is presented in Section [3.4.3](#).



Note: Background concentrations are ozone concentrations that would exist in the absence of anthropogenic emissions from the U.S., Canada, and Mexico. United States background is similarly defined, but includes transport from Canada and Mexico in addition to intercontinental transport.

Figure 3-7 Schematic overview of contributions to North American background concentrations of ozone.

3.4.1 Contributions from Natural Sources

1 Natural sources contributing to background O₃ include the stratospheric-tropospheric
 2 exchange (STE) of O₃ and photochemical reactions involving natural O₃ precursor
 3 emissions of VOCs, NO_x, and CO. Natural sources of O₃ precursors include biogenic
 4 emissions, wildfires, and lightning. Biogenic emissions from agricultural activities in
 5 CNA (or the U.S.) are not considered in the formation of NA (or U.S.) background O₃.
 6 Contributions from natural sources are an important component of background
 7 concentrations and are discussed in greater detail below.

3.4.1.1 Contributions from the Stratosphere

8 The basic atmospheric dynamics and thermodynamics of STE were outlined in the 2006
 9 O₃ AQCD ([U.S. EPA, 2006b](#)); as noted there, stratospheric air rich in O₃ is transported
 10 into the troposphere. Ozone is produced naturally by photochemical reactions in the
 11 stratosphere as shown in [Figure 3-1](#). Some of this O₃ is transported downward into the
 12 troposphere throughout the year, with maximum contributions at mid-latitudes during late

1 winter and early spring mainly coming from a process known as tropopause folding.
2 These folds occur behind most cold fronts, bringing stratospheric air with them. The
3 tropopause should not be interpreted as a material surface through which there is no
4 exchange. Rather these folds should be thought of as regions in which mixing of
5 tropospheric and stratospheric air is occurring ([Shapiro, 1980](#)). This imported
6 stratospheric air contributes to the natural background of O₃ in the troposphere, especially
7 in the free troposphere during winter and spring. STE also occurs during other seasons
8 including summer.

9 Methods for estimating the contribution of stratospheric intrusions rely on the use of
10 tracers of stratospheric origin that can be either dynamical or chemical. [Thompson et al.](#)
11 [\(2007\)](#) found that roughly 20-25% of tropospheric O₃ over northeastern North America
12 during July-August 2004 was of stratospheric origin based on an analysis of ozonesonde
13 data. This O₃ can be mixed into the PBL where it can either be destroyed or transported
14 to the surface. They relied on the combined use of low relative humidity and high
15 (isentropic) potential vorticity (PV) (>2 PV units) to identify stratospheric contributions.
16 PV has been a widely used tracer for stratospheric air; see the 2006 O₃ AQCD ([U.S.](#)
17 [EPA, 2006b](#)). [Lefohn et al. \(2011\)](#) used these and additional criteria to assess
18 stratospheric influence on sites in the Intermountain West and in the Northern Tier.
19 Additional criteria include consideration of trajectories originating at altitudes above the
20 380 K potential temperature surface with a residence time requirement at these heights.
21 Based on these criteria, they identified likely stratospheric influence at the surface sites
22 on a number of days during spring of 2006 to 2008. However, they noted that their
23 analysis of stratospheric intrusions captures only the frequency and vertical penetration of
24 the intrusions but does not provide information about the contribution of the intrusions to
25 the measured O₃ concentration. These results are all generally consistent with what was
26 noted in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). [Fischer \(2004\)](#) analyzed the O₃ record
27 during summer at Mount Washington and identified a stratospheric contribution to 5% of
28 events during the summers of 1998 -2003 when O₃ was >65 ppb; the air was dry and
29 trajectories originated from altitudes where PV was elevated (PV >1 PV unit). However,
30 this analysis did not quantify the relative contributions of anthropogenic and stratospheric
31 O₃ sources, because as they note identifying stratospheric influences is complicated by
32 transport over industrialized/urban source regions. Stratospheric O₃ was hypothesized to
33 influence the summit during conditions also potentially conducive to photochemical O₃
34 production, which make any relative contribution calculations difficult without additional
35 measurements of anthropogenic and stratospheric tracers.

36 Although most research has been conducted on tropopause folding as a source of
37 stratosphere to troposphere exchange, this is not the only mechanisms by which
38 stratospheric O₃ can be brought to lower altitudes. [Tang et al. \(2011\)](#) estimated that deep

1 convection capable of penetrating the tropopause can increase the overall downward flux
2 of O₃ by ~20%. This mechanism operates mainly during summer in contrast with
3 tropopause folding which is at a maximum from late winter through spring and at lower
4 latitudes. [Yang et al. \(2010\)](#) estimated that roughly 20% of free tropospheric O₃ above
5 coastal California in 2005 and 2006 was stratospheric in origin. Some of this O₃ could
6 also contribute to O₃ at the surface.

7 It should be noted that there is considerable uncertainty in the magnitude and distribution
8 of this potentially important source of tropospheric O₃. Stratospheric intrusions that reach
9 the surface are much less frequent than intrusions which penetrate only to the middle and
10 upper troposphere. However, O₃ transported to the upper and middle troposphere can still
11 affect surface concentrations through various exchange mechanisms that mix air from the
12 free troposphere with air in the PBL.

13 Several instances of STE producing high concentrations of O₃ around Denver and
14 Boulder, CO were analyzed by [Langford et al. \(2009\)](#) and several likely instances of
15 STE, including one of the cases analyzed by [Langford et al. \(2009\)](#) were also cited in
16 Annex AX2-3 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). Clear examples of STE have
17 also been observed in southern Quebec province by [Hocking et al. \(2007\)](#), in accord with
18 previous estimates by [Wernli and Bourqui \(2002\)](#) and [James et al. \(2003\)](#). As also noted
19 in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)), the identification of stratospheric O₃ and the
20 calculation of its contributions to ambient air requires data for other tracers of
21 stratospheric origin. In some cases, stratospheric ozone intrusions can be identified based
22 on measurements of low relative humidity, high potential vorticity and low ratios of
23 O₃/PM. Strong stratospheric ozone intrusion events that typically occur during winter or
24 spring have been readily identified using these types of data ([Langford et al., 2009](#)).
25 However, it remains challenging to accurately estimate the contributions from smaller
26 direct or indirect (i.e., resulting from shallow intrusions into the mid and upper
27 troposphere that are then mixed downward into the planetary boundary layer)
28 contributions of stratospheric ozone to ambient air.

3.4.1.2 Contributions from Other Natural Sources

29 Biomass burning consists of wildfires and the intentional burning of vegetation to clear
30 new land for agriculture and for population resettlement; to control the growth of
31 unwanted plants on pasture land; to manage forest resources with prescribed burning; to
32 dispose of agricultural and domestic waste; and as fuel for cooking, heating, and water
33 sterilization. Biomass burning also exhibits strong seasonality and interannual variability
34 ([van der Werf et al., 2006](#)), with most biomass burned during the local dry season. This is

1 true for both prescribed burns and wildfires. Globally, most wildfires may be ignited
2 directly as the result of human activities, leaving only 10-30% initiated by lightning
3 ([Andreae, 1991](#)). However, because fire management practices suppress natural wildfires,
4 the buildup of fire fuels increases the susceptibility of forests to more severe but less
5 frequent fires. Thus there is considerable uncertainty in attributing the fraction of wildfire
6 emissions to human activities because the emissions from naturally occurring fires that
7 would have been present in the absence of fire suppression practices are not known.
8 Contributions to NO_x, CO and VOCs from wildfires and prescribed fires are considered
9 as precursors to background O₃ formation in this assessment.

10 Estimating contributions from wildfires is subject to considerable uncertainty.
11 [McDonald-Buller et al. \(2011\)](#) note that “Models generally find little O₃ production in
12 wildfire plumes for short aging times (days) because NO_x emissions are low and
13 conversion to peroxyacetylnitrate (PAN) is rapid. In contrast, observations show large O₃
14 production from at least some regional wildfires that may significantly elevate O₃ at low
15 altitude sites on a monthly basis, and persist over long distances from the burned region.”
16 They also note that fire plumes transported on intercontinental scales can contain very
17 high O₃ concentrations. However [Singh et al. \(2010b\)](#) found appreciable increases of O₃
18 in California fire plumes only when they are mixed with urban pollution. [Jaffe and](#)
19 [Wigder \(2012\)](#) note that this result could have also been due to suppression of O₃
20 production near the source. Factors such as the stage of combustion (smoldering to
21 flaming), fuel nitrogen content, ambient meteorological conditions, and the availability of
22 solar ultraviolet radiation need to be considered when evaluating the potential of fires for
23 producing O₃.

24 [Jaffe et al. \(2008\)](#) examined the effects of wildfires on O₃ in the western U.S. They found
25 a strong relation ($R^2 = 0.60$) between summer mean O₃ measured at various national park
26 and CASTNET sites and area burned in the western U.S. They also found generally
27 higher concentrations within surrounding 5° × 5° and 10° × 10° of burned areas. Smaller
28 correlations were found within the surrounding 1° × 1° areas, reflecting near source
29 consumption of O₃ and the time necessary for photochemical processing of emissions to
30 form O₃. [Jaffe et al. \(2008\)](#) estimate that burning 1 million acres in the western U.S.
31 during summer results in an increase in O₃ of 2 ppb across the region; this translates to an
32 average O₃ increase across the entire western U.S. of 3.5 and 8.8 ppb during mean and
33 maximum fire years. The unusually warm and dry weather in central Alaska and western
34 Yukon in the summer of 2004 contributed to the burning of 11 million acres there.
35 Subsequent modeling by [Pfister et al. \(2005\)](#) showed that the CO contribution from these
36 fires in July 2004 was 33.1 (± 5.5) MT that summer, roughly comparable to total U.S.
37 anthropogenic CO emissions during the same period.

1 These results underscore the importance of wildfires as a source of important O₃
2 precursors. In addition to emissions from forest fires in the U.S., emissions from forest
3 fires in other countries can be transported to the U.S., for example from boreal forest fires
4 in Canada ([Mathur, 2008](#)), Siberia ([Generoso et al., 2007](#)) and tropical forest fires in the
5 Yucatan Peninsula and Central America ([Wang et al., 2006](#)). These fires have all resulted
6 in notable increases in O₃ concentrations in the U.S.

7 Estimates of biogenic VOC, NO and CO emissions can be made using the BEIS model
8 with data from the BELD and annual meteorological data or MEGAN. VOC emissions
9 from vegetation were described in Section [3.2](#).

10 As discussed in Section [3.2.1](#), NO_x is produced by lightning. [Kaynak et al. \(2008\)](#) found
11 lightning contributes 2 to 3 ppb to surface-level background O₃ centered mainly over the
12 southeastern U.S. during summer. Although total column estimates of lightning produced
13 NO_x are large compared to anthropogenic NO_x during summer, lightning produced NO_x
14 does not contribute substantially to the NO_x burden in the continental boundary layer.
15 For example, ([Fang et al., 2010](#)) estimated that only 2% of NO_x production by lightning
16 occurs within the boundary layer and most occurs in the free troposphere. In addition,
17 much of the NO_x produced in the free troposphere is converted to more oxidized
18 N species during downward transport. Note that contributions of natural sources to North
19 American background arise from everywhere in the world.

3.4.2 Contributions from Anthropogenic Emissions

20 In addition to emissions from North America, anthropogenic emissions from Eurasia
21 have contributed to the global burden of O₃ in the atmosphere and to the U.S. ([NRC,](#)
22 [2009, and references therein](#)). Because the mean tropospheric lifetime of O₃ is on the
23 order of a few weeks ([Hsu and Prather, 2009](#)), O₃ can be transported from continent to
24 continent and around the globe in the Northern Hemisphere. Ozone produced by U.S.
25 emissions can, therefore, be recirculated around northern mid-latitudes back to the U.S.
26 High elevation sites are most susceptible to the intercontinental transport of pollution
27 especially during spring. For example, a number of occurrences of O₃>60 ppb from mid-
28 April to mid-May of 2006 were observed at Mt. Bachelor Observatory, OR (elevation
29 2,700 m) with a maximum O₃ concentration of ~85 ppb observed on April 22, 2006.
30 Calculations using GEOS-Chem, a global-scale CTM, indicate that Asia contributed
31 9 ± 3 ppb to a modeled mean concentration of 53 ± 9 ppb O₃ at Mt. Bachelor during the
32 same period compared to measured concentrations of 54 ± 10 ppb ([Zhang et al., 2008](#)).
33 [Zhang et al. \(2008\)](#) also calculated a contribution of 5 to 7 ppb to surface O₃ over the
34 western U.S. during that period from Asian anthropogenic emissions. They also estimated

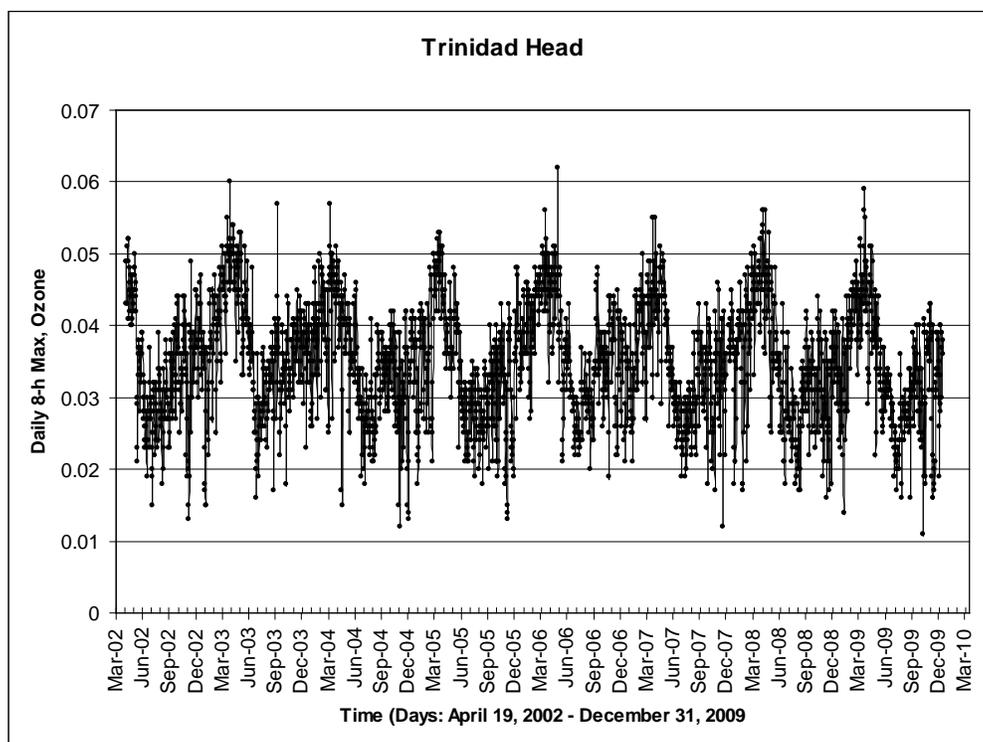
1 an increase in NO_x emissions of ~44% from Asia from 2001 to 2006 resulting in an
2 increase of 1-2 ppb in O₃ over North America.

3 [Cooper et al. \(2010\)](#) analyzed all available O₃ measurements in the free troposphere
4 above western North America at altitudes of 3-8 km (above sea level) during April and
5 May of 1995 to 2008 (i.e., times when intercontinental transport is most prominent).
6 They derived a trend of $+0.63 \pm 0.34$ ppb/year in median O₃ concentrations with
7 indication of a similar rate of increase since 1984. Back trajectories that were likely to
8 have been strongly and recently influenced by North American emissions were filtered
9 out, resulting in a trend of $+0.71 \pm 0.45$ ppb/year. Considering only trajectories with an
10 Asian origin resulted in a trend of $+0.80 \pm 0.34$ ppb/year. These results suggest that local
11 North American emissions were not responsible for the measured O₃ increases. This O₃
12 could have been produced from natural and anthropogenic precursors in Asia and Europe
13 with some contribution from North American emissions that have circled the globe.

14 [Cooper et al. \(2010\)](#) also found that it is unlikely that the trends in tropospheric O₃ are
15 associated with trends in stratospheric intrusions. Note, however, that these results relate
16 to O₃ trends above ground level and not to surface O₃. Model results ([Zhang et al., 2008](#))
17 show that surface O₃ contributions from Asia are much smaller than those derived in the
18 free troposphere because of dilution and chemical destruction during downward transport
19 to the surface. These processes tend to reduce the strength of associations between free
20 tropospheric and surface O₃ especially if air from other sources is sampled by the surface
21 monitoring sites.

22 Trinidad Head, CA is one sampling location at which measurements might be expected to
23 reflect in large measure NA background O₃ contributions, at times during the spring
24 ([Oltmans et al., 2008](#); [Goldstein et al., 2004](#)). The monitoring station at Trinidad Head is
25 on an elevated peninsula extending out from the mainland of northern California, and so
26 might be expected at times to intercept air flowing in from the Pacific Ocean with little or
27 no influence from sources on the mainland. [Figure 3-8](#) shows the time series of MDA8
28 O₃ concentrations measured at Trinidad Head from April 18, 2002 through December 31,
29 2009. The data show pronounced seasonal variability with spring maxima and summer
30 minima. Springtime concentrations typically range from 40 to 50 ppb with a number of
31 occurrences >50 ppb. The two highest daily maxima were 60 and 62 ppb. The data also
32 show much lower concentrations during summer, with concentrations typically ranging
33 between 20 and 30 ppb. [Oltmans et al. \(2008\)](#) examined the time series of O₃ and back
34 trajectories reaching Trinidad Head. They found that springtime maxima (April-May)
35 were largely associated with back trajectories passing over the Pacific Ocean and most
36 likely entraining emissions from Asia, with minimal interference from local sources.
37 However, [Parrish et al. \(2009\)](#) noted that only considering trajectories coming from a
38 given direction is not sufficient for ruling out local continental influences, as sea breeze

1 circulations are complex phenomena involving vertical mixing and entrainment of long-
2 shore components. They found that using a wind speed threshold in addition to a criterion
3 for wind direction allowed determination of background trajectories not subject to local
4 influence. This was confirmed by measurements of chemical tracers of local influence
5 such as CO₂, MTBE and radon. By applying the two criteria for wind speed and
6 direction, they found that Trinidad Head met these criteria only 30% of the time during
7 spring. [Goldstein et al. \(2004\)](#) used CO₂ as an indicator of exchange with the local
8 continental environment and found that O₃ concentrations were higher by about 2-3 ppb
9 when filtered against local influence indicating higher O₃ in air arriving from over the
10 Pacific Ocean. At other times of the year, Trinidad Head is less strongly affected by air
11 passing over Asia and the northern Pacific Ocean; and many trajectories have long
12 residence times over the semi-tropical and tropical Pacific Ocean where O₃
13 concentrations are much lower than they are at mid-latitudes. The use of the Trinidad
14 Head data to derive contributions from background sources requires the use of screening
15 procedures adopted by [Parrish et al. \(2009\)](#) and the application of photochemical models
16 to determine the extent either of titration of O₃ by fresh NO_x emissions and the extent of
17 local production of O₃ from these emissions. As noted above, anthropogenic emissions
18 from North America also contribute to hemispheric background and must be filtered out
19 from observations even when it is thought that air sampled came directly from over the
20 Pacific Ocean and was not influenced by local pollutant emissions.



Source: Reprinted with permission of Elsevier Ltd., ([Oltmans et al., 2008](#)); and NOAA Climate Monitoring Diagnostics Laboratory for data from 2008-2009.

Figure 3-8 Time series of daily maximum 8-h avg (MDA8) ozone concentrations (ppm) measured at Trinidad Head, CA, from April 18, 2002 through December 31, 2009.

1 [Parrish et al. \(2009\)](#) also examined data obtained at other marine boundary layer sites on
 2 the Pacific Coast. These include Olympic NP, Redwood NP, Point Arena, and Point
 3 Reyes. Using data from these sites, they derived trends in O₃ of +0.46 ppb/year (with a
 4 95% confidence interval of 0.13 ppb/year) during spring and +0.34 ppb/year
 5 (0.09 ppb/year) for the annual mean O₃ increase in air arriving from over the Pacific
 6 during the past two decades. Although O₃ data are available from the Channel Islands,
 7 [Parrish et al. \(2009\)](#) noted that these data are not suitable for determining background
 8 influence because of the likelihood of circulating polluted air from the South Coast Basin.

9 The 2010 Intercontinental Chemical Transport Experiment Ozone Network Study (IONS-
 10 2010) and Research at the Nexus of Air Quality and Climate Change (CalNex) study
 11 conducted in May through June of 2010 had discerning the contributions of Asian
 12 emissions to air quality in California as a major focus. [Cooper et al. \(2011\)](#) examined O₃
 13 profiles measured above four coastal sites in California, including Trinidad Head. Based
 14 on trajectory analyses coupled with comparison with the O₃ profiles, they suggested that

1 Asian pollution, stratospheric intrusions and international shipping made substantial
2 contributions to lower tropospheric O₃ (typically 0 to 3 km above sea level, meant as a
3 rough approximation of planetary boundary layer height) measured at inland California
4 sites. These contributions tended to increase on a relative basis in going from south to
5 north. In particular, no contribution from local pollution was needed to explain lower
6 tropospheric O₃ in the northern Central Valley; and the contribution of local pollution to
7 lower tropospheric O₃ in the LA basin ranged from 32 to 63% (depending on layer depth;
8 either 0 to 1.5 km or 0 to 3 km). It should be noted that the extent of photochemical
9 production and loss occurring in the descending air masses between the coastal and
10 inland sites remains to be determined. [Cooper et al. \(2011\)](#) also note that very little of the
11 O₃ observed above California reaches the eastern U.S. However, this does not necessarily
12 mean that the pathways by which Asian O₃ could reach the eastern U.S. were fully
13 captured in this analysis.

14 [Lin et al. \(2012\)](#) used the AM3 model (~50 × 50 km resolution globally) and satellite data
15 to characterize the influence of Asian emissions and stratospheric intrusions on O₃
16 concentrations in southern California and Arizona during CalNex (May-June 2010). The
17 model simulates sharp O₃ gradients in the upper troposphere and the interweaving and
18 mixing of stratospheric air and Asian plumes. Similar phenomena were also found during
19 field campaigns conducted in the North Atlantic as noted in Annex AX2.3.1 of the 2006
20 O₃ AQCD ([U.S. EPA, 2006b](#)) and introduces uncertainty into attempts to attribute O₃ to
21 these sources, based solely on observations, because this mixing will affect relationships
22 between CO (mainly a marker for polluted air that is commonly used to separate air
23 influenced by anthropogenic pollution from stratospheric air) and O₃ (a pollutant and a
24 stratospheric component). [Lin et al. \(2012\)](#) found that Asian emissions contributed from
25 20-30% to O₃ in the mid troposphere over the California coast and remnants of
26 stratospheric intrusions contributed from 50 to 60% to O₃ in discrete layers in the same
27 altitude range. This O₃ then has the potential to mix downward into the planetary
28 boundary layer. [Lin et al. \(2012\)](#) also found evidence of Asian contributions of up to 8 -
29 15 ppb in surface air during strong transport events in southern California. These
30 contributions are in addition to contributions from dominant local pollution sources.
31 Their results suggest that the influence of background sources on high surface O₃
32 concentrations is not always confined to high elevation sites. However, it is not clear to
33 what extent the contributions inferred by [Cooper et al. \(2011\)](#) and [Lin et al. \(2012\)](#) are
34 likely to be found in other years or how long they would extend into summer.

3.4.3 Estimating Background Concentrations

1 Historically, two approaches to estimating NA background concentrations (previously
2 referred to as PRB) have been considered in past O₃ assessments. In the 1996 and earlier
3 O₃ AQCDs, measurements from remote monitoring sites were used. In the 2006 O₃
4 AQCD, the use of CTMs was adopted, because as noted in Section 3.9 of the 2006 O₃
5 AQCD ([U.S. EPA, 2006b](#)), estimates of background concentrations cannot be obtained
6 directly by examining measurements of O₃ obtained at relatively remote monitoring sites
7 in the U.S. because of the long-range transport from anthropogenic source regions within
8 North America. The 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) also noted that it is impossible to
9 determine sources of O₃ without ancillary data that could be used as tracers of sources or
10 to calculate photochemical production and loss rates. As further noted by [Reid et al.](#)
11 ([2008](#)), the use of monitoring data for estimating background concentrations is essentially
12 limited to the edges of the domain of interest. The current definition of NA background
13 implies that only CTMs (see Section 3.3 for description and associated uncertainties) can
14 be used to estimate the range of background concentrations. An advantage to using
15 models is that the entire range of O₃ concentrations measured in different environments
16 can be used to evaluate model performance. In this regard, data from the relatively small
17 number of monitoring sites at which large background contributions are expected are best
18 used to evaluate model predictions.

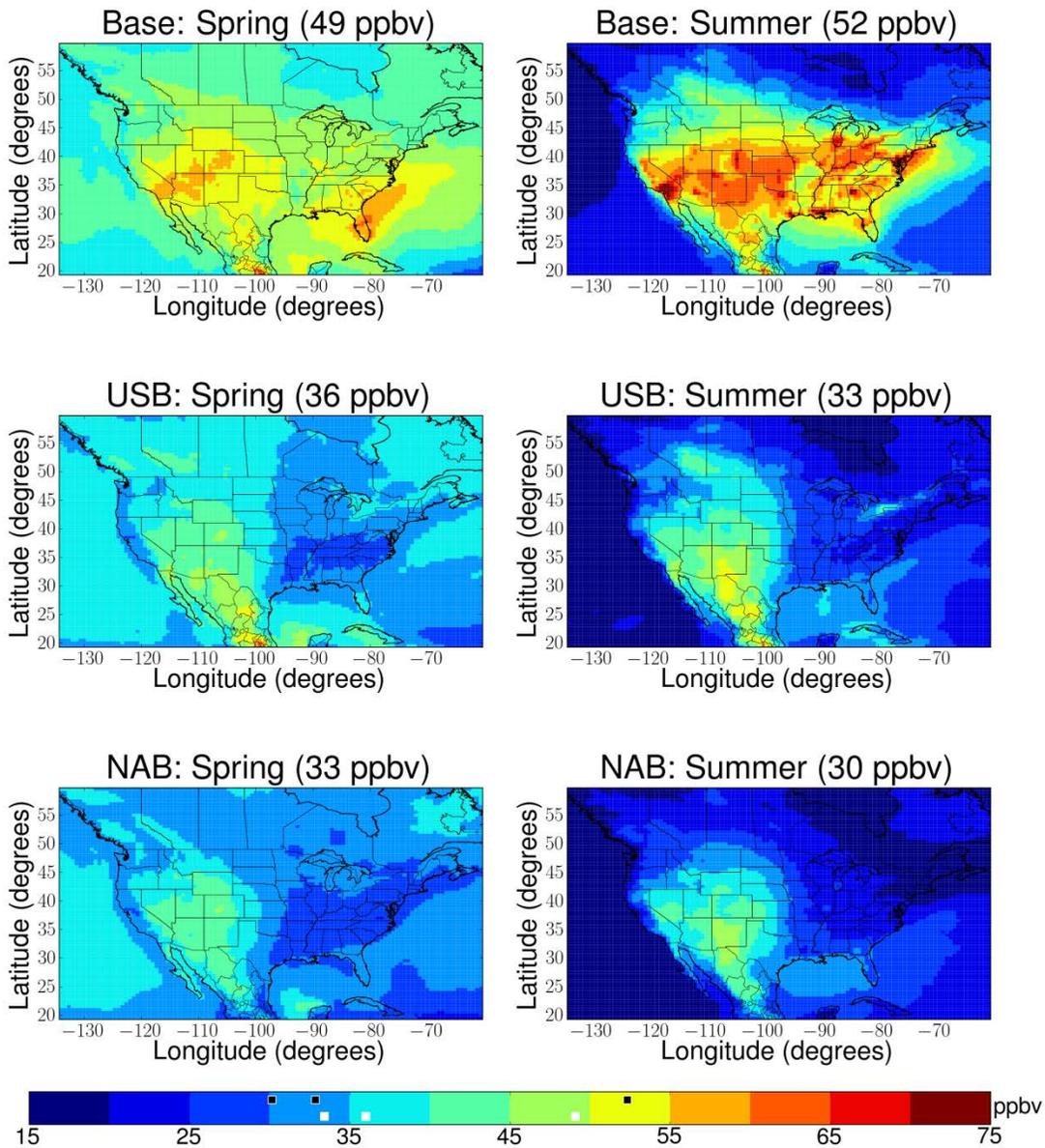
19 Estimates of NA background concentrations in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#))
20 were based on output from the GEOS-Chem (v4.3.3) model ([Fiore et al., 2003](#)) with
21 2° × 2.5° horizontal resolution. The GEOS-Chem model estimates indicated that NA
22 background O₃ concentrations in eastern U.S. surface air were 25 ± 10 ppb (or generally
23 15-35 ppb) from June through August, based on conditions for 2001. Values reported by
24 [Fiore et al. \(2003\)](#) represent averages from 1 p.m. to 5 p.m.; all subsequent values given
25 for background concentrations refer to MDA8 O₃ concentrations. Background
26 concentrations decline from spring to summer. Background O₃ concentrations may be
27 higher, especially at high altitude sites during the spring, due to enhanced contributions
28 from (1) pollution sources outside North America; and (2) stratospheric O₃ exchange. At
29 the time, only the GEOS-Chem model ([Harvard University, 2010b](#)) was documented in
30 the literature for calculating background O₃ concentrations ([Fiore et al., 2003](#)). The
31 simulated monthly mean concentrations in different quadrants of the U.S. were typically
32 within 5 ppbv of observations at CASTNET sites, with no discernible bias, except in the
33 Southeast in summer when the model was 8-12 ppbv too high. This bias was attributed to
34 excessive background O₃ transported in from the Gulf of Mexico and the tropical Atlantic
35 Ocean in the model ([Fiore et al., 2003](#)).

1 Although many of the features of the day-to-day variability in O₃ at relatively remote
2 monitoring sites in the U.S. were simulated reasonably well by GEOS-Chem ([Fiore et al.,
3 2003](#)), uncertainties in the calculation of the temporal variability of O₃ originating from
4 different sources on shorter time scales must be recognized. The uncertainties stem in
5 part from an underestimate in the seasonal variability in the STE of O₃ ([Fusco and Logan,
6 2003](#)), the geographical variability of this exchange, and the variability in the exchange
7 between the free troposphere and the PBL in the model. In addition, the relatively coarse
8 spatial resolution in that version of GEOS-Chem (2° × 2.5°) limited the ability to provide
9 separate estimates for cities located close to each other, and so only regional estimates
10 were provided for the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) based on the results of [Fiore et
11 al. \(2003\)](#).

12 [Wang et al. \(2009a\)](#) recomputed NA background concentrations for 2001 using GEOS-
13 Chem (v7-01-01) at higher spatial resolution (1° × 1°) over North America and not only
14 for afternoon hours but for the daily maximum 8-h O₃ concentration. The resulting
15 background concentrations, 26.3 ± 8.3 ppb for summer, are consistent with those of
16 26 ± 7 ppb for summer reported by [Fiore et al. \(2003\)](#), suggesting horizontal resolution
17 was not a substantial factor limiting the accuracy of the earlier results. In addition to
18 computing NA background concentrations, [Wang et al. \(2009a\)](#) also computed U.S.
19 background concentrations of 29.6 ± 8.3 ppb with higher concentrations in the Northeast
20 (up to 15 ppb higher) and the Southwest (up to 13 ppb higher) for summer means.

3.4.3.1 Updated GEOS-Chem Model Estimates of Background Concentrations

21 [Zhang et al. \(2011\)](#) computed NA background, U.S. background and natural background
22 O₃ concentrations using GEOS-Chem (v8-02-03) at an even finer grid spacing of
23 0.5° × 0.667° over North America for 2006 through 2008. For March through August
24 2006, mean NA background O₃ concentrations of 29 ± 8 ppb at low elevation (<1,500 m)
25 and 40 ± 8 ppb at high elevation (>1,500 m) were predicted. Spring and summer mean O₃
26 concentrations calculated for the base case (i.e., including all natural and anthropogenic
27 sources worldwide), U.S. background, and NA background in surface air for spring and
28 summer 2006 calculated by [Zhang et al. \(2011\)](#) are shown in the upper, middle and lower
29 panels of [Figure 3-9](#).



Note: Values in parentheses refer to continental U.S. means and are shown as black squares in the color bar for summer and white squares for spring.

Source: Adapted from [Zhang et al. \(2011\)](#).

Figure 3-9 Mean MDA8 ozone concentrations in surface air for spring and summer 2006 calculated by GEOS-Chem for the base case (Base), U.S. background (USB), and NA background (NAB).

1 As noted above [Zhang et al. \(2011\)](#) found increases in Asian emissions only accounted
2 for an average increase of between 1 to 2 ppb in background O₃ across the U.S. even
3 though Asian emissions have increased by about 44% from 2001 to 2006. As can be seen
4 from [Figure 3-9](#), U.S. background and NA background concentrations are very similar
5 throughout most of the U.S. [Zhang et al. \(2011\)](#) also found that NA background
6 concentrations are ~4 ppb higher, on average, in the 0.5° × 0.667° version than in the
7 coarser 2° × 2.5° version. This difference was not entirely due to higher resolution, but to
8 the combination of changes in lightning and Asian emission estimates as well as higher
9 model resolution.

10 As can be seen from the middle and lower panels in [Figure 3-9](#), U.S. background and NA
11 background concentrations tend to be higher in the West, particularly in the
12 Intermountain West and in the Southwest compared to the East in both spring and
13 summer. U.S. background and NA background concentrations tend to be highest in the
14 Southwest during summer in the GEOS-Chem model, driven by lightning NO_x.

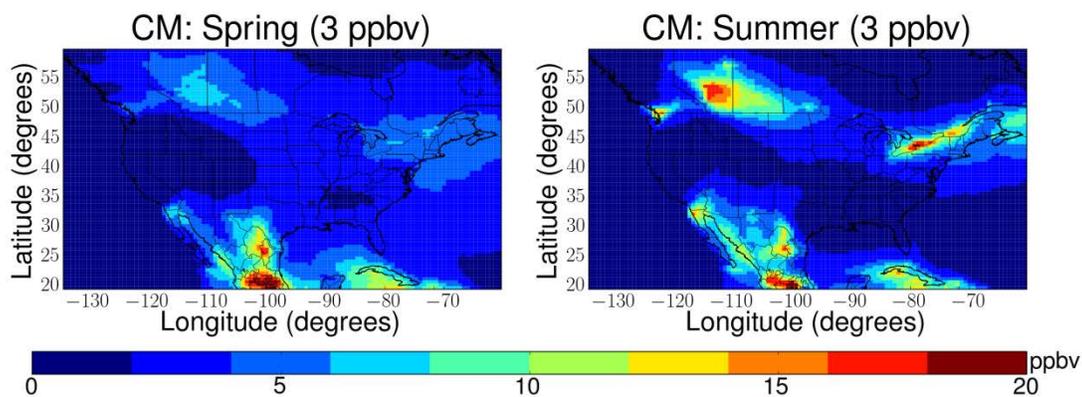
15 Intercontinental transport and stratospheric intrusions are major contributors to the high
16 elevation, Intermountain West during spring with wildfires becoming more important
17 sources during summer. The base case O₃ concentrations (upper panels) show two broad
18 maxima with highest concentrations extending throughout the Southwest, Intermountain
19 West and the East in both spring and summer. These maxima extend over many
20 thousands of kilometers demonstrating that O₃ is a regional pollutant. Low-level outflow
21 from the Northeast out over the Atlantic Ocean and from the Southeast out over the Gulf
22 of Mexico is also apparent.

23 Lower bounds to NA background concentrations tend to be higher by several parts per
24 billion at high elevations than at low elevations, reflecting the increasing importance of
25 background sources such as stratospheric intrusions and intercontinental transport with
26 altitude. In addition, background concentrations tend to increase with increasing base
27 model (and measured) concentrations at higher elevation sites, particularly during spring.

28 Although results of [Zhang et al. \(2011\)](#) are broadly consistent with results from earlier
29 coarser resolution versions of GEOS-Chem used by [Fiore et al. \(2003\)](#) and [Wang et al.
30 \(2009a\)](#), there are some apparent differences. Concentrations of O₃ for both the base case
31 and the NA background case in [Zhang et al. \(2011\)](#) are higher in the Intermountain West
32 than in earlier versions. In addition, background concentrations in many eastern areas
33 tend to be higher on days when predicted total O₃ is >60 ppb or at least do not decrease
34 with increasing total O₃ [Zhang et al. \(2011\)](#).

35 [Figure 3-10](#) shows seasonal mean estimates of contributions to O₃ from Canadian and
36 Mexican emissions calculated by [Zhang et al. \(2011\)](#) as the difference between U.S.

1 background and NA background values and then averaged over spring and summer
2 following the procedure in [Wang et al. \(2009a\)](#). U.S. background concentrations are on
3 average 3 ppb higher than NA background concentrations during spring and summer
4 across the United States. Highest values in [Figure 3-10](#) (in the U.S.) are found over the
5 Northern Tier of New York State (19.1 ppb higher than NA background) in summer.
6 High values are also found in other areas bordering Canada and Mexico. Although the
7 contributions from Canada and Mexico were obtained by differencing, it should be
8 remembered that relations between O₃ and precursors are subject to non-linear effects
9 that are strongest near concentrated sources of precursors, as noted in Section [3.2.4](#).
10 Therefore, the values shown in the figure are only estimates of contributions to total O₃
11 coming from Canada and Mexico.

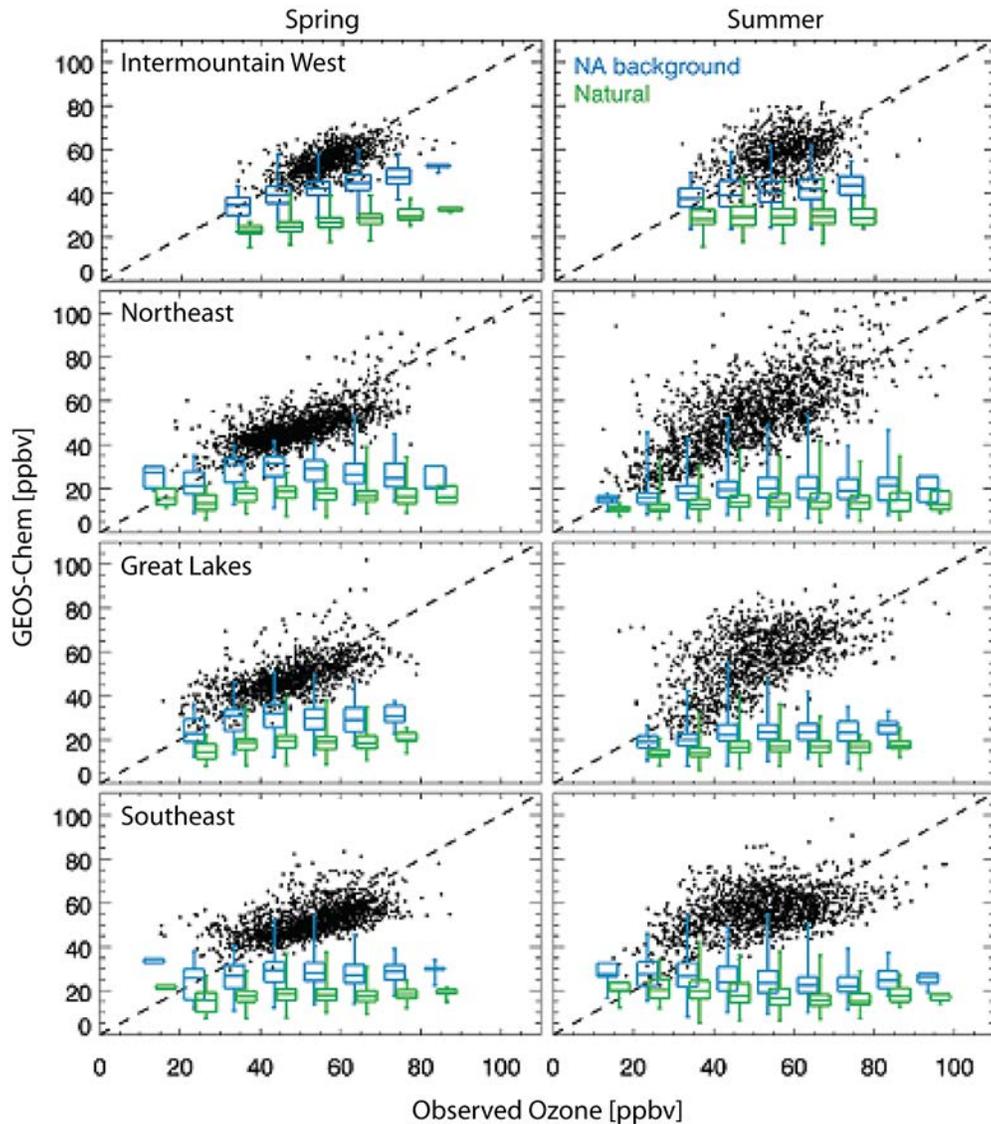


Note: Values in parentheses show mean difference (ppb) across the U.S.

Source: Adapted from [Zhang et al. \(2011\)](#).

Figure 3-10 Spring and summer mean Canadian and Mexican (CM) contributions to MDA8 ozone determined as the difference between the U.S. background and NA background.

12 [Figure 3-11](#) shows MDA8 O₃ concentrations for spring (March-May) and summer (June-
13 August) 2006 simulated by GEOS-Chem vs. measured by the ensemble of CASTNET
14 sites in the Intermountain West, Northeast, Great Lakes, and Southeast ([Zhang et al.](#)
15 [2011](#)). Shown is the 1:1 line and NA background (blue) and natural background (green)
16 model statistics as box plots (minimum, 25th, 50th, 75th percentile, and maximum) for
17 10-ppbv bins of observed ozone concentrations. These plots show that NA background
18 constitute a larger fraction of modeled base case O₃ at the upper end of the concentration
19 distribution for the Intermountain West than for other regions of the country.



Note: Shown is the 1:1 line and North American (NA) background (blue) and natural background (green) model statistics as box plots (minimum, 25th, 50th, 75th percentile, and maximum) for 10-ppbv bins of observed ozone concentrations.
 Source: Adapted from [Zhang et al. \(2011\)](#).

Figure 3-11 MDA8 ozone concentrations for spring (March-May) and summer (June-August) 2006 simulated by GEOS-Chem vs. measured by the ensemble of CASTNET sites in the Intermountain West, Northeast, Great Lakes, and Southeast.

1 Comparisons between GEOS-Chem and measurements of the mean MDA8 O₃ between
 2 March and August at individual CASTNET sites across the country are shown as
 3 supplemental material in Section 3.8, [Figure 3-58](#) through [Figure 3-64](#). In general, the
 4 GEOS-Chem predictions tend to show better agreement with observations at the high-

1 altitude sites than at the low-altitude sites. Overall agreement between model results for
2 the base case and measurements is within a few parts per billion for spring-summer
3 means in the Northeast (see [Figure 3-58](#) in Section 3.8) and the Southeast (see
4 [Figure 3-59](#) in Section 3.8), except in and around Florida where the base case
5 overpredicts O₃ by 10 ppb on average. In the Upper Midwest ([Figure 3-60](#) in
6 Section 3.8), the Intermountain West ([Figure 3-61](#) and [Figure 3-62](#) in Section 3.8), and
7 the West ([Figure 3-63](#) in Section 3.8) including most sites in California ([Figure 3-64](#) in
8 Section 3.8), the model predictions are within 5 ppb of measurements. The model
9 underpredicts O₃ by 10 ppb at the Yosemite site ([Figure 3-64](#) in Section 3.8). These
10 results suggest that the model is capable of calculating March to August mean MDA8 O₃
11 to within ~5 ppb at most (26 out of 28) sites chosen.

12 Comparison between results in [Wang et al. \(2009a\)](#) for 2001 with data obtained in the
13 Virgin Islands indicate that GEOS-Chem over-predicts summer mean MDA8 O₃
14 concentrations there by 10 ppb (28 vs. 18 ppb). Ozone concentrations at the Virgin
15 Islands NP site appear not to have been affected by U.S. emissions, based on the close
16 agreement between the base case and the NA background case. Wind roses calculated for
17 the Virgin Islands site indicate that wind patterns affecting this site are predominantly
18 easterly/southeasterly in spring and summer. The over-predictions at the Virgin Islands
19 site imply that modeled O₃ over the tropical Atlantic Ocean is too high. As a result,
20 inflow of O₃ over Florida and into the Gulf of Mexico is also likely to be too high as
21 winds are predominantly easterly at these low latitudes. Similar considerations apply to
22 the results of [Zhang et al. \(2011\)](#). Possible explanations include deficits in model
23 chemistry (for example, reactions involving halogens are not included) and/or subsidence
24 that is too strong over tropical oceans in the model. No clear explanation can be provided
25 on why the model under-predicts mean O₃ at Yosemite (elevation 1,680 m) by ~10 ppb
26 (see [Figure 3-64](#) in Section 3.8). However, March to August mean MDA8 O₃
27 concentrations are simulated to within a few parts per billion at an even higher elevation
28 site in California (Converse Station, elevation 1,837 m) and at the low elevation sites.

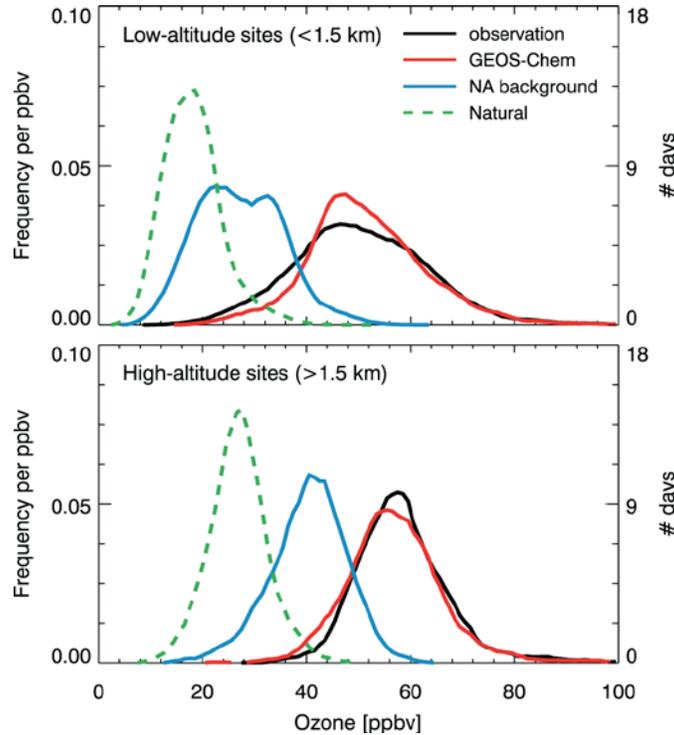
29 [Figure 3-65](#) in Section 3.8 shows a comparison of GEOS-Chem output with
30 measurements at Mt. Bachelor, OR and Trinidad Head, CA from March-August, 2006
31 from [Zhang et al. \(2011\)](#). For the Mt. Bachelor model runs, model estimates are given for
32 both a coarse (2° × 2.5°) and fine (0.5° × 0.667°) resolution model. In general, mean
33 concentrations are simulated reasonably well at both coarse and finer grid resolution
34 versions of the model with mean values 2 ppb higher in the finer resolution model.
35 Although the finer resolution version provides some additional day to day variability and
36 can capture the timing of peaks, it still does not adequately resolve peak concentrations as
37 can be seen for an event in the second half of April.

1 [Figure 3-66](#) in Section [3.8](#) shows a comparison of vertical profiles (mean $\pm 1\sigma$) calculated
2 by GEOS-Chem with ozonesondes launched at Trinidad Head, CA and Boulder, CO. As
3 can be seen from the figure, variability in both model and measurements increases with
4 altitude, but variability in the model results is much smaller at high altitudes than seen in
5 the observations. This may be due in part to the inability of grid-point models to capture
6 the fine-scale, layered structure often seen in O₃ in the mid and upper troposphere
7 ([Rastigejev et al., 2010](#); [Newell et al., 1999](#)) and to inadequacies in parameterizations of
8 relevant chemistry and dynamics. [Figure 3-67](#) and [Figure 3-68](#) in Section [3.8](#) show a
9 comparison of vertical profiles simulated by AM3 at 50 × 50 km global resolution ([Lin et
10 al., 2012](#)) with ozonesondes launched at several locations in California during May-June
11 2010. Note that in contrast to comparing measured mean monthly O₃ profiles to monthly
12 mean profiles calculated by GEOS-CHEM (see, for example, [Figure 3-66](#) in Section [3.8](#)),
13 AM3 is sampled for comparison to individual measurements of O₃ profiles. This model
14 has likely had the most success in simulating vertical O₃ gradients in the upper
15 troposphere and in capturing layered structures in the mid and upper troposphere.

16 The natural background for O₃ averages 18 ± 6 ppbv at the low-elevation sites and
17 27 ± 6 ppbv at the high-elevation sites in the GEOS-Chem model [Zhang et al. \(2011\)](#). In
18 regions where non-linear effects are small, far from concentrated sources of O₃
19 precursors, the difference between NA background and natural background O₃
20 concentrations provides an estimate of contributions from intercontinental pollution
21 including anthropogenic methane (given by the difference between values in 2006 and
22 the pre-industrial era, or 1,760 ppb and 700 ppb). The difference between the two
23 backgrounds averages 9 ppbv at the low-elevation sites and 13 ppbv at sites in the
24 Intermountain West. Based on the [Zhang et al. \(2011\)](#) model runs, anthropogenic
25 methane emissions are estimated to contribute ~4-5 ppb to global annual mean O₃ surface
26 concentrations. North American emissions of methane are uncertain, but are a small
27 fraction of total anthropogenic input. This suggests that slightly less than half of the
28 difference between North American background and natural background is due to the
29 increase of methane since the beginning of the industrial era and the other half is due to
30 anthropogenic emissions of shorter lived VOCs and NO_x. However, the relative
31 importance of methane for O₃ production is expected to increase in the future. Indeed,
32 variations in methane concentrations account for approximately 75% of the wide spread
33 (~5 ppb) in tropospheric O₃ projections between Representative Concentration Pathway
34 (RCP) scenarios for the next century ([Wild et al., 2012](#)); see Section [10.3.6.1](#) in
35 Chapter [10](#) for more on the RCP scenarios.

36 [Figure 3-12](#) shows frequency distributions for observations at low-altitude and high-
37 altitude CASTNET sites along with GEOS-Chem frequency distributions for the base
38 case, NA background and natural background. Most notable is the shift to higher

1 concentrations and the narrowing of the concentration distributions for all three
2 simulations and the observations in going from low to high altitudes. However, maximum
3 concentrations show little if any dependence on altitude, except for the natural
4 background which tends to be slightly higher at high altitude sites.



Note: Observations (black) as well as GEOS-Chem estimates for the base case (red), NA background (blue), and natural background (green dashed).

Source: [Zhang et al. \(2011\)](#).

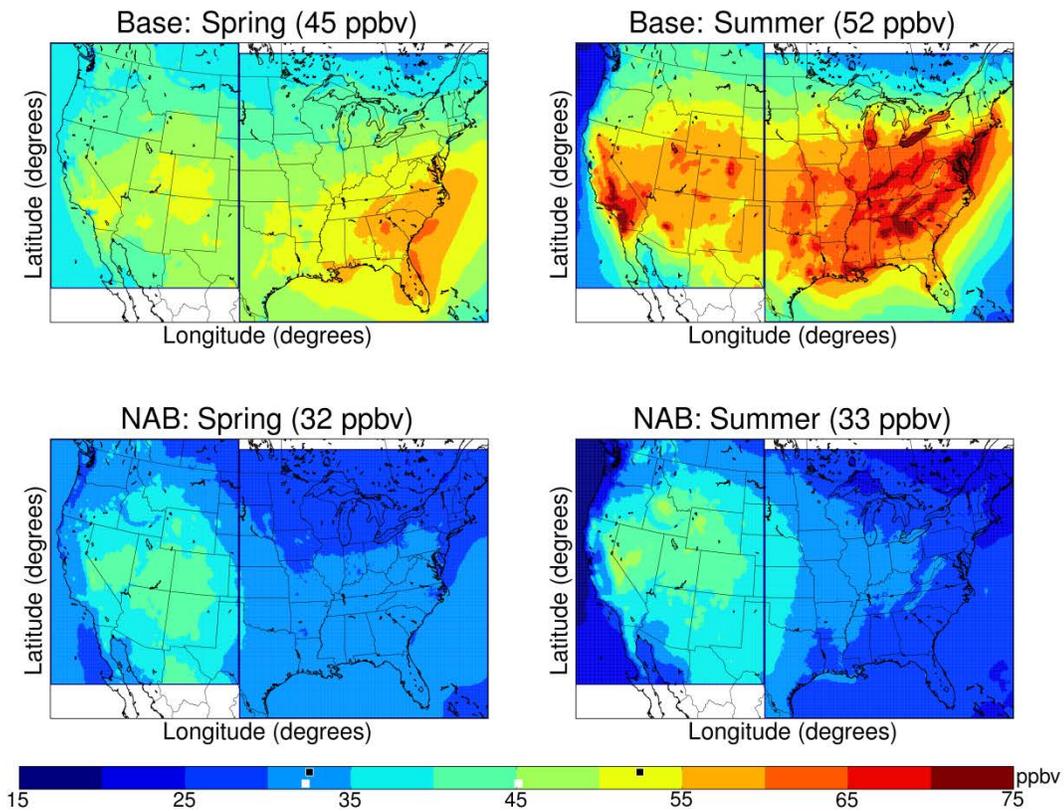
Figure 3-12 Frequency distributions of MDA8 ozone concentrations in March-August 2006 for the ensemble of low-altitude (<1,500 meters) and high-altitude CASTNET sites (>1,500 meters) in the U.S.

3.4.3.2 Using Other Models to Estimate Background Concentrations

5 Another approach to modeling background concentrations involves using a regional CTM
6 such as CMAQ or CAMx with boundary conditions taken from a global scale CTM such
7 as GEOS-Chem (see Section 3.3 for discussion of this approach). [Mueller and Mallard](#)
8 [\(2011a\)](#), while not calculating NA background values exactly as defined here, calculated
9 contributions from natural sources and inflow from the boundaries to O₃ for 2002 using

1 MM5 and CMAQ for the outermost domain (36 km resolution) shown in [Figure 3-4](#) with
2 boundary conditions from GEOS-Chem. The overall bias based on comparison with AQS
3 monitors for the base case is about 3 ppb; the annual mean fractional bias and mean
4 fractional error were 7% and 21% for the O₃ season across the U.S. Note that Figure 2 in
5 their paper is mislabeled, as it should refer to the case with total emissions - not to natural
6 emissions in North America only ([Mueller and Mallard, 2011b](#)). However, boundary
7 conditions are fixed according to monthly averages based on an earlier version of GEOS-
8 Chem and do not reflect shorter term variability or trends in Northern Hemispheric
9 emissions of pollution. In addition, fluxes of O₃ from the stratosphere are not included
10 explicitly. Note that their natural background includes North American natural
11 background emissions only and influence from boundary conditions and thus is not a
12 global natural background. Calculated values including natural emissions from North
13 America and from fluxes through the boundaries are somewhat larger than given in
14 [Zhang et al. \(2011\)](#), in large measure because of much larger contributions from wildfires
15 and lightning. Wildfire contributions reach values of ~140 ppb in Redwoods National
16 Park, CA and higher elsewhere in the U.S. and in Quebec in the simulations by [Mueller
17 and Mallard \(2011a\)](#). Lightning contributions (ranging up to ~30 ppb) are substantially
18 larger than estimated by [Kaynak et al. \(2008\)](#) (see Section [3.4.1.2](#)). The reasons for much
19 larger contributions from wildfires and lightning found by [Mueller and Mallard \(2011a\)](#)
20 are not clear and need to be investigated further.

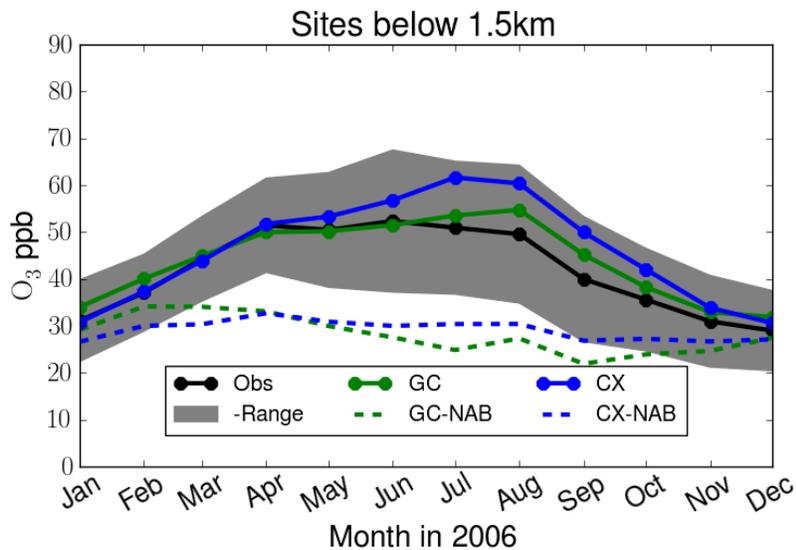
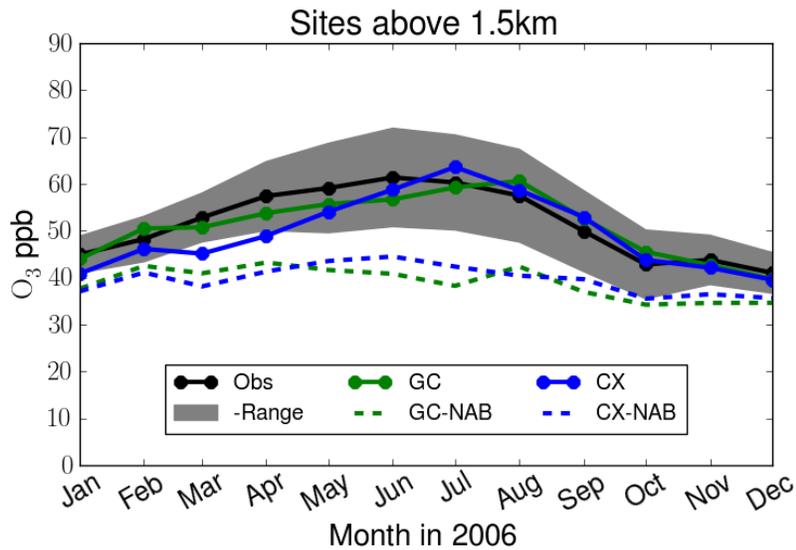
21 [Emery et al. \(2012\)](#) used CAMx in conjunction with boundary conditions from a coarse
22 resolution version of GEOS-Chem (2° × 2.5° or ~200 km resolution) to derive NA
23 background concentrations of O₃. The nested CAMx simulations were run at a horizontal
24 resolution of 12 km separately for the eastern and western U.S. The following paragraphs
25 compare results from the [Emery et al. \(2012\)](#) nested GEOS-Chem/CAMx simulations
26 (hereafter referred to as CAMx) at 12 km resolution with those obtained by [Zhang et al.
27 \(2011\)](#) using GEOS-Chem simulations at 0.5° × 0.667° (~50 km) resolution. This is in
28 contrast to the comparison reported in [Emery et al. \(2012\)](#) using a 2° × 2.5° (~200 km)
29 resolution GEOS-Chem model. [Figure 3-13](#) shows seasonal mean MDA8 O₃
30 concentrations calculated by [Emery et al. \(2012\)](#) using CAMx for 2006 for the base case
31 and for NA background. [Figure 3-14](#) shows a comparison of monthly average O₃
32 concentrations calculated by GEOS-Chem ([Zhang et al., 2011](#)) with those calculated by
33 CAMx ([Emery et al., 2012](#)). Comparison of the base case for GEOS-Chem with that for
34 CAMx in [Figure 3-14](#) indicates broad agreement in spatial patterns.



Note: Values in parentheses refer to continental U.S. means and are shown as black squares in the color bar for summer and white squares for spring.

Source: Adapted from [Emery et al. \(2012\)](#).

Figure 3-13 Mean MDA8 ozone concentrations in surface air during spring and summer 2006 (top) calculated by GEOS-Chem/CAMx for the base case (Base, top) and NA background (NAB, bottom).



Note: Shaded area shows 1 SD range about the mean of observations.

Source: Adapted [with permission of Elsevier, [Emery et al. \(2012\)](#)] and [Zhang et al. \(2011\)](#).

Figure 3-14 Monthly average MDA8 ozone concentrations observed (Obs) and predicted for the base case and NA background (NAB) by GEOS-Chem (GC) and GEOS-Chem/CAMx (CX) at CASTNET sites above 1,500 meters elevation (upper panel) and CASTNET sites below 1,500 meters elevation (lower panel).

1 Supplemental figures ([Figure 3-69](#) through [Figure 3-74](#)) in Section [3.8](#) show box plots
2 comparing MDA8 O₃ concentrations calculated by GEOS-Chem at 0.5° × 0.667°
3 resolution and CAMx for March-August 2006 at the combined set of CASTNET sites
4 used by both groups for model evaluation. Note that the individual model results and the
5 observations are un-paired in time. At CASTNET sites in the Northern Rockies, both
6 models tend to underpredict maximum O₃ concentrations, but they are generally higher in
7 CAMx than in GEOS-Chem (typically by 5-10 ppb). The distribution of MDA8 values
8 from GEOS-Chem is consistent with measured distributions (i.e., cannot be rejected
9 using Mann-Whitney rank sum test, p-value <0.01) at 18 of 39 sites in spring and 21 of
10 39 sites in summer. The distribution of MDA8 values from CAMx is consistent with
11 measured distributions at 13 of 39 sites in spring and 18 of 39 sites in summer. When
12 spring and summer are pooled, both simulations are consistent with measured
13 distributions at 16 out of 39 sites (but not the same 16 sites). There are examples in which
14 either model over- or under- simulates maximum concentrations. However, over-
15 predictions are made more often by CAMx. At high elevations in the Intermountain West
16 (see [Figure 3-72](#) in Section [3.8](#)), both models tend to under-predict maxima, but their
17 interquartile range agrees much better with observations. As [McDonald-Buller et al.](#)
18 [\(2011\)](#) noted, complex topography in some regions of the U.S. could influence surface O₃
19 through fine-scale, orographically induced flow regimes. In addition, numerical diffusion
20 broadly affects the ability of models to capture observed maxima, particularly at
21 mountain sites. [McDonald-Buller et al. \(2011\)](#) also note there are regions in the U.S.
22 where global models show consistent biases. For example, models are generally unable to
23 simulate the low O₃ concentrations observed at Gulf Coast sites in summer during
24 onshore flow from the Gulf of Mexico, which could reflect marine boundary layer
25 chemistry and/or stratification that is not properly represented in the model. Both models
26 overpredict O₃ at two sites in Florida (Sumatra and Indian River Lagoon). However,
27 further inland, CAMx tended to overpredict O₃ at the Coffeerville, MS; Sand Mountain,
28 AL; and Georgia Station, GA sites whereas GEOS-Chem did not. The same is true for
29 higher elevation sites (Great Smoky Mountain, NC-TN; Shenandoah, VA). In the
30 Northeast, there is a general tendency for both models to overpredict the measured
31 distributions with somewhat higher maximum concentrations in CAMx compared to
32 GEOS-Chem and observations (see [Figure 3-69](#) to [Figure 3-74](#) in Section [3.8](#)).

33 The most readily discernible differences in model formulation are in the model grid
34 spacing and the treatment of wildfires. The finer resolution in CAMx allows for
35 topography to be better-resolved producing higher maximum O₃ concentrations in the
36 Intermountain West. For wildfires, treatment differences include emission composition,
37 emission time averaging, and associated chemistry. Wildfires produce more O₃ in CAMx
38 simulations than in GEOS-Chem simulations, and [Emery et al. \(2012\)](#) attribute these
39 enhancements to shorter emission time averaging. The CAMx emissions average fire

1 emissions at hourly resolution based on the SmartFire algorithm, whereas GEOS-Chem
2 uses monthly averages from GFED2. Each model representation also uses different
3 emission compositions. The emissions used by [Emery et al. \(2012\)](#) include a larger
4 number of VOCs and additional categories of VOCs than used by [Zhang et al. \(2011\)](#).
5 Following emission, [Emery et al. \(2012\)](#) note that photochemical aging of wildfire
6 emissions depends on the chemical mechanism. Neither chemical mechanism was
7 designed specifically for these type of events. GEOS-Chem has traditionally focused on
8 the chemistry of the non-urban troposphere and does not represent secondary products of
9 fast reacting VOCs as does CB05. A lack of reactivity of secondary products would cause
10 a dampening of fire contributions to O₃. CB05 has traditionally focused on urban
11 chemistry and does not explicitly includes ketones ([Henderson et al., 2011](#)), which are
12 among the top ten VOCs emitted from fires ([Andreae and Merlet, 2001](#)). The O₃
13 increases seen in [Emery et al. \(2012\)](#) and [Mueller and Mallard \(2011a\)](#), however, are
14 subject to uncertainties in the representation of physics in the wildfire plumes. The
15 improvements in characterizing emissions would lead to smoke plumes that attenuate
16 light, thereby reducing photolysis and photoreactivity ([e.g., Real et al., 2007](#)). The
17 wildfires would also alter temperature and convective activity that influences plume rise
18 and the height of the planetary boundary layer. [Emery et al. \(2012\)](#) note the need for
19 more research to improve simulation of O₃ from fires. Using a sensitivity analysis of
20 CAMx, the authors showed that removing wildfires in the West (California, Oregon, and
21 Idaho) resulted in reductions of NA background O₃ of 10 to 50 ppb, with smaller
22 reductions elsewhere. Further, [Emery et al. \(2012\)](#) note that their calculated O₃ increases
23 in the vicinity of wildfires is consistent with that of [Mueller and Mallard \(2011a\)](#).

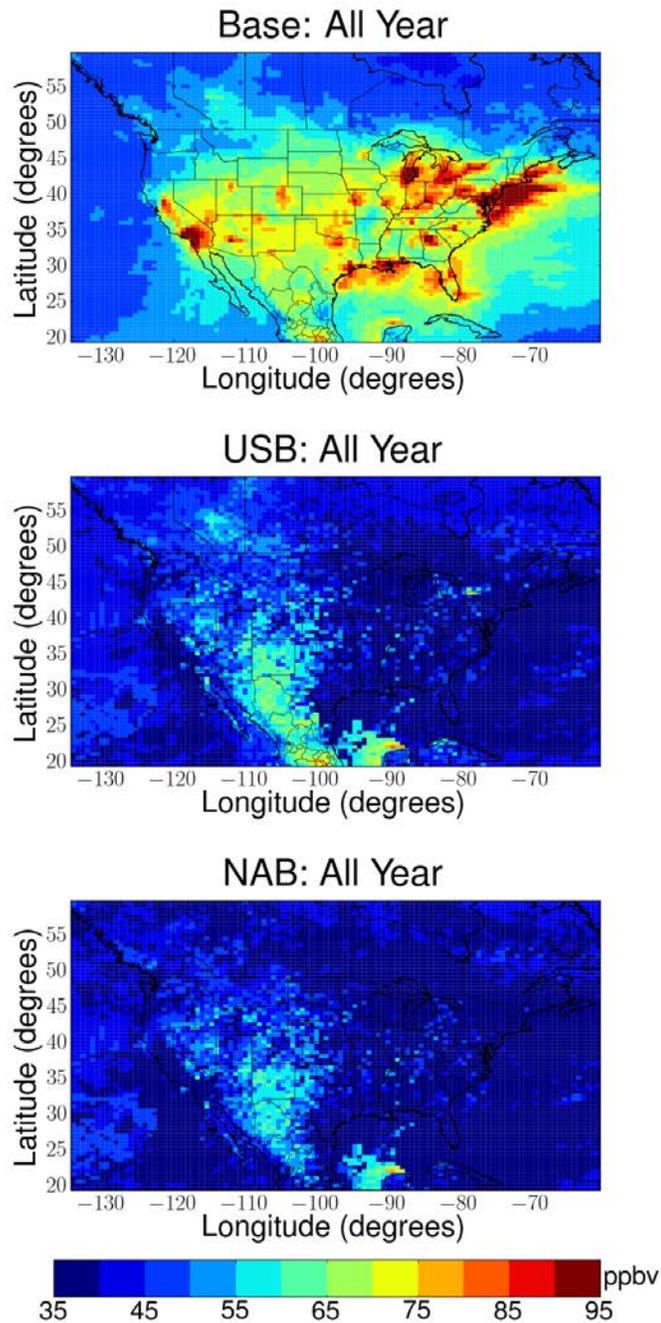
24 [Emery et al. \(2012\)](#) captured the timing of a possible stratospheric intrusion at Gothic,
25 CO on April 19-20, 2006 and predicted an MDA8 value of ~73 ppb using CAMx on
26 April 20 compared to a measured value of 87 ppb. GEOS-Chem (at 0.5° × 0.667°)
27 predicted ~65 ppb for this event. The higher spatial resolution in CAMx likely
28 contributed to the improvement in model performance, but this may not be the only
29 factor. AM3, another global scale CTM ([Lin et al., 2012](#)) at ~2° × 2.5° resolution
30 predicted ~75 ppb for that event suggesting that differences in dynamical cores between
31 WRF and AM3, different treatments of the stratospheric O₃ source, and perhaps the
32 spatial extent of the intrusion's effect on surface O₃ should be considered in addition to
33 model resolution. Note that all three models (CAMx, GEOS-Chem, and AM3) under-
34 predicted the magnitude of this event. These results indicate a need for process-oriented
35 evaluation and targeted measurements that yield insight into both chemical and
36 dynamical processes. The R² for comparison of AM3 with observations of MDA8 O₃
37 from March-August 2006 was 0.33 with lower R² for GEOS-Chem and CAMx. All three
38 models predicted very similar means for March to August, 55.0 ppb for the fine

1 resolution version of GEOS-Chem, 55.0 ppb for CAMx and 58.4 ppb for AM3 compared
2 to 56.1 ppb for measurements (see [Figure 3-75](#) in Section [3.8](#)).

3 The results from either model have also been compared to more urban oriented sites in
4 the AQS network. As noted earlier, comparisons between model results and observations
5 become problematic near concentrated sources of O₃ precursors (NO_x and VOCs) in
6 urban cores. [Emery et al. \(2012\)](#) note that in coarse resolution models rural biogenic and
7 urban precursor emissions are mixed immediately leading to higher production efficiency
8 for O₃. Finer resolution models are better able to separate these two source categories and
9 to resolve features of urban chemistry such as titration of O₃ by NO_x emitted by traffic
10 and subsequent processing of NO_x emissions during transport downwind. CAMx at
11 12 × 12 km resolution is better able to capture these features than GEOS-Chem at
12 50 × 50 km resolution. Both models tend to over-predict O₃ at the low O₃ concentrations
13 in areas where O₃ scavenging by NO_x is evident. In these situations, NA background O₃
14 concentrations are often higher than in the respective models for the base case. At high
15 O₃ concentrations downwind of source areas, both models predict NA background O₃
16 concentrations that are much lower than observed or base case O₃. The latter results are in
17 accord with results shown in [Figure 3-11](#) for rural CASTNET sites at low elevations,
18 which show lower ratios between NA background O₃ and either observations or base case
19 O₃ at high O₃ than at low O₃ concentrations.

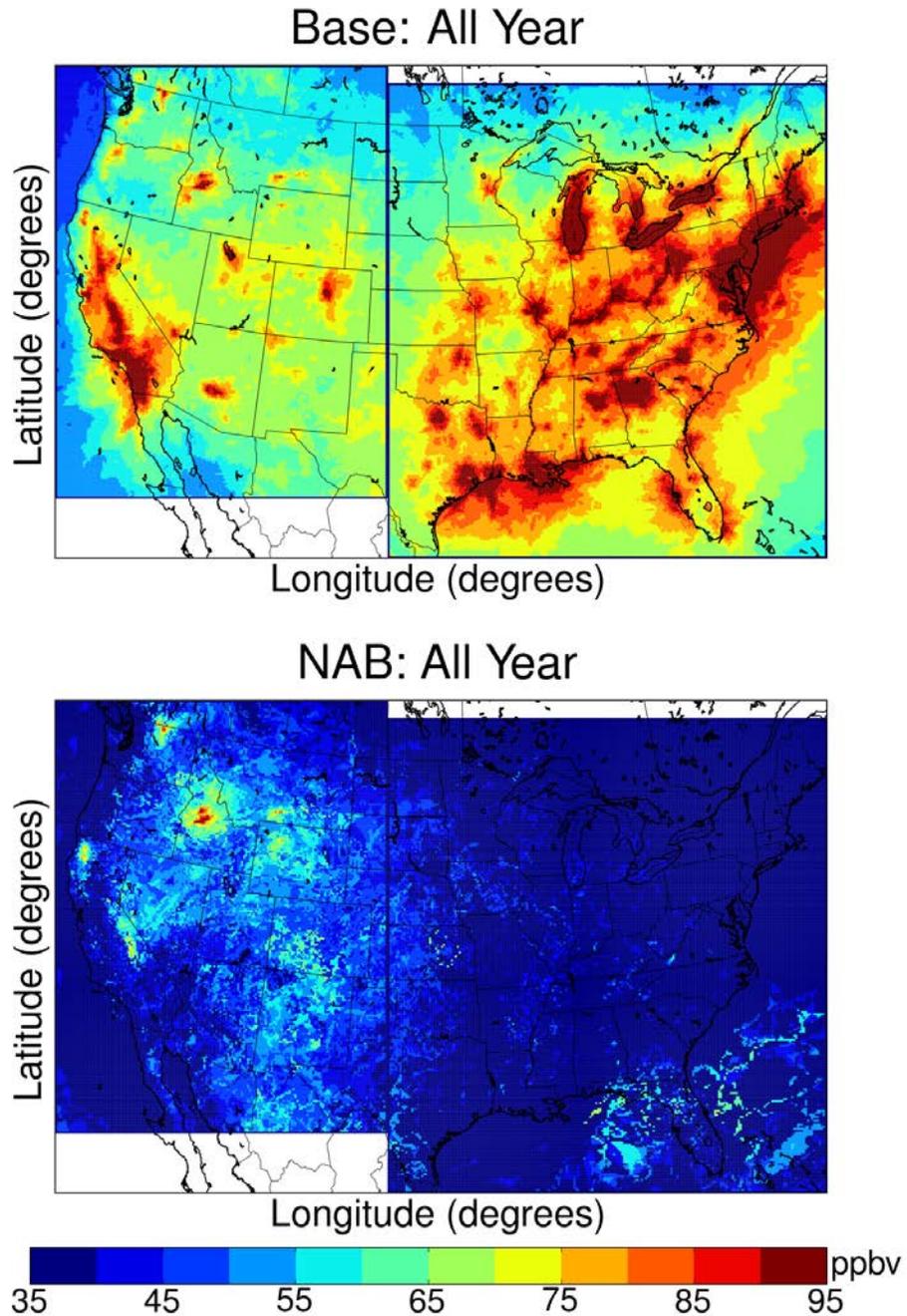
20 [Figure 3-15](#) shows the annual 4th highest MDA8 O₃ predicted by GEOS-Chem (at
21 0.5° × 0.667° resolution) for the base case (upper panel), and corresponding U.S.
22 background (middle panel) and NA background (lower panel) MDA8 O₃ on the same
23 days for 2006. [Figure 3-16](#) shows corresponding values predicted by CAMx for the base
24 case (upper panel) and NA background (lower panel) MDA8 O₃ on the same days for
25 2006. As can be seen from [Figure 3-15](#) and [Figure 3-16](#), on those days when models
26 predicted their annual 4th highest MDA8 O₃, the corresponding NA background
27 concentrations are 36 ± 9 ppb in the eastern U.S. Base case concentrations are much
28 higher indicating that regional pollution is mainly responsible for the models 4th highest
29 concentrations. In the western U.S. on the other hand, NA background concentrations are
30 generally higher and make up a larger fraction of the calculated 4th highest MDA8 O₃ in
31 both models, but for different reasons. GEOS-Chem predicts highest values in the
32 Southern Rockies because of over-production of NO_x by lightning. CAMx predicts
33 highest values in ID, OR and WA from wildfires. The CAMx run includes day specific
34 values for area burned, but GEOS-Chem uses monthly averages. (A more recent version
35 of GEOS-Chem also incorporates day specific estimates for area burned.) Remaining
36 areas of relatively high background levels (>60 ppb) are due mainly to some combination
37 of stratospheric intrusions and Eurasian emissions. There are a few examples that can be
38 used to give a rough idea of the magnitudes of episodically high background

1 contributions. A comparison of the annual 4th highest MDA8 O₃ concentration simulated
2 by CAMx including wildfires and omitting them indicates that wildfires contributed ~ 30
3 to 40 ppb in Idaho, Montana, and Washington with a potentially larger contribution in the
4 upper northwestern corner of California. Estimated contributions from strong
5 stratospheric intrusions to surface O₃ in AM3 could range up to ~ 70 ppb in the western
6 U.S.



Source: Adapted from [Zhang et al. \(2011\)](#).

Figure 3-15 Annual 4th highest MDA8 ozone predicted by GEOS-Chem ($0.5^\circ \times 0.667^\circ$) for the base case (Base) with corresponding U.S. background (USB) and NA background (NAB) MDA8 ozone for the same days in 2006.



Source: Adapted from [Emery et al. \(2012\)](#).

Figure 3-16 Annual 4th highest MDA8 ozone predicted by CAMx for the base case (Base) and corresponding NA background (NAB) MDA8 ozone for the same days in 2006.

1 All models undergo continuous updating of inputs, parameterizations of physical and
2 chemical processes, and improvements in model resolution. Inputs that might be
3 considered most relevant include emissions inventories, chemical reactions, and
4 meteorological fields. This leads to uncertainty in model predictions in part because there
5 is typically a lag between updated information for the above inputs—as outlined in
6 Section [3.2](#) for chemical processes and emissions and in Section [3.3](#) for model
7 construction—and their implementation in CTMs including GEOS-Chem or the other
8 models described above. Quantitative estimates of uncertainties from meteorological and
9 emission inputs and chemical mechanisms are problematic because simulations designed
10 to quantify uncertainties from these sources have not been performed for these model
11 runs. At best, these uncertainties can be estimated by comparison with observations while
12 recognizing that compensating errors likely exist.

13 Since NA background is a construct that cannot be directly measured, the range of
14 background O₃ concentrations must be estimated using CTMs. Results from the [Zhang et al. \(2011\)](#)
15 [GEOS-Chem](#) and [Emery et al. \(2012\)](#) [GEOS-Chem/CAMx](#) (hereafter referred
16 to as CAMx) model estimates were chosen for further analysis because these models
17 have produced the latest estimates for background O₃ concentrations documented in the
18 open literature. The main results from these two modeling efforts can be described as
19 follows:

- 20 ■ Both models show background concentrations vary spatially and temporally;
- 21 ■ Simulated mean background concentrations are highest in the Intermountain
22 West (i.e., at high altitude) in spring and lowest in the Northeast during
23 summer;
- 24 ■ Background concentrations tend to increase with total (i.e., base case) O₃
25 concentrations at high elevation, but that tendency is not as clear at low
26 elevations.

27 The most pronounced differences between the [Zhang et al. \(2011\)](#) [GEOS-Chem](#) and the
28 [Emery et al. \(2012\)](#) [CAMx](#) models—when compared with observations—are at the upper
29 end of the concentration distribution. At high elevations, differences are likely to be the
30 result of underpredictions of background contributions which are driven mainly by
31 episodic events such as stratospheric intrusions and wildfires. In general, CAMx predicts
32 higher values at the upper end of the concentration distribution than does GEOS-Chem.
33 At low elevations (<1,500 meters)—located mainly in the East—the reasons for
34 underpredictions at the upper end of the concentration distribution are more complex and
35 likely involve extensive interactions between anthropogenic and natural sources.

36 [Table 3-1](#) summarizes modeling results for seasonal mean MDA8 O₃ by region simulated
37 by the two models. The regions in [Table 3-1](#) are shown in [Figure 3-50](#). As can be seen

1 from the table, seasonal means predicted by GEOS-Chem are within a few parts per
 2 billion of measurements in both spring and summer for all regions shown except for
 3 California in the spring. Although CASTNET sites are meant to represent regional
 4 background air, they can be heavily influenced by polluted air masses, particularly in
 5 California where the underpredictions are largest. Seasonal means are simulated by
 6 CAMx to within 2-5 ppb except in California in the spring where they are underpredicted
 7 by 8 ppb and at sites in the Northeast and Southeast where they are overpredicted by 8-
 8 9 ppb in summer. When compared to observations, the mean R² within each region—
 9 except for California in the spring—is higher for CAMx than for GEOS-Chem suggesting
 10 better ability to track day-to-day variability by CAMx. It is clear from these results that
 11 model resolution (at least for the model resolutions considered here) is not the dominant
 12 factor determining agreement of the means between simulations or between simulations
 13 and measurements. Differences in model chemistry and physics must also be considered.

Table 3-1 Comparison of seasonal mean MDA8 ozone concentrations simulated by the GEOS-Chem and CAMx base case models for 2006, with measurements at CASTNET sites.

| Region | CASTNET | | GEOS-Chem | | CAMx | |
|-----------------------------|----------------------|---------|---|-------------------------|-------------------------|-------------------------|
| | Spring | Summer | Spring | Summer | Spring | Summer |
| California (5) ^a | 58 ± 12 ^b | 69 ± 14 | 52 ± 11; 0.52 ^c 38 ± 7 ^d | 66 ± 18; 0.22 37 ± 9 | 50 ± 10; 0.50 39 ± 6 | 66 ± 13; 0.30 42 ± 6 |
| West (14) | 54 ± 9 | 55 ± 11 | 53 ± 7; 0.30 42 ± 6 | 55 ± 11; 0.12 40 ± 9 | 49 ± 8; 0.39 40 ± 7 | 57 ± 10; 0.33 41 ± 8 |
| North Central (6) | 47 ± 10 | 50 ± 12 | 47 ± 8; 0.52 33 ± 6 | 51 ± 14; 0.44 27 ± 7 | 45 ± 11; 0.63 30 ± 6 | 54 ± 13; 0.48 31 ± 5 |
| Northeast (5) | 48 ± 10 | 45 ± 14 | 45 ± 7; 0.44 33 ± 7 | 45 ± 13; 0.47 24 ± 7 | 46 ± 11; 0.53 30 ± 5 | 53 ± 14; 0.54 27 ± 6 |
| Southeast (9) | 52 ± 11 | 52 ± 16 | 51 ± 7; 0.42 32 ± 7 | 54 ± 9; 0.21 29 ± 10 | 54 ± 9; 0.56 33 ± 6 | 61 ± 12; 0.45 30 ± 6 |

^aValues in parentheses after each region name refer to the number of sites.

^bShown are seasonal (spring, summer) mean MDA8 O₃ concentrations (ppb ± standard deviation);

^cShown are mean R² of all model-measurement pairs at individual CASTNET sites.

^dNorth American (NA) background seasonal mean MDA8 O₃ concentrations (ppb ± standard deviation) are shown beneath the base case seasonal means.

Source: Data from [Zhang et al. \(2011\)](#) for GEOS-Chem and [Emery et al. \(2012\)](#) for CAMx.

14 [Table 3-2](#) summarizes modeling results for the annual 4th highest (99th –percentile)
 15 MDA8 O₃ for the same seasons and regions used in [Table 3-1](#). As can be seen, the
 16 GEOS-Chem and the CAMx models both underestimate mean day specific 4th highest
 17 values in California by ~20 ppb. In general, CAMx simulates MDA8 O₃ concentrations
 18 that are higher and in better agreement with measurements. Shown alongside the model
 19 estimates is the number of days the modeled MDA8 O₃ concentrations are within 5 ppb

1 of observed. The lower portions of the entries for the models in [Table 3-2](#) show model
2 predicted 4th highest MDA8 O₃ concentrations that are not calculated on the same day as
3 the 4th highest values measured at CASTNET sites. It can be seen that simulated regional
4 means of the 4th highest MDA8 O₃ are in better agreement with measurements when
5 results are un-paired by date. In other words, the models do not predict their annual
6 4th highest MDA8 O₃ concentrations on the same day as they are observed.

7 These results underscore the uncertainties inherent in any model's attempts to simulate
8 day specific 4th highest O₃ concentrations. As noted earlier, uncertainties in calculating
9 day specific O₃ concentrations are especially challenging because of the lack of day
10 specific data for emissions of many species. While progress is being made in obtaining
11 day specific data for lightning strikes and area burned in wildfires, the emission factors
12 for precursors from these episodic sources such as lightning and wildfires are still
13 uncertain. In addition to uncertainty in emissions, uncertainties in models' treatments of
14 transport and chemical mechanisms must also be considered.

15 Comparison of GEOS-Chem results for natural and NA background indicate that
16 methane is also a major contributor to NA background O₃, accounting for slightly less
17 than half of the increase in background since the preindustrial era and whose relative
18 contribution is projected to grow in the future. U.S. background concentrations are on
19 average 2.6 ppb higher than NA background concentrations during spring and 2.7 ppb
20 during summer across the United States. Highest values for U.S. background (in the U.S.)
21 are found over the Northern Tier of New York State (19.1 ppb higher than local NA
22 background concentrations) in summer. High values are also found in other areas
23 bordering Canada and Mexico.

Table 3-2 Comparison of annual 4th-highest MDA8 ozone concentrations measured at CASTNET sites in 2006 with MDA8 ozone concentrations simulated by the GEOS-Chem and CAMx base case models.

| Region | CASTNET | GEOS-Chem | | CAMx | |
|-----------------------------|----------------------|--|----------------|-------------------|---|
| California (5) ^a | 90 ± 13 ^b | 71 ± 15 ^c 85 ± 19 ^e | 0 ^d | 71 ± 9 85 ± 13 | 0 |
| West (14) | 70 ± 4 | 62 ± 8 68 ± 7 | 4 | 63 ± 8 71 ± 7 | 6 |
| North Central (6) | 71 ± 5 | 58 ± 10 69 ± 10 | 1 | 63 ± 7 73 ± 8 | 1 |
| Northeast (5) | 71 ± 4 | 61 ± 6 68 ± 5 | 0 | 72 ± 7 75 ± 3 | 3 |
| Southeast (9) | 76 ± 8 | 61 ± 6 71 ± 5 | 2 | 71 ± 11 79 ± 9 | 5 |

^aValues in parentheses after each region name refer to the number of sites.

^bShown are annual 4th highest (99th-percentile) MDA8 O₃ concentration regional means (ppb ± standard deviation).

^cShown are calculated MDA8 O₃ concentrations on days when the 4th highest MDA8 O₃ concentrations was measured.

^dShown are the number of days the model predicted MDA8 O₃ concentrations were within 5 ppb of observed 4th-highest concentrations.

^eShown are model predicted annual 4th highest MDA8 O₃ concentrations.

Source: Data from [Zhang et al. \(2011\)](#) for GEOS-Chem and [Emery et al. \(2012\)](#) for CAMx.

1 Analyses of results from GEOS-Chem and CAMx presented here and shown in [Table 3-1](#)
2 and [Table 3-2](#) are in accord with results from [Kasibhatla and Chameides \(2000\)](#) who
3 found that the accuracy of simulations improved as the averaging time of both the
4 simulation and the observations increased (see Section [3.3](#)). Note that any CTM—not just
5 the ones considered here—will have difficulty in predicting day specific quantities. When
6 analyzing results over long time periods (e.g., months), special care should be taken to
7 examine temporal trends in bias because this will improve understanding of the modeling
8 results.

9 Overall, these results suggest that GEOS-Chem is capable of simulating seasonal or
10 monthly mean MDA8 O₃ to within a few parts per billion on a regional basis throughout
11 the U.S., except in California. These results suggest that CAMx is capable of simulating
12 seasonal or monthly mean MDA8 O₃ to within a few ppb, though, CAMx also shows
13 relatively large disagreements in California and, in addition, shows relatively large
14 positive bias in seasonal mean MDA8 O₃ in the eastern U.S. However, differences
15 between the models in the East are likely to narrow with updates to chemistry. Neither
16 model is capable of simulating 4th highest MDA8 O₃ to within suitable bounds on a
17 day-specific basis at all sites, or even most sites. However, agreement between simulated

1 vs. observed 4th highest MDA8 O₃ is improved for either model when the models and the
2 measurements are sampled on different days.

3 Note that the calculations of background concentrations presented in this section were
4 formulated to answer the question, “what would O₃ concentrations be if there were no
5 anthropogenic sources”. This is different from asking, “how much of the O₃ measured or
6 simulated in a given area is due to background contributions”. Because of potentially
7 strong non-linearities (i.e., the fate, or lifetime, of the background O₃ transported into the
8 urban area will depend on the concentration of the background O₃ in addition to
9 interactions of background O₃ with the local chemical regime) in many urban areas, these
10 estimates by themselves should not be used to answer the second question posed above.
11 The extent of these non-linearities will generally depend on location and time, the
12 strength of concentrated sources and the nature of the chemical regime. Further work is
13 needed on how these estimates of regional background concentrations can be used to help
14 determine the contributions of background sources of O₃ to urban concentrations.

3.5 Monitoring

3.5.1 Routine Monitoring Techniques

15 The federal reference method (FRM) for O₃ measurement is called the
16 Chemiluminescence Method (CLM) and is based on the detection of chemiluminescence
17 resulting from the reaction of O₃ with ethylene gas. The UV absorption photometric
18 analyzers were approved as federal equivalent methods (FEMs) in 1977 and gained rapid
19 acceptance for NAAQS compliance purposes due to ease of operation, relatively low
20 cost, and reliability. The UV absorption method is based on the principle that O₃
21 molecules absorb UV radiation at a wavelength of 254 nm from a mercury lamp. The
22 concentration of O₃ is computed from Beer’s law using the radiation absorbed across a
23 fixed path length, the absorption coefficient, and the measured pressure and temperature
24 in the detection cell. UV absorption photometry is the predominant method for assessing
25 compliance with the NAAQS for O₃. Almost all of the state and local air monitoring
26 stations (SLAMS) that reported data to EPA AQS from 2005 to 2009 used UV absorption
27 photometer FEMs. No CLM monitors, approved as FRMs or FEMs, reported O₃ data to
28 AQS from 2005 to 2009 and only one monitor reported data using a long-path or open
29 path Differential Optical Absorption Spectrometer (DOAS) FEM during this period.

30 The rationale, history, and calibration of O₃ measurements were summarized in the 1996
31 and 2006 O₃ AQCDs ([U.S. EPA, 2006b](#), [1996a](#)) and focused on the state of ambient O₃

1 measurements at that time as well as evaluation of interferences and new developments.
2 This discussion will continue with the current state of O₃ measurements, interferences,
3 and new developments for the period 2005 to 2010.

4 UV O₃ monitors use mercury lamps as the source of UV radiation and employ an O₃
5 scrubber (typically manganese dioxide) to generate an ozone-free air flow to serve as a
6 reference channel for O₃ measurements. There are known interferences with UV O₃
7 monitors. The 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) reported on the investigation of the
8 effects of water vapor, aromatic compounds, ambient particles, mercury vapor and
9 alternative materials in the instrument's O₃ scrubber. The overall conclusions from the
10 review of the scientific literature covered in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) are
11 briefly summarized below.

12 [Kleindienst et al. \(1993\)](#) found water vapor to have no measurable impact and aromatic
13 compounds to have a minor impact (as much as 3% higher than the FRM extrapolated to
14 ambient conditions) on UV absorption measurements. UV O₃ monitor response evaluated
15 by chamber testing using cigarette smoke, reported an elimination of the O₃ monitor
16 response to the smoke when a particle filter was used that filtered out particles less than
17 0.2 μm in diameter ([Arshinov et al., 2002](#)). One study ([Leston et al., 2005](#)) in
18 Mexico City compared a UV O₃ FEM to a CLM FRM. The UV FEM reported
19 consistently higher O₃ than the CLM FRM. They suggested that O₃ measured in ambient
20 air could be too high by 20 to 40 ppb under specific conditions due to positive
21 interference by a number of organic compounds, mainly those produced during the
22 oxidation of aromatic hydrocarbons and some primary compounds such as styrene and
23 naphthalene. However, the concentrations of these compounds were many times higher in
24 both of these environments than are typically found at ambient air monitoring sites in the
25 U.S. Although Hg is also potentially a strong interfering agent, because the Hg resonance
26 line is used in this technique, its concentration would also have to be many times higher
27 than is typically found in ambient air, e.g., as might be found in power plant plumes.
28 Thus, it seems unlikely that such interferences would amount to more than one or two
29 ppb (within the design specifications of the FEM), except under conditions conducive to
30 producing high concentrations of the substances they identified as causing interference.
31 [Leston et al. \(2005\)](#) also presented smog chamber data which demonstrated that heated
32 metal and heated silver wool scrubbers perform better in the presence of aromatic
33 hydrocarbon irradiations than manganese dioxide scrubbers when compared to the FRM.
34 They also suggested the use of humidified calibration gas and alternative scrubber
35 materials to improve UV O₃ measurements. Some O₃ monitor manufacturers now offer
36 heated silver wool scrubbers as an alternative to manganese dioxide. Another possible
37 solution to the O₃ scrubber problem may be the use of a gas phase scrubber such as NO.
38 A commercial version of this has recently been introduced by 2B Technologies as an

1 option on their model 202 FEM; however, it has not been field tested or approved for use
2 as an FEM.

3 Review of the recent literature is summarized below. Study of UV monitors by [Williams
4 et al. \(2006\)](#) concluded that well maintained monitors showed no substantial interferences
5 when operated in locations with high concentrations of potentially interfering VOCs
6 including Nashville, Houston, and the Gulf of Maine. Monitors were tested in urban and
7 suburban environments, as well as on board a ship in both polluted and clean marine air.
8 Comparisons of UV measurements to a non-FRM/FEM NO based CLM demonstrated
9 agreement to within 1%. At the Houston location, they did observe a brief period on one
10 day for about 30 minutes where the UV measurements exceeded the CLM by about 8 ppb
11 (max). This was attributed to probable instrument malfunction.

12 [Wilson and Birks \(2006\)](#) investigated water vapor interference in O₃ measurements by
13 four different UV monitors. In extreme cases where a rapid step change in relative
14 humidity between 0 and 90% was presented, large transitory responses (tens to hundreds
15 of ppb) were found for all monitors tested. Rapid changes in relative humidity such as
16 this would not be expected during typical ambient O₃ measurements and could only be
17 expected during measurement of vertical profiles from balloon or aircraft. The magnitude
18 of the interference and the direction (positive or negative) was dependent on the
19 manufacturer and model. [Wilson and Birks \(2006\)](#) also hypothesized that water vapor
20 interference is caused by physical interactions of water vapor on the detection cell. The
21 O₃ scrubber was also thought to act as a reservoir for water vapor and either added or
22 removed water vapor from the air stream, subsequently affecting the detector signal and
23 producing either a positive or negative response. They demonstrated that the use of a
24 Nafion permeation membrane just before the O₃ detection cell to remove water vapor
25 eliminated this interference.

26 [Dunlea et al. \(2006\)](#) evaluated multiple UV O₃ monitors with two different O₃ scrubber
27 types (manganese dioxide and heated metal wool) in Mexico City. Large spikes in O₃
28 concentrations were observed while measuring diesel exhaust where large increases in
29 particle number density were observed. The interference due to small particles passing
30 through the Teflon filter and scattering/absorbing light in the detection cell were
31 estimated to cause at most a 3% increase in measurements in typical ambient air
32 environments. This estimate pertains to measurements in the immediate vicinity of fresh
33 diesel emissions and most monitor siting guidelines would not place the monitor close to
34 such sources, so actual interferences are expected to be much less than 3%. [Dunlea et al.
35 \(2006\)](#) also observed no evidence for either a positive or negative interference or
36 dependence due to variations in aromatics during their field study.

1 [Li et al. \(2006c\)](#) verified early reports of gas phase mercury interference with the UV O₃
2 measurement. They found that 300 ng/m³ of mercury produced an instrument response of
3 about 35 ppb O₃. Background concentrations of mercury are around 1-2 ng/m³ and
4 expected to produce an O₃ response that would be <1 ppb.

5 [Spicer et al. \(2010\)](#) examined potential UV O₃ monitor interferences by water vapor,
6 mercury, aromatic compounds, and reaction products from smog chamber simulations.
7 Laboratory tests showed little effect of changing humidity on conventional FEM UV O₃
8 monitors with manganese dioxide or heated metal wool scrubbers in the absence of other
9 interferences. Mercury vapor testing produced an O₃ response by the UV monitors that
10 was <1 ppb O₃ per 1 ppt (about 8 ng/m³) mercury vapor. Interference by aromatic
11 compounds at low (3% RH) and high (80% RH) humidity showed some positive
12 responses that varied by UV monitor and ranged from 0 to 2.2 ppb apparent O₃ response,
13 per ppb of aromatic compound tested. The authors acknowledged that the aromatic
14 compounds most likely to interfere are rarely measured in the atmosphere and therefore,
15 make it difficult to assess the impact of these compounds during ambient air monitoring.
16 Comparison of UV and CLM responses to photochemical reaction products in smog
17 chamber simulations at 74 to 85% RH showed varied responses under low
18 (0.125 ppmv/0.06 ppmv) to high (0.50 ppmv/0.19 ppmv) hydrocarbon/NO_x conditions.
19 The conventional UV monitors were as much as 2 ppb higher than the CLM under low
20 hydrocarbon/NO_x conditions and 6 ppb higher under the high hydrocarbon/NO_x
21 conditions. Two FEM UV monitors were also co-located at six sites in Houston from
22 May to October, 2007 with one UV monitor equipped with Nafion permeation
23 membrane. The average difference between 8-h daily max O₃ concentrations using the
24 UV and the UV with Nafion permeation membrane ranged from -4.0 to 4.1 ppb.

3.5.2 Precision and Bias

25 In order to provide decision makers with an assessment of data quality, EPA's Quality
26 Assurance (QA) group derives estimates of both precision and bias for O₃ and the other
27 gaseous criteria pollutants from the biweekly single point quality control (QC) checks
28 using calibration gas, performed at each site by the monitoring agency. The single-point
29 QC checks are typically performed at concentrations around 90 ppb. Annual summary
30 reports of precision and bias can be obtained for each monitoring site at
31 <http://www.epa.gov/ttn/amtic/qareport.html>. The assessment of precision and bias are
32 based on the percent-difference values, calculated from single-point QC checks. The
33 percent difference is based on the difference between the pollutant concentration
34 indicated by monitoring equipment and the known (actual) concentration of the standard
35 used during the QC check. The monitor precision is estimated from the 90% upper

1 confidence limit of the coefficient of variation (CV) of relative percent difference (RPD)
 2 values. The bias is estimated from the 95% upper confidence limit on the mean of the
 3 absolute values of percent differences. The data quality goal for O₃ precision and bias at
 4 the 90 and 95% upper confidence limits is 7% (40 CFR Part 58, Appendix A). [Table 3-3](#)
 5 presents a summary of the number of monitors that meet the precision and bias goal of
 6 7% for 2005 to 2009. Greater than 96% of O₃ monitors met the precision and bias goal
 7 between 2005 and 2009. Another way to look at the precision (CV) and bias (percent
 8 difference) information using the single-point QC check data from the monitoring
 9 network is to present box plots of the monitors' individual precision and percent-
 10 difference data; [Figure 3-17](#) and [Figure 3-18](#) include this information for O₃ monitors
 11 operating from 2005 to 2009.

Table 3-3 Summary of ozone monitors meeting 40 CFR Part 58, Appendix A Precision and Bias Goals

| Year | Number of Monitors | Monitors with Acceptable Precision (%) | Monitors with Acceptable Bias (%) |
|-------------|---------------------------|---|--|
| 2005 | 879 | 96.5 | 96.7 |
| 2006 | 881 | 98.1 | 97.6 |
| 2007 | 935 | 98.1 | 98.1 |
| 2008 | 955 | 97.1 | 96.7 |
| 2009 | 958 | 97.4 | 97.5 |

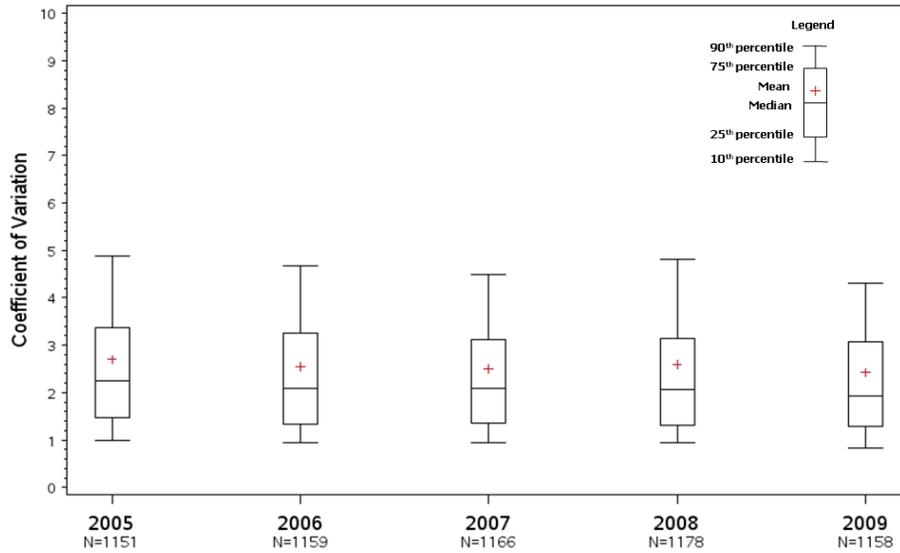


Figure 3-17 Box plots of precision data by year (2005-2009) for all ozone monitors reporting single-point QC check data to AQS.

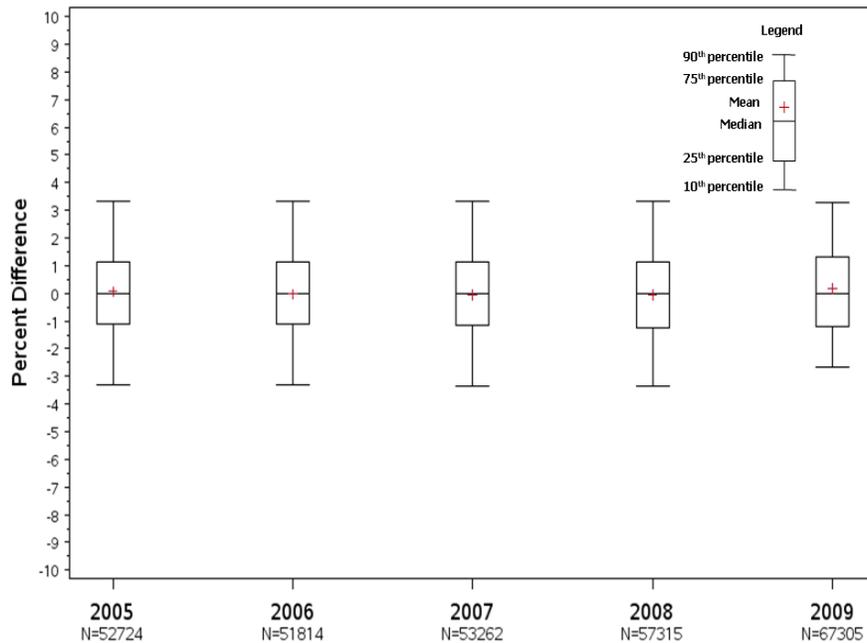


Figure 3-18 Box plots of percent-difference data by year (2005-2009) for all ozone monitors reporting single-point QC check data to AQS.

3.5.2.1 Precision from Co-located UV Ozone Monitors in Missouri

1 The Missouri Department of Natural Resources (MODNR) maintains a network of co-located UV O₃ analyzers. The MODNR provided co-located data from four monitors:
2 co-located at the same monitoring site in Kansas City (AQS ID 290370003) and two
3 co-located at the same monitoring site in St. Louis (AQS ID 291831002). Hourly
4 observations for the co-located measurements at these two sites between April and
5 October, 2006-2009 were used to evaluate precision from co-located UV monitors. These
6 data were then compared with the precision obtained by the biweekly single point QC
7 checks for all sites reporting single-point QC check data to AQS between 2005 and 2009;
8 the method normally used for assessing precision. Box plots of the RPD between the
9 primary and co-located hourly O₃ measurements in Missouri are shown in [Figure 3-19](#)
10 and box plots of the RPD between the actual and indicated QC check for all U.S. sites are
11 shown in [Figure 3-20](#). As mentioned above, the average concentration of the single-point
12 QC check is 90 ppb, whereas the average ambient O₃ concentration measured at the two
13 sites in Missouri was 34 ppb. The mean RPD for the co-located monitors in Missouri and
14 the single-point QC check data from all sites were less than 1 percent.
15

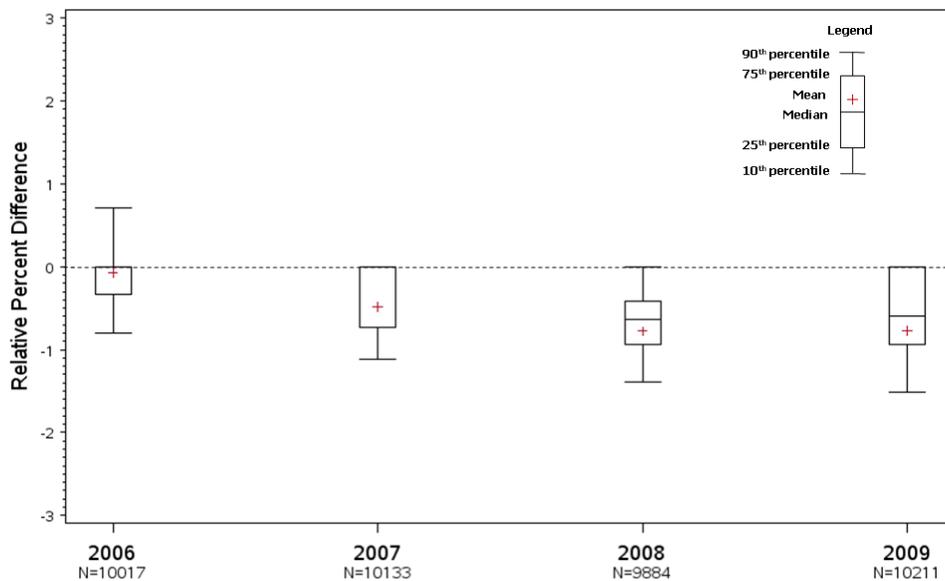


Figure 3-19 Box plots of RPD data by year for the co-located ozone monitors at two sites in Missouri from 2006-2009.

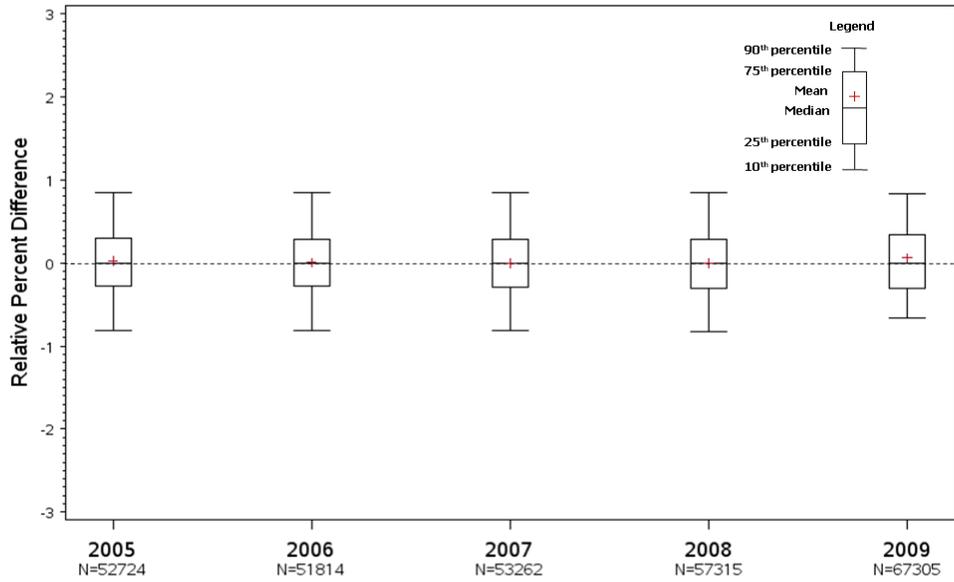


Figure 3-20 Box plots of RPD data by year for all U.S. ozone sites reporting single-point QC check data to AQS from 2005-2009.

3.5.3 Performance Specifications

1 The performance specifications for evaluating and approving new FEMs in accordance
 2 with 40 CFR Part 53 are provided in [Table 3-4](#). These specifications were developed and
 3 originally published in the Federal Register in 1975. Modern, commercially-available
 4 instruments can now perform much better than the requirements specified below. For
 5 example, the lower detectable limit (LDL) performance specification is 10 ppb and the
 6 typical vendor-stated performance for the LDL is now less than 0.60 ppb. The amount of
 7 allowable interference equivalent for total interference substances is 60 ppb, and the
 8 current NAAQS for O₃ is 75 ppb, with an averaging time of 8 hours. Improvements in
 9 new measurement technology have occurred since these performance specifications were
 10 originally developed. These specifications should be revised to more accurately reflect
 11 the necessary performance requirements for O₃ monitors used to support the current
 12 NAAQS.

Table 3-4 Performance specifications for ozone based in 40 CFR Part 53

| Parameter | Specification |
|--------------------------------------|-----------------------|
| Range | 0 – 0.5 ppm (500 ppb) |
| Noise | 0.005 ppm (5 ppb) |
| LDL – defined as two times the noise | 0.01 ppm (10 ppb) |
| Interference equivalent | |
| Each interfering substance | ± 0.02 ppm (20 ppb) |
| Total interfering substances | 0.06 ppm (60 ppb) |
| Zero drift | |
| 12 h | ± 0.02 ppm (20 ppb) |
| 24 h | ± 0.02 ppm (20 ppb) |
| Span Drift, 24 h | |
| 20% of upper range limit | ± 20.0% |
| 80% of upper range limit | ± 5.0% |
| Lag time | 20 min |
| Rise time | 15 min |
| Fall time | 15 min |
| Precision | |
| 20% of upper range limit | 0.01 ppm (10 ppb) |
| 80% of upper range limit | 0.01 ppm (10 ppb) |

3.5.4 Monitor Calibration

1 The calibration of O₃ monitors was summarized in detail in the 1996 O₃ AQCD ([U.S.](#)
2 [EPA, 1996a](#)). The calibration of O₃ monitors is done using an O₃ generator and UV
3 photometers. UV photometry is the prescribed procedure for the calibration of reference
4 methods to measure O₃ in the atmosphere. Because O₃ is unstable and cannot be stored,
5 the O₃ calibration procedure specifically allows the use of transfer standards for
6 calibrating ambient O₃ monitors. A transfer standard is calibrated against a standard of
7 high authority and traceability and then moved to another location for calibration of O₃
8 monitors. The EPA and the National Institute of Standards and Technology (NIST) have
9 established a network of standard reference photometers (SRPs) that are used to verify
10 transfer standards. The International Bureau of Weights and Measures (BIPM) maintain
11 one NIST SRP (SRP27) as the World's O₃ reference standard. NIST maintains two SRPs
12 (SRP0 and SRP2) that are used for comparability to ten other SRPs maintained by the
13 EPA's Regional QA staff.

14 SRPs have been compared to other reference standards. [Tanimoto et al. \(2006\)](#) compared
15 NIST SRP35, owned by the National Institute for Environmental Studies in Japan, to gas

1 phase titration (GPT). The SRP was found to be 2% lower than GPT. GPT is no longer
2 used as a primary or transfer standard in the U.S. [Viallon et al. \(2006\)](#) compared SRP27
3 built at BIPM to four other NIST SRPs maintained by BIPM (SRP28, SRP31, SRP32,
4 and SRP33). A minimum bias of +0.5% was found for all SRP measurement results, due
5 to use of the direct cell length measurement for the optical path length; this bias was
6 accounted for by applying the appropriate correction factor. Study of the bias-corrected
7 SRPs showed systematic biases and measurement uncertainties for the BIPM SRPs. A
8 bias of -0.4% in the instrument O₃ mole fraction measurement was identified and
9 attributed to non-uniformity of the gas temperature in the instrument gas cells, which was
10 compensated by a bias of +0.5% due to an under-evaluation of the UV light path length
11 in the gas cells. The relative uncertainty of the O₃ absorption cross section was 2.1% at
12 253.65 nm and this was proposed as an internationally accepted consensus value until
13 sufficient experimental data is available to assign a new value.

14 In November, 2010, the EPA revised the Technical Assistance Document for *Transfer*
15 *Standards for Calibration of Air Monitoring Analyzers for Ozone* ([U.S. EPA, 2010f](#)) that
16 was first finalized in 1979 ([U.S. EPA, 1979b](#)). The revision removed methods no longer
17 in use and updated definitions and procedures where appropriate. In the revised
18 document, the discussion of transfer standards for O₃ applies to the family of standards
19 that are used beyond SRPs or Level 1 standards. To reduce confusion, EPA reduced the
20 number of common terms that were used in the past such as: primary standard, local
21 primary standard, transfer standard, and working standard. Beyond the SRPs, all other
22 standards are considered transfer standards.

3.5.5 Other Monitoring Techniques

3.5.5.1 Portable UV Ozone Monitors

23 Small, lightweight, and portable UV O₃ monitors with low power consumption are
24 commercially available. These monitors are based on the same principle of UV
25 absorption by O₃ at 254 nm. Monitors of this type are typically used for vertical profiling
26 using balloons, kites, or light aircraft where space and weight are limited. They have also
27 been used for monitoring at remote locations such as National Parks. [Burley and Ray](#)
28 [\(2007\)](#) compared portable O₃ monitor measurements to those from a conventional UV
29 monitor in Yosemite National Park. Calibrations of the portable O₃ monitors against a
30 transfer standard resulted in an overall precision of ± 4 ppb and accuracy of $\pm 6\%$. Field
31 measurement comparisons between the portable and conventional monitor at Turtleback
32 Dome showed the portable monitor to be 3.4 ppb lower on average, with daytime

1 deviation typically on the order of 0-3 ppb. Agreement between the portable and
2 conventional monitor during daylight hours (9:00 a.m. to 5:00 p.m. PST) resulted in an
3 R^2 of 0.95, slope of 0.95, and intercept of 0.36 ppb. Substantial deviations were observed
4 in the predawn hours where the portable monitor was consistently low. These deviations
5 were attributed to the difference in sampling inlet location. The portable monitor was
6 located at 1.3 meters above ground and the conventional monitor was located at
7 10 meters above ground. Agreement between the portable and conventional monitors for
8 all hours sampled resulted in an R^2 of 0.88, slope of 1.06, and intercept of -6.8 ppb.
9 ([Greenberg et al., 2009](#)) also compared a portable UV O₃ monitor to a conventional UV
10 monitor in Mexico City and obtained good agreement for a 14 day period with an R^2 of
11 0.97, slope of 0.97, and intercept of 6 ppb. One portable O₃ monitor was recently
12 approved as an FEM (EQOA-0410-190) on April 27, 2010 (75 FR 22126).

3.5.5.2 NO-based Chemiluminescence Monitors

13 One commercially available NO-based chemiluminescence monitor has been approved as
14 an FEM (EQOA-0611-199) on October 7, 2011 (75 FR 62402). It may also be designated
15 as a second or replacement FRM since the ethene based FRMs are no longer
16 manufactured. Although this is a relatively new monitor, other NO-based CLM
17 instruments have been custom built for various field studies since the early 1970s. A
18 commercial version that measured both O₃ and NO_x was offered in the early 1970s but
19 failed to gain commercial acceptance. Initial testing with SO₂, NO₂, Cl₂, C₂H₂, C₂H₄ and
20 C₃H₆ ([Stedman et al., 1972](#)) failed to identify any interferences. In the intervening years,
21 custom built versions have not been found to have any interference; however, they do
22 experience a slight decrease in response with increasing relative humidity (due to
23 quenching of the excited species by the water molecules). The new NO-based CLM
24 solves this problem with the use of a Nafion membrane dryer. A custom built NO-based
25 CLM similar to the FEM was used by [Williams et al. \(2006\)](#) in Houston, TX; Nashville,
26 TN; and aboard ship along the New England coast. It was found to be in good agreement
27 with a standard UV based FEM and with a custom built DOAS.

3.5.5.3 Passive Air Sampling Devices and Sensors

28 A passive O₃ sampling device depends on the diffusion of O₃ in air to a collecting or
29 indicating medium. In general, passive samplers are not adequate for compliance
30 monitoring because of the limitations in averaging time (typically one week or more),
31 particularly for O₃. However, these devices are valuable for personal human exposure
32 estimates and for obtaining long-term data in rural areas where conventional UV

1 monitors are not practical or feasible to deploy. The 1996 O₃ AQCD ([U.S. EPA, 1996a](#))
2 provided a detailed discussion of passive samplers, along with the limitations and
3 uncertainties of the samplers evaluated and published in the literature from 1989 to 1995.
4 The 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) provided a brief update on available passive
5 samplers developed for use in direct measurements of personal exposure published
6 through 2004. The 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) also noted the sensitivity of these
7 samplers to wind velocity, badge placement, and interference by other co-pollutants that
8 may result in measurement error.

9 Subsequent evaluations of passive diffusion samplers in Europe showed good correlation
10 when compared to conventional UV O₃ monitors, but a tendency for the diffusion
11 samplers to overestimate the O₃ concentration ([Gottardini et al., 2010](#); [Vardoulakis et al.,
12 2009](#); [Buzica et al., 2008](#)). The bias of O₃ diffusion tubes were also found to vary with
13 concentration, season, and exposure duration ([Vardoulakis et al., 2009](#)). Development of
14 simple, inexpensive, passive O₃ measurement devices that rely on O₃ detection papers
15 and a variety of sensors with increased time resolution (sampling for hours instead of
16 weeks) and improved sensitivity have been reported ([Maruo et al., 2010](#); [Ebeling et al.,
17 2009](#); [Miwa et al., 2009](#); [Ohira et al., 2009](#); [Maruo, 2007](#); [Utembe et al., 2006](#)).
18 Limitations for some of these sensors and detection papers include air flow dependence
19 and relative humidity interference.

3.5.5.4 Differential Optical Absorption Spectrometry

20 Optical remote sensing methods can provide direct, sensitive, and specific measurements
21 of O₃ over a broad area or open path in contrast with conventional single-point UV
22 monitors. The 1996 O₃ AQCD ([U.S. EPA, 1996a](#)) provided a brief discussion of DOAS
23 for O₃ measurements and cited references to document the sensitivity (1.5 ppb for a 1-
24 minute averaging time), correlation ($r = 0.89$), and agreement (on the order of 10%) with
25 UV O₃ monitors ([Stevens, 1993](#)). The 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) provided an
26 update on DOAS where a positive interference due to an unidentified absorber was noted
27 ([Reisinger, 2000](#)).

28 More recent study of the accuracy of UV absorbance monitors by [Williams et al. \(2006\)](#)
29 compared UV and DOAS measurements at two urban locations. In order to compare the
30 open path measurements and UV, the data sets were averaged to 30-minute periods and
31 only data when the boundary layer was expected to be well mixed (between 10:00 a.m.
32 and 6:00 p.m. CST) were evaluated. The comparisons showed variations of no more
33 than $\pm 7\%$ (based on the slope of the linear least squares regression over a concentration
34 range from about 20 to 200 ppb) and good correlation ($R^2 = 0.96$ and 0.98). [Lee et al.](#)

1 [\(2008b\)](#) evaluated DOAS and UV O₃ measurements in Korea and found the average
2 DOAS concentration to be 8.6% lower than the UV point measurements with a good
3 correlation ($R^2 = 0.94$).

4 DOAS has also been used for the measurement of HNO₂ (or HONO). DOAS was
5 compared to chemical point-measurement methods for HONO. [Acker et al. \(2006\)](#)
6 obtained good results when comparing wet chemical and DOAS during well mixed
7 atmospheric conditions (wet chemical = $0.009 + 0.92 \times \text{DOAS}$; $r = 0.7$). [Kleffmann and](#)
8 [Wiesen \(2008\)](#) noted that interferences with the HONO wet chemical methods can affect
9 results from inter-comparison studies if not addressed. In an earlier study, [Kleffmann et](#)
10 [al. \(2006\)](#) demonstrated that when the interferences were addressed, excellent agreement
11 with DOAS can be obtained. [Stutz et al. \(2009\)](#) found good agreement (15% or better)
12 between DOAS and a wet chemical method (Mist Chamber/Ion Chromatography) in
13 Houston, TX except generally during mid-day when the chemical method showed a
14 positive bias that may have been related to concentrations of O₃. DOAS remains
15 attractive due to its sensitivity, speed of response, and ability to simultaneously measure
16 multiple pollutants; however, further inter-comparisons and interference testing are
17 recommended.

3.5.5.5 Satellite Remote Sensing

18 Satellite observations for O₃ are growing as a resource for many purposes, including
19 model evaluation, assessing emissions reductions, pollutant transport, and air quality
20 management. Satellite remote sensing instruments do not directly measure the
21 composition of the atmosphere. Satellite retrievals are conducted using the solar
22 backscatter or thermal infrared emission spectra and a variety of algorithms. Most
23 satellite measurement systems have been developed for stratospheric measurement of the
24 total O₃ column. Mathematical techniques have been developed and must be applied to
25 derive information from these systems about tropospheric O₃ ([Tarasick and Slater, 2008](#);
26 [Ziemke et al., 2006](#)). Direct retrieval of global tropospheric O₃ distributions from solar
27 backscattered UV spectra have been reported from OMI and the Global Ozone
28 Monitoring Experiment (GOME) ([Liu et al., 2006](#)). Another satellite measurement
29 system, Tropospheric Emission Spectrometer (TES), produces global-scale vertical
30 concentration profiles of tropospheric O₃ from measurements of thermal infrared
31 emissions. TES has been designed specifically to focus on mapping the global
32 distribution of tropospheric O₃ extending from the surface to about 10-15 km altitude
33 ([Beer, 2006](#)).

1 In order to improve the understanding of the quality and reliability of the data, satellite-
2 based observations of total column and tropospheric O₃ have been validated in several
3 studies using a variety of techniques, such as aircraft observations, ozonesondes, CTMs,
4 and ground-based spectroradiometers. [Antón et al. \(2009\)](#) compared satellite data from
5 two different algorithms (OMI-DOAS and OMI-TOMS) with total column O₃ data from
6 ground-based spectroradiometers at five locations. The satellite total column O₃ data
7 underestimated ground-based measurements by less than 3%. [Richards et al. \(2008\)](#)
8 compared TES tropospheric O₃ profiles using airborne differential absorption lidar
9 (DIAL) and found TES to have a 7 ppbv positive bias relative to DIAL throughout the
10 troposphere. [Nassar et al. \(2008\)](#) compared TES O₃ profiles and ozonesonde coincidences
11 and found a positive bias of 3-10 ppbv for TES. [Worden et al. \(2007a\)](#) also compared
12 TES with ozonesondes and found TES O₃ profiles to be biased high in the upper
13 troposphere (average bias of 16.8 ppbv for mid-latitudes and 9.8 ppbv for the tropics) and
14 biased low in the lower troposphere (average bias of -2.6 ppbv for mid-latitudes and -
15 7.4 ppbv for the tropics). Comparisons of TES and OMI with ozonesondes by [Zhang et](#)
16 [al. \(2010b\)](#) showed a mean positive bias of 5.3 ppbv (10%) for TES and 2.8 ppbv (5%) for
17 OMI at 500 hPa. In addition, [Zhang et al. \(2010b\)](#) used a CTM (GEOS-Chem) to
18 determine global differences between TES and OMI. They found differences between
19 TES and OMI were generally ± 10 ppbv except at northern mid-latitudes in summer and
20 over tropical continents. Satellite observations have also been combined (e.g., OMI and
21 TES) to improve estimates of tropospheric O₃ ([Worden et al., 2007b](#)).

3.5.6 Ambient Ozone Network Design

3.5.6.1 Monitor Siting Requirements

22 To monitor compliance with the NAAQS, state and local monitoring agencies operate O₃
23 monitoring sites at various locations depending on the area size (population and
24 geographic characteristics¹) and typical peak concentrations (expressed in percentages
25 below, or near the O₃ NAAQS). SLAMS make up the ambient air quality monitoring
26 sites that are primarily needed for NAAQS comparisons, but may also serve some other
27 basic monitoring objectives that include: providing air pollution data to the general public
28 in a timely manner; emissions strategy development; and support for air pollution
29 research. SLAMS include National Core (NCore), Photochemical Assessment
30 Monitoring Stations (PAMS), and all other State or locally-operated stations except for
31 the monitors designated as special purpose monitors (SPMs).

¹ Geographic characteristics such as complexity of terrain, topography, land use, etc.

1 The SLAMS minimum monitoring requirements to meet the O₃ design criteria are
2 specified in 40 CFR Part 58, Appendix D. Although NCore and PAMS are a subset of
3 SLAMS, the monitoring requirements for those networks are separate and discussed
4 below. The minimum number of O₃ monitors required in a Metropolitan Statistical Area
5 (MSA) ranges from zero for areas with a population of at least 50,000 and under 350,000
6 with no recent history of an O₃ design value¹ greater than 85 percent of the NAAQS, to
7 four for areas with a population greater than 10 million and an O₃ design value greater
8 than 85 percent of the NAAQS. Within an O₃ network, at least one site for each MSA, or
9 Combined Statistical Area (CSA) if multiple MSAs are involved, must be designed to
10 record the maximum concentration for that particular metropolitan area. More than one
11 maximum concentration site may be necessary in some areas. The spatial scales for O₃
12 sites are neighborhood, urban and regional.

- 13 ▪ Neighborhood scale: represents concentrations within some extended area of
14 the city that has relatively uniform land use with dimensions in the 0.5-4.0 km
15 range. The neighborhood and urban scales listed below have the potential to
16 overlap in applications that concern secondary or homogeneously distributed
17 primary air pollutants.
- 18 ▪ Urban scale: represents concentrations within an area of city-like dimensions,
19 on the order of 4-50 km. Within a city, the geographic placement of sources
20 may result in there being no single site that can be said to represent air quality
21 on an urban scale.
- 22 ▪ Regional scale: usually defines a rural area of reasonably homogeneous
23 geography without large sources, and extends from tens to hundreds of
24 kilometers.

25 Since O₃ concentrations decrease appreciably in the colder parts of the year in many
26 areas, O₃ is required to be monitored at SLAMS monitoring sites only during the “ozone
27 season.” Table D-3 of 40 CFR Part 58, Appendix D lists the beginning and ending month
28 of the ozone season for each U.S. state or territory. Most operate O₃ monitors only during
29 the ozone season. Those that operate some or all of their O₃ monitors on a year-round
30 basis include Arizona, California, Hawaii, Louisiana, Nevada, New Mexico, Puerto Rico,
31 Texas, American Samoa, Guam and the Virgin Islands.

32 The total number of SLAMS O₃ sites needed to support the basic monitoring objectives
33 includes more sites than the minimum numbers required in 40 CFR Part 58, Appendix D.
34 In 2010, there were 1250 O₃ monitoring sites reporting values to the EPA AQS database

¹ A design value is a statistic that describes the air quality status of a given area relative to the level of the NAAQS. Design values are typically used to classify nonattainment areas, assess progress towards meeting the NAAQS, and develop control strategies. See <http://epa.gov/airtrends/values.html> (U.S. EPA, 2010a) for guidance on how these values are defined.

1 (Figure 3-21). Monitoring site information for EPA’s air quality monitoring networks is
2 available in spreadsheet format (CSV) and keyhole markup language format (KML or
3 KML or KMZ) that is compatible with Google Earth™ and other software applications on the
4 AirExplorer website (U.S. EPA, 2011d). States may operate O₃ monitors in non-urban or
5 rural areas to meet other objectives (e.g., support for research studies of atmospheric
6 chemistry or ecosystem impacts). These monitors are often identified as SPMs and can be
7 operated up to 24 months without being considered in NAAQS compliance
8 determinations. The current monitor and probe siting requirements have an urban focus
9 and do not address the siting for SPMs or monitors in non-urban, rural areas to support
10 ecosystem impacts and the secondary standards.

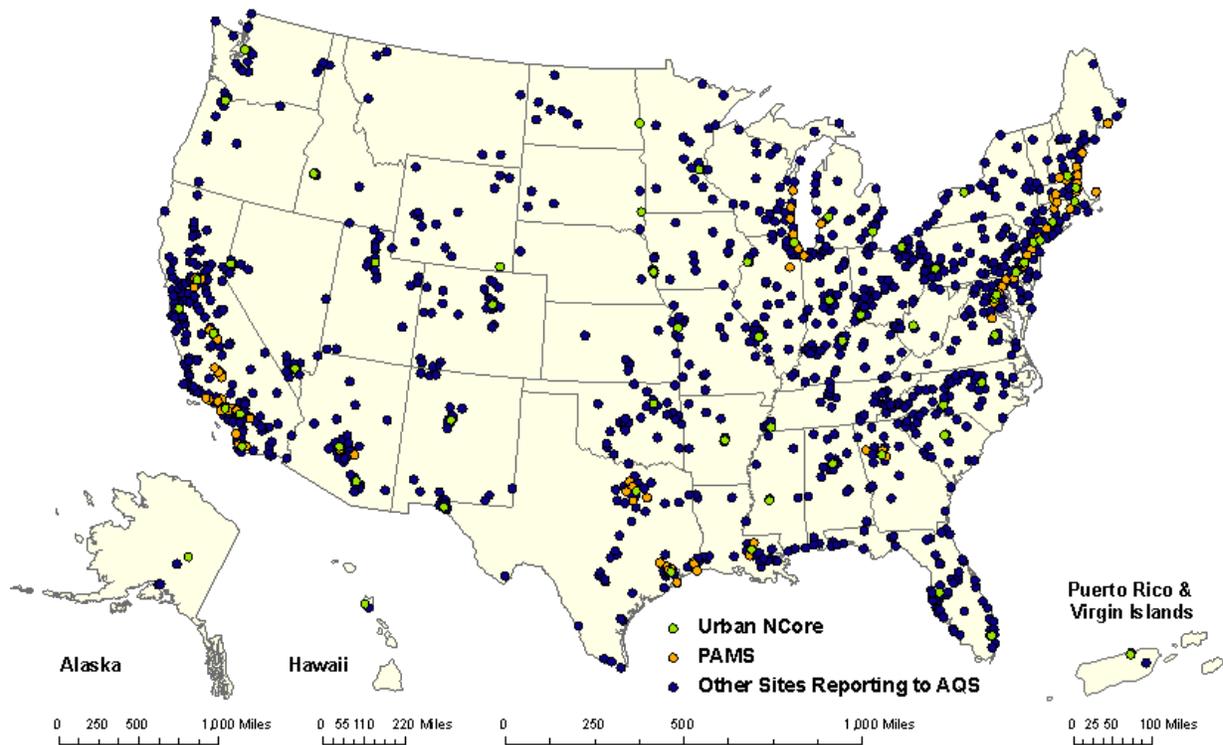


Figure 3-21 U.S. ozone sites reporting data to AQS in 2010.

11 NCore is a new multipollutant monitoring network implemented to meet multiple
12 monitoring objectives. Those objectives include: timely reporting of data to the public
13 through AirNow (U.S. EPA, 2011a); support for the development of emission reduction
14 strategies; tracking long-term trends of criteria pollutants and precursors; support to
15 ongoing reviews of the NAAQS and NAAQS compliance; model evaluation; support for

1 scientific research studies; and support for ecosystem assessments. Each state is required
2 to operate at least one NCore site. The NCore monitoring network began January 1, 2011
3 at about 80 stations (about 60 urban and 20 rural sites). NCore has leveraged the use of
4 sites in existing networks; for example, some IMPROVE sites also serve as rural NCore
5 sites. In addition to O₃, other components including CO, NO_x, NO_y, SO₂, and basic
6 meteorology are also measured at NCore sites. The spatial scale for urban NCore stations
7 is urban or neighborhood; however, a middle-scale¹ site may be acceptable in cases
8 where the site can represent many such locations throughout a metropolitan area. Rural
9 NCore sites are located at a regional or larger scale, away from any large local emission
10 sources so that they represent ambient concentrations over an extensive area. Ozone
11 monitors at NCore sites are operated year round.

12 PAMS provides more comprehensive data on O₃ in areas classified as serious, severe, or
13 extreme nonattainment for O₃. In addition to O₃, PAMS provides data for NO_x, NO_y,
14 VOCs, carbonyls, and meteorology. The PAMS network design criteria are based on
15 locations relative to O₃ precursor source areas and predominant wind directions
16 associated with high O₃ concentrations. The overall network design is location specific
17 and geared toward enabling characterization of precursor emission sources in the area, O₃
18 transport, and photochemical processes related to O₃ nonattainment. Minimum
19 monitoring for O₃ and its precursors is required annually during the months of June, July,
20 and August when peak O₃ concentrations are expected. In 2006, the EPA reduced the
21 minimum PAMS monitoring requirements (71 FR 61236). There were a total of 92
22 PAMS sites reporting values to the AQS data base in 2010.

23 CASTNET is a regional monitoring network established to assess trends in acidic
24 deposition due to emission reduction regulations. CASTNET also provides concentration
25 measurements of air pollutants involved in acidic deposition, such as sulfate and nitrate,
26 in addition to the measurement of O₃. CASTNET O₃ monitors operate year round and are
27 primarily located in rural areas. In 2010, there were 80 CASTNET sites located in, or
28 near, rural areas. As part of CASTNET, the National Park Service (NPS) operates 23
29 sites located in national parks and other Class-i areas. Ozone data collected at the 23 NPS
30 sites is compliant with the SLAMS QA requirements in 40 CFR Part 58, Appendix A.
31 Ozone measurements at the remaining CASTNET sites were not collected with the QA
32 requirements for SLAMS outlined in 40 CFR Part 58, Appendix A, and therefore, these
33 O₃ data cannot be used for NAAQS compliance purposes. The SLAMS QA requirements
34 and procedures are currently being implemented at the remaining sites.

35 The NPS also operates a Portable Ozone Monitoring Systems (POMS) network. The
36 POMS couples the small, low-power O₃ monitor with a data logger, meteorological

¹ Middle scale defines an area up to several city blocks in size with dimensions ranging from about 100 to 500 m.

1 measurements, and solar power in a self contained system for monitoring in remote
2 locations. Typical uses for the POMS data include research projects, survey monitoring,
3 and assessments of spatial O₃ distribution. The portable O₃ monitor in use by the NPS
4 was recently designated as an equivalent method for O₃ (75 FR 22126). Seventeen NPS
5 POMS monitors were operating in 2010 (NPS, 2011). A map of the rural NCore sites,
6 along with the CASTNET, and the NPS POMS sites are shown in Figure 3-22. As can be
7 seen from Figure 3-21 and Figure 3-22, vast rural areas of the country still exist without
8 any monitor coverage. Monitoring opportunities exist in these areas where relatively few
9 and easily characterized precursor sources dominate and could be used to improve
10 understanding of O₃ formation.

11
12

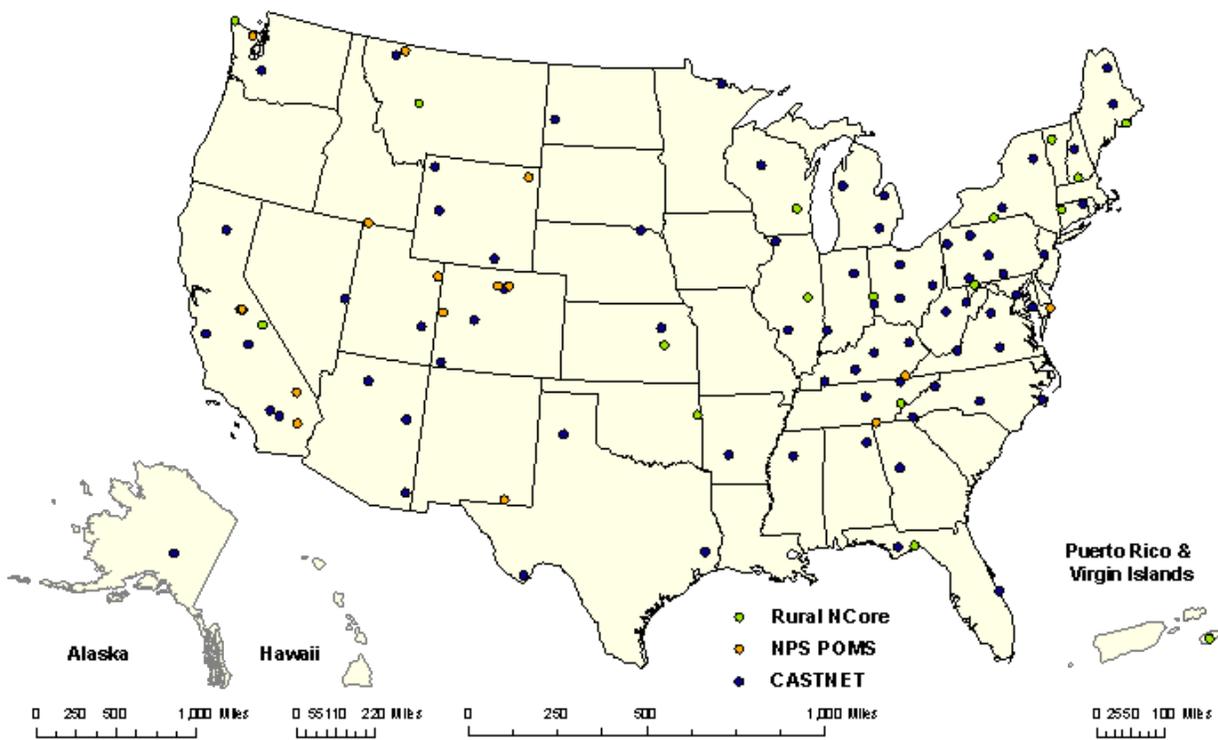


Figure 3-22 U.S. Rural NCore, CASTNET and NPS POMS ozone sites in 2010.

3.5.6.2 Probe/Inlet Siting Requirements

1 Probe and monitoring path siting criteria for ambient air quality monitoring are contained
2 in 40 CFR Part 58, Appendix E. For O₃, the probe must be located between 2 and
3 15 meters above ground level and be at least 1 meter away (both in the horizontal and
4 vertical directions) from any supporting structure, walls, etc. If it is located on the side of
5 a building, it must be located on the windward side, relative to prevailing wind direction
6 during the season of highest potential O₃ concentration. Ozone monitors are placed to
7 determine air quality in larger areas (neighborhood, urban, or regional scales) and
8 therefore, placement of the monitor probe should not be near local, minor sources of NO,
9 O₃-scavenging hydrocarbons, or O₃ precursors. The probe or inlet must have unrestricted
10 air flow in an arc of at least 180 degrees and be located away from any building or
11 obstacle at a distance of at least twice the height of the obstacle. The arc of unrestricted
12 air flow must include the predominant wind direction for the season of greatest O₃
13 concentrations. Some exceptions can be made for measurements taken in street canyons
14 or sites where obstruction by buildings or other structures is unavoidable. The scavenging
15 effect of trees on O₃ is greater than other pollutants and the probe/inlet must be located at
16 least 10 meters from the tree drip line to minimize interference with normal air flow.
17 When siting O₃ monitors near roadways, it is important to minimize the destructive
18 interferences from sources of NO, since NO reacts readily with O₃. For siting
19 neighborhood and urban scale O₃ monitors, guidance on the minimum distance from the
20 edge of the nearest traffic lane is based on roadway average daily traffic count (40 CFR
21 Part 58, Appendix E, Table E-1). The minimum distance from roadways is 10 meters
22 (average daily traffic count ≤ 1,000) and increases to a maximum distance of 250 meters
23 (average daily traffic count ≥ 110,000).

3.6 Ambient Concentrations

24 This section investigates spatiotemporal variability in ambient O₃ concentrations and
25 associations between O₃ and copollutants. To set the stage for the rest of the section,
26 common O₃ measurement units, metrics, and averaging times are described and
27 compared in Section [3.6.1](#). Spatial variability is covered in Section [3.6.2](#) and is divided
28 into urban-focused variability and rural-focused variability. Urban-focused variability is
29 organized by scale, extending from national-scale down to neighborhood-scale and the
30 near-road environment. Rural-focused variability is organized by region and includes
31 observations of ground-level vertical O₃ gradients where available. Temporal variability
32 is covered in Section [3.6.3](#) and is organized by time, extending from multiyear trends
33 down to hourly (diel) variability. In many instances, spatial and temporal variability are

1 inseparable (e.g., seasonal dependence to spatial variability), resulting in some overlap
2 between Section [3.6.2](#) and Section [3.6.3](#). Finally, Section [3.6.4](#) covers associations
3 between O₃ and co-pollutants including CO, SO₂, NO₂, PM_{2.5} and PM₁₀.

4 As noted in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)), O₃ is the only photochemical oxidant
5 other than nitrogen dioxide (NO₂) that is routinely monitored and for which a
6 comprehensive database exists. Data for other photochemical oxidants (e.g., PAN, H₂O₂,
7 etc.) typically have been obtained only as part of special field studies. Consequently, no
8 data on nationwide patterns of occurrence are available for these other oxidants; nor are
9 extensive data available on the relationships of concentrations and patterns of these
10 oxidants to those of O₃. As a result, this section focuses solely on O₃, the NAAQS
11 indicator for photochemical oxidants. The majority of ambient O₃ data reported in this
12 section were obtained from AQS, EPA's repository for detailed, hourly data that has been
13 subject to EPA quality control and assurance procedures (the AQS network was
14 described in Section [3.5](#)).

3.6.1 Measurement Units, Metrics, and Averaging Times

15 Several approaches are commonly used for reporting O₃ data. In atmospheric sciences
16 and epidemiology, O₃ is frequently reported as a concentration, expressed as a volume-to-
17 volume mixing ratio, commonly measured in ppm or ppb. In human exposure, O₃ is
18 frequently reported as a cumulative exposure, expressed as a mixing ratio times time
19 (e.g., ppm-h). In ecology, cumulative exposure indicators are frequently used that extend
20 over longer time periods, such as growing season or year. This section focuses on
21 ambient concentrations derived primarily from hourly average O₃ measurements and
22 concentrations are reported in ppb wherever possible. Further details on human and
23 ecological exposure metrics can be found in Chapter [4](#) and Chapter [9](#), respectively.

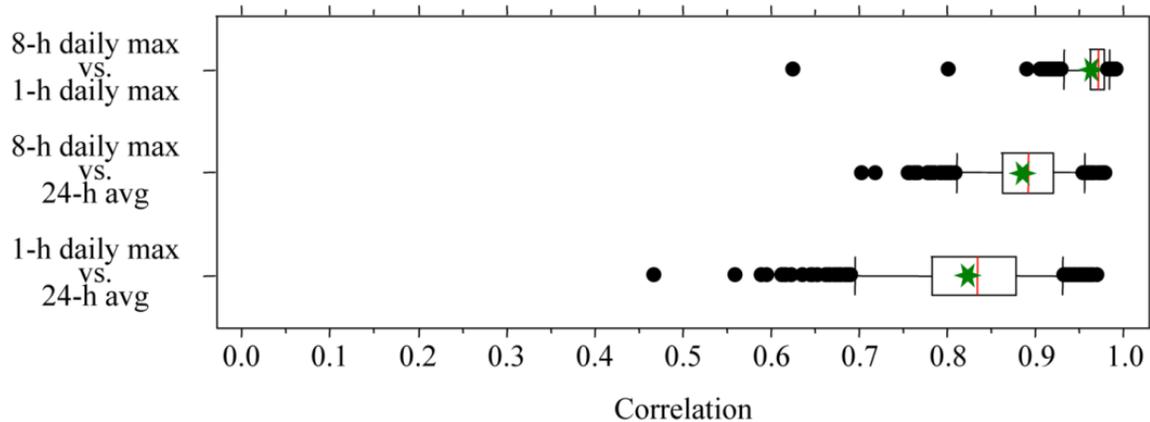
24 As discussed in Section [3.5](#), most continuous O₃ monitors report hourly average
25 concentrations to AQS with a required precision of 10 ppb and LDL of 10 ppb (see
26 [Table 3-4](#)). This data can be used as reported (1-h avg), or further summarized in one of
27 several ways to focus on important aspects of the data while simultaneously reducing the
28 volume of information. Three common daily reporting metrics include: (1) the average of
29 the hourly observations over a 24-h period (24-h avg); (2) the maximum hourly
30 observation occurring in a 24-h period (1-h daily max); and (3) the maximum 8-h running
31 average of the hourly observations occurring in a 24-h period (8-h daily max)¹.

32 Throughout this ISA and the literature, O₃ concentrations are reported using different

¹ For O₃ regulatory monitoring purposes, the 8-h daily max is calculated by first generating all 8-h running averages and storing these averages hourly by the first hour in the 8-h period. The 8-h daily max is then set equal to the maximum of the 24 individual 8-h avg occurring in a given day.

1 averaging times as appropriate, making it important to recognize the differences between
2 these metrics.

3 Nation-wide, year-round 1-h avg O₃ data reported to AQS from 2007-2009 was used to
4 compare these different daily metrics. Correlations between the 24-h avg, 1-h daily max
5 and 8-h daily max metrics were generated on a site-by-site basis. [Figure 3-23](#) contains
6 box plots of the distribution in correlations from all sites. The top comparison in
7 [Figure 3-23](#) is between 8-h daily max and 1-h daily max O₃. Not surprisingly, these two
8 metrics are very highly correlated (median r = 0.97, IQR = 0.96-0.98). There are a couple
9 outlying sites, with correlations between these two metrics as low as 0.63, but 95% of
10 sites have correlations above 0.93. The middle comparison in [Figure 3-23](#) is between 8-h
11 daily max and 24-h avg O₃. For these metrics, the distribution in correlations is shifted
12 down and broadened out (median r = 0.89, IQR = 0.86-0.92). Finally, the bottom
13 comparison in [Figure 3-23](#) is between 1-h daily max and 24-h avg O₃. Again, for these
14 metrics the distribution in correlations is shifted down and broadened out relative to the
15 other two comparisons (median r = 0.83, IQR = 0.78-0.88). The correlation between the
16 two daily-maximum metrics (1-h daily max and 8-h daily max) are quite high for most
17 sites, but correlations between the daily maximum metrics and the daily average metric
18 (24-h avg) are lower. This illustrates the influence of the overnight period on the 24-h avg
19 O₃ concentration. In contrast, the 1-h daily max and 8-h daily max are more indicative of
20 the daytime, higher O₃ periods. The correlation between these metrics, however, can be
21 very site-specific, as is evident from the broad range in correlations in [Figure 3-23](#) for all
22 three comparisons. Therefore, understanding which O₃ metric is being used in a given
23 study is very important since they capture different aspects of O₃ temporal variability.



Note: Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers), and extremes (black circles).

Figure 3-23 Distribution in nation-wide year-round site-level correlations between daily ozone metrics including 24-h avg, 1-h daily max and 8-h daily max using AQS data, 2007-2009.

1 The median 1-h daily max, 8-h daily max, and 24-h avg O₃ concentrations across all sites
 2 included in the 3-year nation-wide data set were 44, 40, and 29 ppb, respectively.
 3 Representing the upper end of the distribution, the 99th percentiles of these same metrics
 4 across all sites were 94, 80, and 60 ppb, respectively. While the ratio of these metrics will
 5 vary by location, typically the 1-h daily max will be the highest value representing peak
 6 concentrations and the 24-h avg will be considerably lower representing daily average
 7 concentrations incorporating the overnight period. The 8-h daily max typically represents
 8 the higher mid-day concentrations and will generally lie somewhere between the other
 9 two metrics¹.

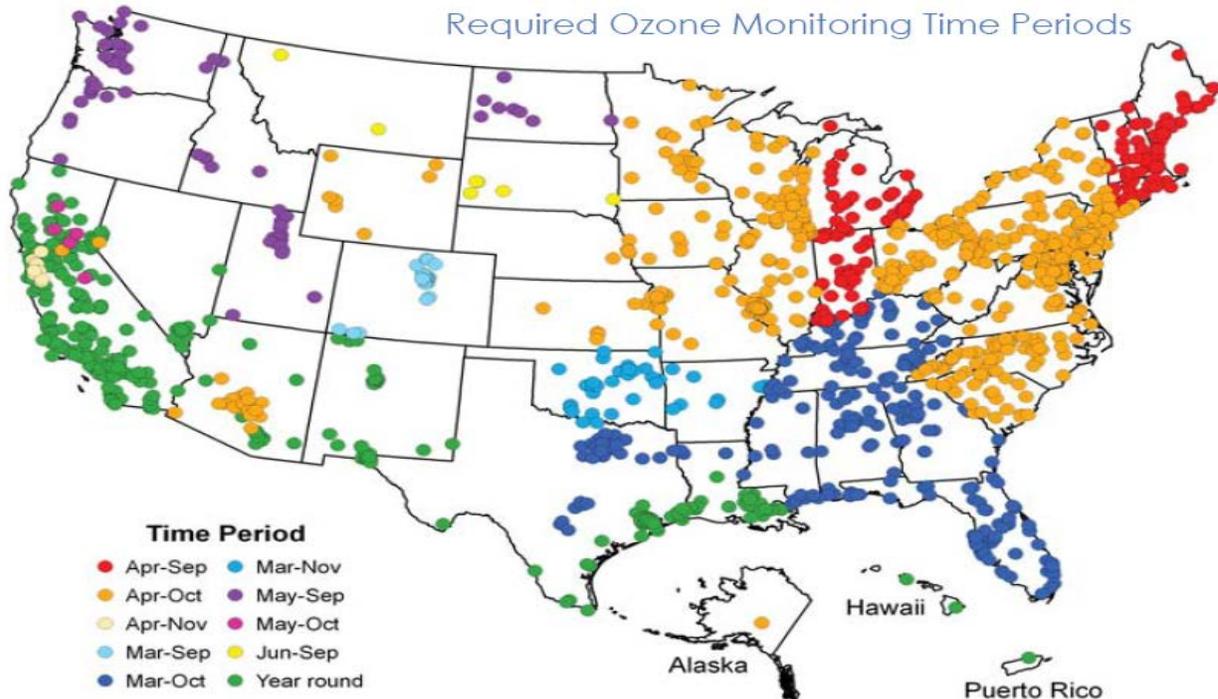
¹ The 8-h daily max is not strictly limited to lie between the 1-h daily max and the 24-h avg since the 8-h averaging period used to calculate the 8-h daily max can extend into the morning hours of the subsequent day. However, the 8-h daily max typically incorporates the middle of the day when O₃ concentrations are at their highest, resulting in an 8-h daily max somewhere between the 1-h daily max and the 24-h avg calculated for that day.

3.6.2 Spatial Variability

3.6.2.1 Urban-Focused Variability

National-Scale Variability

1 AQS contains a large depository of national O₃ data collected to meet the monitoring
2 objectives described in Section 3.5.6. In many areas, O₃ concentrations decrease
3 appreciably during months with lower temperatures and decreased sunlight. As a result,
4 year-round O₃ monitoring is only required in certain areas. Table D-3 of 40 CFR Part 58,
5 Appendix D lists the beginning and ending month of the ozone season (defined in
6 Section 3.5.6.1) by geographic area and Figure 3-24 illustrates these time periods on a
7 monitor-by-monitor basis. Monitoring is optional outside the ozone season and many
8 states elect to operate their monitors year-round or for time periods outside what is
9 strictly mandated.



Source: [U.S. EPA \(2008d\)](#).

Figure 3-24 Required ozone monitoring time periods (ozone season) identified by monitoring site.

Hourly FRM and FEM O₃ data reported to AQS for the period 2007-2009 were used to investigate national-scale spatial variability in O₃ concentrations. Given the variability in O₃ monitoring time periods available in AQS as a result of the regionally-varying ozone seasons, the analyses in this section were based on two distinct data sets:

- a **year-round** data set: data only from monitors reporting year-round;
- a **warm-season** data set: data from all monitors reporting May through September.

The warm-season data set was used to capture the majority of ozone season data while providing a consistent time-frame for comparison across states. All available monitoring data including data from year-round monitors was included in the warm-season data set after removing observations outside the 5-month window. Data were retrieved from AQS on February 25, 2011 for these two data sets, and all validated data was included regardless of flags or regional concurrence¹. A summary of the two O₃ data sets including the applied completeness criteria is provided in [Table 3-5](#), [Figure 3-25](#) and [Figure 3-26](#) show the location of the 457 year-round and 1,064 warm-season monitors meeting the completeness criteria for all three years (2007-2009).

Table 3-5 Summary of ozone data sets originating from AQS

| | Year-Round Data Set | Warm-Season Data Set |
|--|--|--|
| Years | 2007-2009 | 2007-2009 |
| Months | January - December (12 mo) | May - September (5 mo) |
| Completeness Criteria | 75% of hours in a day | 75% of hours in a day |
| | 75% of days in a calendar quarter | 75% of days between May - September |
| | All 4 quarters per year | |
| Number of monitors meeting completeness criteria | 618 containing at least one valid year in 2007-2009 | 1,267 containing at least one valid year in 2007-2009 |
| | 550 containing at least two valid years in 2007-2009 | 1,169 containing at least two valid years in 2007-2009 |
| | 457 containing all three valid years in 2007-2009 | 1,064 containing all three valid years in 2007-2009 |

¹ Concentrations that might have been affected by exceptional events (and contribute to a violation of the NAAQS) can be flagged in the Air Quality System (AQS) by the reporting organization. Exceptional events are defined as unusual or naturally occurring events that can affect air quality but are not reasonably controllable using techniques that tribal, state or local air agencies may implement in order to attain and maintain the National Ambient Air Quality Standards (NAAQS). The corresponding EPA Regional Office is responsible for reviewing the data and evidence of the event, and deciding whether to concur with the flag. Flagged data that has been concurred by the Regional office is typically excluded for regulatory purposes.

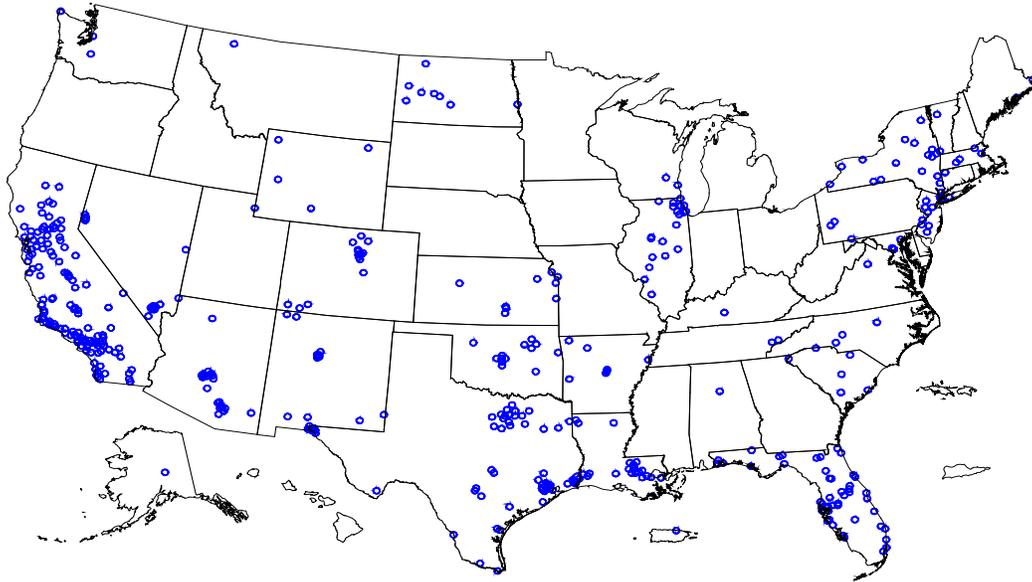


Figure 3-25 Location of the 457 ozone monitors meeting the year-round data set completeness criterion for all 3 years between 2007 and 2009.

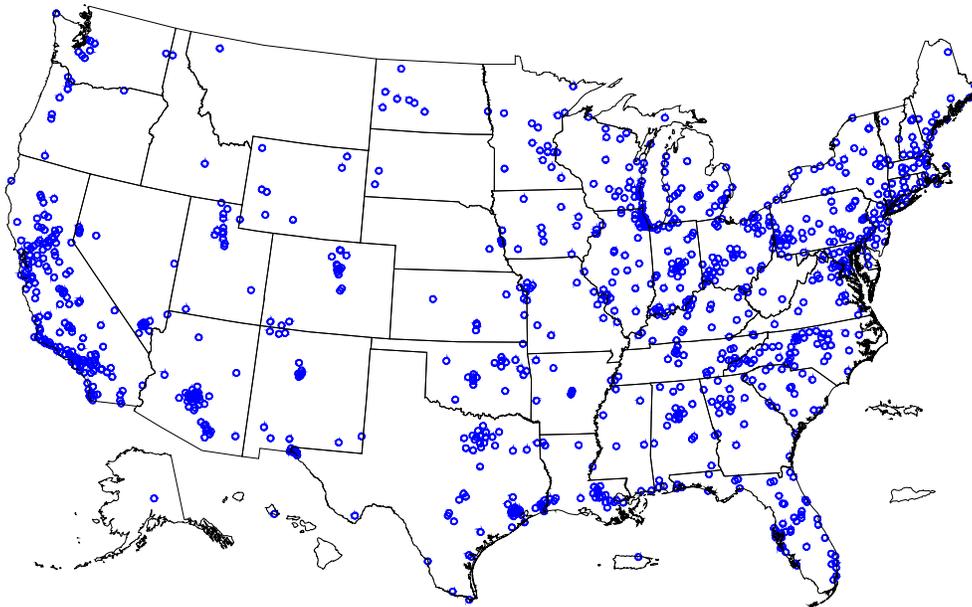


Figure 3-26 Location of the 1,064 ozone monitors meeting the warm-season data set completeness criteria for all 3 years between 2007 and 2009.

1 Tabulated statistics generated from the year-round and warm-season data sets are
2 included in [Table 3-6](#) and

3 [Table 3-7](#), respectively. This information was used to compare (1) the year-round and
4 warm-season data sets; (2) the O₃ distribution variability across years (2005-2009); and
5 (3) four different averaging times (1-h avg, 24-h avg, 1-h daily max, and 8-h daily max).
6 Summary statistics for 2005 and 2006 were added to these tables in order to gain a
7 broader view of year-to-year variability, but the year-round and warm-season data sets
8 used for analyses in the rest of this section are limited to 2007-2009 as described above
9 and in [Table 3-5](#). The 8-h daily max pooled by site was also included in these tables to
10 show the distribution of the annual and 3-year (2007-2009) site-averages of the 8-h daily
11 max statistic.

12 The year-round data set includes data from roughly half the number of monitors as the
13 warm-season data set and a larger fraction of the year-round monitors are located in the
14 southern half of the U.S. due to extended monitoring requirements in these areas. Despite
15 these differences, the mean, SD and percentiles of the nation-wide O₃ concentrations
16 were quite similar for the year-round data presented in [Table 3-6](#) and the warm-season
17 data presented in

18 [Table 3-7](#). In both data sets, there was very little variability across years in the central
19 statistics; for example, the median 1-h avg concentrations between 2005 and 2009 ranged
20 from 28 to 29 ppb for the year-round data and from 29 to 30 ppb for the warm-season
21 data. The 8-h daily max showed similar uniformity in median across the five years, with
22 concentrations ranging from 39 to 41 ppb for the year-round data and from 40 to 43 for
23 the warm-season data. The upper percentiles (95th and above) showed a general
24 downward trend from 2005 to 2009 in both nation-wide data sets. For example, the 99th
25 percentile of the 8-h daily max observed in the warm-season data dropped from 85 ppb in
26 2005 to 75 ppb in 2009. Trends in O₃ concentrations investigated over a longer time
27 period are included in Section [3.6.3.1](#).

Table 3-6 Nationwide distributions of ozone concentrations (ppb) from the year-round data set.

| Time Period | N Monitors | N Obs | Mean | SD | Min | 1 | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 98 | 99 | Max | Max Site ID ^b |
|---|------------|------------|------|----|-----|----|----|----|----|----|----|----|----|----|-----|-----|--------------------------|
| 1-h avg^a | | | | | | | | | | | | | | | | | |
| 2005 | 499 | 4,284,219 | 29 | 18 | 2 | 2 | 2 | 2 | 15 | 28 | 41 | 53 | 61 | 71 | 78 | 182 | 060710005 |
| 2006 | 532 | 4,543,205 | 30 | 18 | 2 | 2 | 2 | 5 | 16 | 29 | 42 | 54 | 61 | 71 | 78 | 175 | 060370016 |
| 2007 | 522 | 4,547,280 | 29 | 18 | 2 | 2 | 2 | 5 | 16 | 29 | 41 | 52 | 60 | 68 | 75 | 237 | 450790021 |
| 2008 | 520 | 4,470,065 | 30 | 17 | 2 | 2 | 2 | 6 | 17 | 29 | 41 | 52 | 59 | 67 | 74 | 222 | 450210002 |
| 2009 | 551 | 4,716,962 | 29 | 16 | 2 | 2 | 2 | 6 | 17 | 29 | 40 | 50 | 56 | 64 | 70 | 188 | 720770001 |
| 2007-2009 | 599 | 13,734,307 | 29 | 17 | 2 | 2 | 2 | 6 | 17 | 29 | 40 | 51 | 58 | 67 | 73 | 237 | 450790021 |
| 24-h avg^a | | | | | | | | | | | | | | | | | |
| 2005 | 504 | 183,815 | 29 | 13 | 2 | 4 | 9 | 13 | 20 | 28 | 37 | 46 | 51 | 57 | 61 | 103 | 060719002 |
| 2006 | 536 | 194,884 | 30 | 13 | 2 | 5 | 10 | 14 | 21 | 29 | 38 | 47 | 52 | 58 | 62 | 102 | 061070009 |
| 2007 | 531 | 194,873 | 29 | 12 | 2 | 5 | 11 | 14 | 20 | 29 | 37 | 45 | 50 | 56 | 60 | 96 | 060651016 |
| 2008 | 528 | 191,875 | 30 | 12 | 2 | 5 | 11 | 14 | 21 | 29 | 38 | 46 | 50 | 56 | 61 | 98 | 060710005 |
| 2009 | 556 | 202,142 | 29 | 11 | 2 | 6 | 11 | 14 | 21 | 28 | 37 | 44 | 48 | 53 | 57 | 95 | 060710005 |
| 2007-2009 | 611 | 588,890 | 29 | 12 | 2 | 5 | 11 | 14 | 21 | 29 | 37 | 45 | 49 | 55 | 60 | 98 | 060710005 |
| 1-h daily max^a | | | | | | | | | | | | | | | | | |
| 2005 | 504 | 183,815 | 48 | 18 | 2 | 11 | 21 | 26 | 35 | 46 | 58 | 71 | 80 | 91 | 100 | 182 | 060710005 |
| 2006 | 536 | 194,884 | 48 | 18 | 2 | 13 | 23 | 28 | 36 | 46 | 58 | 71 | 80 | 91 | 100 | 175 | 060370016 |
| 2007 | 531 | 194,873 | 47 | 17 | 2 | 14 | 23 | 28 | 36 | 45 | 57 | 69 | 77 | 87 | 94 | 237 | 450790021 |
| 2008 | 528 | 191,875 | 47 | 17 | 2 | 14 | 23 | 27 | 35 | 45 | 56 | 67 | 76 | 87 | 96 | 222 | 450210002 |
| 2009 | 556 | 202,142 | 45 | 15 | 2 | 14 | 22 | 27 | 35 | 44 | 54 | 64 | 72 | 83 | 91 | 188 | 720770001 |
| 2007-2009 | 611 | 588,890 | 46 | 16 | 2 | 14 | 23 | 27 | 35 | 44 | 55 | 67 | 75 | 86 | 94 | 237 | 450790021 |
| 8-h daily max^a | | | | | | | | | | | | | | | | | |
| 2005 | 504 | 183,279 | 42 | 16 | 2 | 7 | 16 | 21 | 30 | 40 | 52 | 63 | 70 | 78 | 84 | 145 | 060710005 |
| 2006 | 536 | 194,285 | 42 | 16 | 2 | 9 | 18 | 23 | 31 | 41 | 52 | 63 | 70 | 79 | 85 | 142 | 060710005 |
| 2007 | 528 | 194,266 | 41 | 15 | 2 | 10 | 19 | 23 | 31 | 40 | 51 | 61 | 68 | 75 | 81 | 137 | 060710005 |
| 2008 | 528 | 191,283 | 41 | 15 | 2 | 11 | 19 | 23 | 31 | 40 | 51 | 60 | 66 | 75 | 82 | 172 | 450210002 |
| 2009 | 556 | 201,536 | 40 | 14 | 2 | 11 | 18 | 23 | 30 | 39 | 49 | 57 | 63 | 71 | 77 | 128 | 060712002 |
| 2007-2009 | 608 | 587,085 | 41 | 15 | 2 | 10 | 19 | 23 | 31 | 40 | 50 | 60 | 66 | 74 | 80 | 172 | 450210002 |
| 8-h daily max (pooled by site)^a | | | | | | | | | | | | | | | | | |
| 2005 | 508 | 508 | 42 | 6 | 23 | 27 | 32 | 34 | 38 | 42 | 45 | 48 | 51 | 53 | 55 | 61 | 060710005 |
| 2006 | 538 | 538 | 42 | 6 | 12 | 28 | 31 | 34 | 38 | 43 | 46 | 50 | 52 | 54 | 55 | 61 | 060719002 |
| 2007 | 538 | 538 | 41 | 6 | 17 | 27 | 31 | 34 | 38 | 41 | 45 | 49 | 51 | 54 | 55 | 63 | 060719002 |
| 2008 | 529 | 529 | 41 | 6 | 20 | 28 | 31 | 34 | 37 | 40 | 45 | 50 | 52 | 55 | 57 | 61 | 060719002 |
| 2009 | 558 | 558 | 40 | 6 | 20 | 26 | 30 | 33 | 36 | 39 | 44 | 48 | 50 | 53 | 54 | 60 | 060719002 |
| 2007-2009 | 457 | 457 | 41 | 6 | 19 | 29 | 32 | 34 | 38 | 40 | 45 | 49 | 51 | 54 | 55 | 61 | 060719002 |

^aIncludes all validated data regardless of flags or regional concurrence and therefore may differ from data used for regulatory purposes

^bAQS Site ID corresponding to the observation in the Max column

Table 3-7 Nationwide distributions of ozone concentrations (ppb) from the warm-season data set.

| Time Period | N Monitors | N Obs | Mean | SD | Min | 1 | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 98 | 99 | Max | Max Site ID ^b |
|---|------------|------------|------|----|-----|----|----|----|----|----|----|----|----|----|----|-----|--------------------------|
| 1-h avg^a | | | | | | | | | | | | | | | | | |
| 2005 | 1,023 | 7,455,018 | 30 | 19 | 2 | 2 | 2 | 5 | 16 | 29 | 43 | 55 | 64 | 73 | 79 | 182 | 060710005 |
| 2006 | 1,036 | 7,590,796 | 31 | 18 | 2 | 2 | 2 | 6 | 17 | 30 | 43 | 55 | 62 | 71 | 77 | 175 | 060370016 |
| 2007 | 1,021 | 7,711,463 | 31 | 18 | 2 | 2 | 2 | 6 | 18 | 30 | 43 | 55 | 63 | 71 | 77 | 237 | 450790021 |
| 2008 | 1,034 | 7,701,597 | 31 | 17 | 2 | 2 | 2 | 7 | 18 | 30 | 42 | 53 | 60 | 68 | 74 | 222 | 450210002 |
| 2009 | 1,029 | 7,835,074 | 29 | 16 | 2 | 2 | 2 | 7 | 17 | 29 | 40 | 50 | 56 | 63 | 69 | 259 | 311090016 |
| 2007-2009 | 1,103 | 23,248,134 | 30 | 17 | 2 | 2 | 2 | 7 | 18 | 30 | 42 | 53 | 60 | 68 | 74 | 259 | 311090016 |
| 24-h avg^a | | | | | | | | | | | | | | | | | |
| 2005 | 1,103 | 319,410 | 30 | 12 | 2 | 5 | 10 | 14 | 22 | 30 | 39 | 46 | 51 | 57 | 61 | 103 | 060719002 |
| 2006 | 1,110 | 324,993 | 31 | 12 | 2 | 6 | 12 | 15 | 22 | 30 | 39 | 47 | 52 | 58 | 61 | 102 | 061070009 |
| 2007 | 1,100 | 330,197 | 31 | 12 | 2 | 6 | 12 | 16 | 23 | 31 | 39 | 47 | 51 | 57 | 61 | 96 | 060651016 |
| 2008 | 1,120 | 329,918 | 31 | 12 | 2 | 6 | 12 | 16 | 22 | 30 | 38 | 46 | 50 | 56 | 60 | 98 | 060710005 |
| 2009 | 1,141 | 335,669 | 29 | 11 | 2 | 6 | 12 | 15 | 21 | 29 | 37 | 44 | 48 | 53 | 56 | 95 | 060710005 |
| 2007-2009 | 1,197 | 995,784 | 30 | 12 | 2 | 6 | 12 | 16 | 22 | 30 | 38 | 45 | 50 | 55 | 59 | 98 | 060710005 |
| 1-h daily max^a | | | | | | | | | | | | | | | | | |
| 2005 | 1,103 | 319,410 | 50 | 18 | 2 | 12 | 23 | 28 | 38 | 49 | 61 | 74 | 81 | 91 | 99 | 182 | 060710005 |
| 2006 | 1,110 | 324,993 | 50 | 17 | 2 | 15 | 25 | 29 | 38 | 48 | 60 | 72 | 80 | 90 | 98 | 175 | 060370016 |
| 2007 | 1,100 | 330,197 | 50 | 17 | 2 | 16 | 25 | 30 | 38 | 48 | 60 | 72 | 80 | 88 | 95 | 237 | 450790021 |
| 2008 | 1,120 | 329,918 | 48 | 16 | 2 | 16 | 25 | 29 | 37 | 47 | 58 | 69 | 76 | 86 | 93 | 222 | 450210002 |
| 2009 | 1,141 | 335,669 | 46 | 15 | 2 | 15 | 23 | 28 | 36 | 45 | 54 | 64 | 71 | 80 | 87 | 259 | 311090016 |
| 2007-2009 | 1,197 | 995,784 | 48 | 16 | 2 | 16 | 24 | 29 | 37 | 47 | 58 | 68 | 76 | 85 | 93 | 259 | 311090016 |
| 8-h daily max^a | | | | | | | | | | | | | | | | | |
| 2005 | 1,104 | 318,771 | 44 | 16 | 2 | 9 | 18 | 23 | 32 | 43 | 55 | 66 | 72 | 79 | 85 | 145 | 060710005 |
| 2006 | 1,112 | 324,327 | 44 | 16 | 2 | 11 | 20 | 25 | 33 | 43 | 54 | 64 | 70 | 78 | 84 | 142 | 060710005 |
| 2007 | 1,097 | 329,482 | 44 | 15 | 2 | 12 | 20 | 25 | 33 | 43 | 54 | 65 | 71 | 78 | 82 | 137 | 060710005 |
| 2008 | 1,120 | 329,223 | 43 | 15 | 2 | 12 | 20 | 25 | 33 | 42 | 52 | 61 | 67 | 74 | 80 | 172 | 450210002 |
| 2009 | 1,141 | 334,972 | 40 | 13 | 2 | 12 | 19 | 24 | 31 | 40 | 49 | 57 | 63 | 69 | 75 | 128 | 060712002 |
| 2007-2009 | 1,194 | 993,677 | 42 | 15 | 2 | 12 | 20 | 24 | 32 | 42 | 52 | 61 | 67 | 75 | 80 | 172 | 450210002 |
| 8-h daily max (pooled by site)^a | | | | | | | | | | | | | | | | | |
| 2005 | 1,141 | 1,141 | 45 | 6 | 14 | 28 | 34 | 36 | 41 | 46 | 49 | 52 | 54 | 56 | 57 | 61 | 040139508 |
| 2006 | 1,152 | 1,152 | 44 | 6 | 12 | 29 | 34 | 37 | 41 | 45 | 48 | 51 | 54 | 58 | 59 | 65 | 060170020 |
| 2007 | 1,164 | 1,164 | 45 | 7 | 17 | 28 | 34 | 36 | 40 | 45 | 50 | 54 | 56 | 58 | 59 | 64 | 471550102 |
| 2008 | 1,163 | 1,163 | 43 | 6 | 20 | 29 | 33 | 36 | 39 | 44 | 48 | 50 | 53 | 56 | 58 | 61 | 060719002 |
| 2009 | 1,173 | 1,173 | 41 | 5 | 20 | 28 | 32 | 35 | 38 | 41 | 44 | 47 | 50 | 53 | 55 | 63 | 060651016 |
| 2007-2009 | 1,064 | 1,064 | 43 | 6 | 19 | 29 | 34 | 36 | 39 | 43 | 47 | 50 | 52 | 55 | 57 | 61 | 060719002 |

^aIncludes all validated data regardless of flags or regional concurrence and therefore may differ from data used for regulatory purposes.

^bAQS Site ID corresponding to the observation in the Max column.

1 Given the strong diurnal pattern in O₃ concentrations, the selection of averaging time has
 2 a substantial effect on the magnitude of concentration reporting. The nation-wide median
 3 1-h avg, 24-h avg, 1-h daily max, and 8-h daily max concentrations for the year-round
 4 data set in 2009 were 29, 28, 44 and 39 ppb, respectively. The median concentrations for

1 the warm-season data set in 2009 were: 29, 29, 45 and 40 ppb, respectively. The 1-h avg
2 and 24-h avg both include the lowest concentrations typically observed in the overnight
3 period which lowers their values relative to the daily maximum statistics.

4 A strong seasonal pattern in O₃ concentrations can also be seen in the year-round data.
5 [Table 3-8](#) shows the 8-h daily max stratified by season, with the seasons defined as:

- 6 ▪ winter: December-February;
- 7 ▪ spring: March-May;
- 8 ▪ summer: June-August; and
- 9 ▪ fall: September-November.

10 In addition, warm-season (May-Sept) and cold-season (Oct-Apr) stratifications of the
11 year-round data set are included in the table for comparison with the four seasonal
12 stratifications. Substantial seasonal variability in the 8-h daily max concentration for the
13 period 2007-2009 was evident with lower concentrations present in fall
14 (median = 36 ppb) and winter (median = 32 ppb) and higher concentrations in spring
15 (median = 47 ppb) and summer (median = 46 ppb). The seasonal differences were even
16 more pronounced in the upper percentiles. For example, the 99th percentile in the 8-h
17 daily max over the 2007-09 time period ranged from 52 ppb in winter to 90 ppb in
18 summer. The distribution in 8-h daily max O₃ during the warm-season (as defined above)
19 and during summer were very similar, which is not surprising given their close overlap in
20 months. The distribution during the cold-season (as defined above) is shifted toward
21 higher 8-h daily max O₃ concentrations compared with the distribution during winter.
22 This is a result of including the four transition months (Oct, Nov, Mar and Apr) in the
23 cold-season when high O₃ concentrations can occur. Further investigation of temporal
24 variability including multiyear trends and diel behavior is included in [Section 3.6.3](#).

Table 3-8 Seasonally stratified distributions of 8-h daily max ozone concentrations (ppb) from the year-round data set (2007-2009).

| Time Period | N Monitors | N Obs | Mean | SD | Min | 1 | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 98 | 99 | Max | Max Site ID ^b |
|--|------------|---------|------|----|-----|----|----|----|----|----|----|----|----|----|----|-----|--------------------------|
| 8-h daily max (2007-2009)^a | | | | | | | | | | | | | | | | | |
| Year-round | 608 | 587,085 | 41 | 15 | 2 | 10 | 19 | 23 | 31 | 40 | 50 | 60 | 66 | 74 | 80 | 172 | 450210002 |
| 8-h daily max by season (2007-2009)^a | | | | | | | | | | | | | | | | | |
| Winter (Dec-Feb) | 608 | 143,855 | 31 | 10 | 2 | 6 | 14 | 18 | 25 | 32 | 38 | 43 | 46 | 49 | 52 | 172 | 450210002 |
| Spring (Mar-May) | 612 | 148,409 | 47 | 12 | 2 | 20 | 28 | 33 | 40 | 47 | 55 | 62 | 67 | 72 | 77 | 118 | 060370016 |
| Summer (Jun-Aug) | 613 | 148,280 | 47 | 16 | 2 | 16 | 22 | 26 | 35 | 46 | 57 | 67 | 75 | 84 | 90 | 137 | 060710005 |
| Fall (Sep-Nov) | 608 | 146,541 | 37 | 13 | 2 | 10 | 17 | 21 | 28 | 36 | 45 | 54 | 61 | 68 | 75 | 116 | 060370016 |
| Warm-season (May-Sep) | 616 | 246,233 | 47 | 16 | 2 | 16 | 22 | 27 | 35 | 46 | 57 | 66 | 73 | 81 | 87 | 137 | 060710005 |
| Cold-season (Oct-Apr) | 608 | 340,852 | 36 | 12 | 2 | 8 | 16 | 21 | 28 | 36 | 44 | 52 | 57 | 63 | 67 | 172 | 450210002 |

^aIncludes all validated data regardless of flags or regional concurrence and therefore may differ from data used for regulatory purposes.

^bAQS Site ID corresponding to the observation in the Max column.

1 A national picture of AQS O₃ concentrations was generated from the year-round and
 2 warm-season data sets by aggregating the 8-h daily max observations by U.S. county. For
 3 this purpose, the 8-h daily max concentrations at each site were averaged over one or
 4 more calendar years and then the highest site in each county was selected for that county.
 5 [Figure 3-27](#) contains the county-scale 8-h daily max O₃ concentrations from the year-
 6 round data set for 2007-2009 (top map) with seasonal stratification (bottom four maps).
 7 [Figure 3-28](#) contains the county-scale 8-h daily max O₃ concentrations from the warm-
 8 season data set for 2007-2009 (top map) along with individual maps for each calendar
 9 year between 2007 and 2009 (bottom three maps). These maps are meant to illustrate the
 10 general national-scale distribution in long-term average 8-h daily max O₃ concentrations
 11 and are not representative of O₃ concentrations at all locations or times within the
 12 counties shown; considerable spatial variability can exist within a county. This is
 13 particularly important in the West where counties are larger on average than in the East.
 14 These maps are limited by monitor availability, resulting in the majority of U.S. counties
 15 not having available data (the white regions in [Figure 3-27](#) and [Figure 3-28](#)).

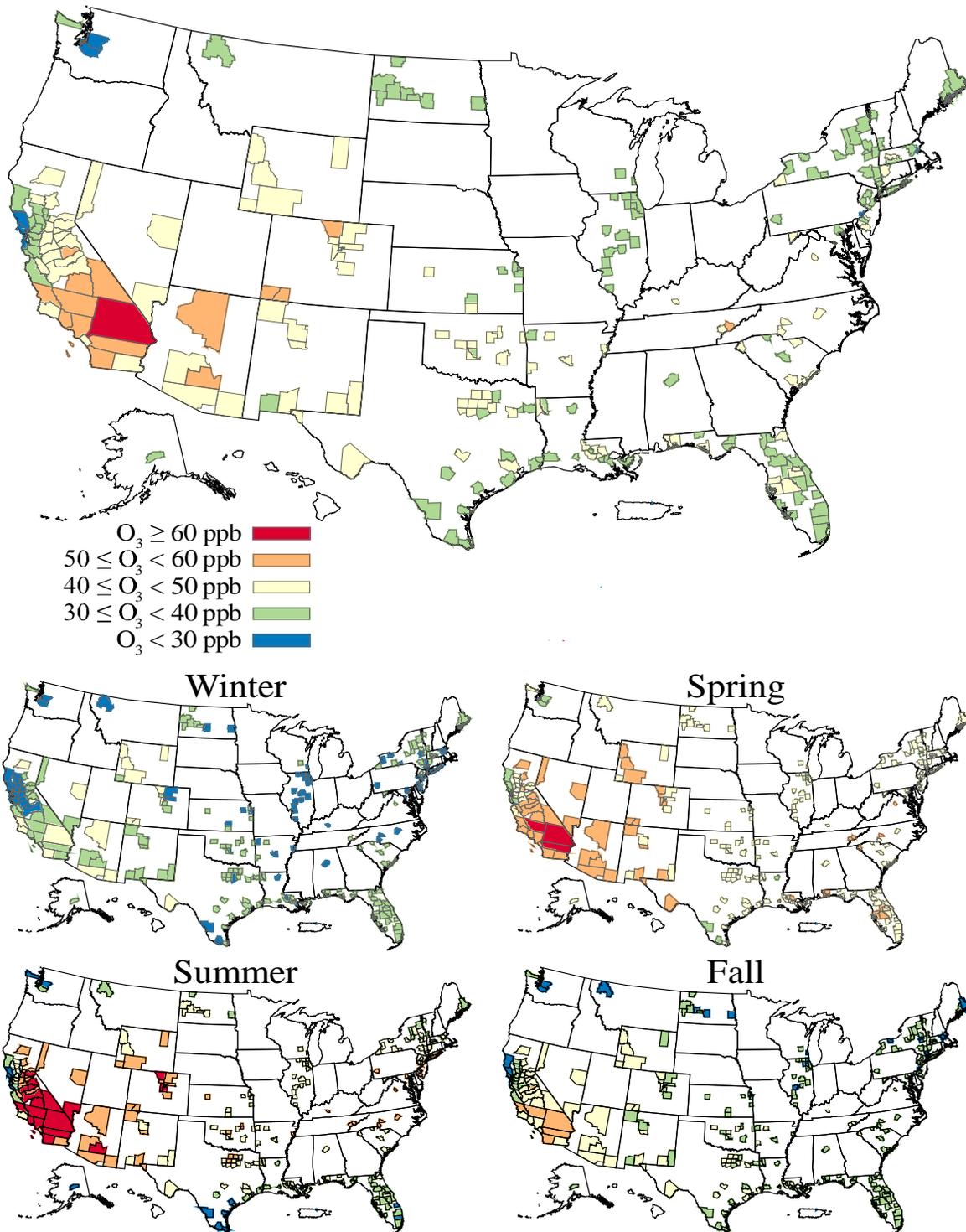


Figure 3-27 Highest monitor (by county) 3-year avg (2007-2009) of the 8-h daily max ozone concentration based on the year-round data set (top map) with seasonal stratification (bottom 4 maps).

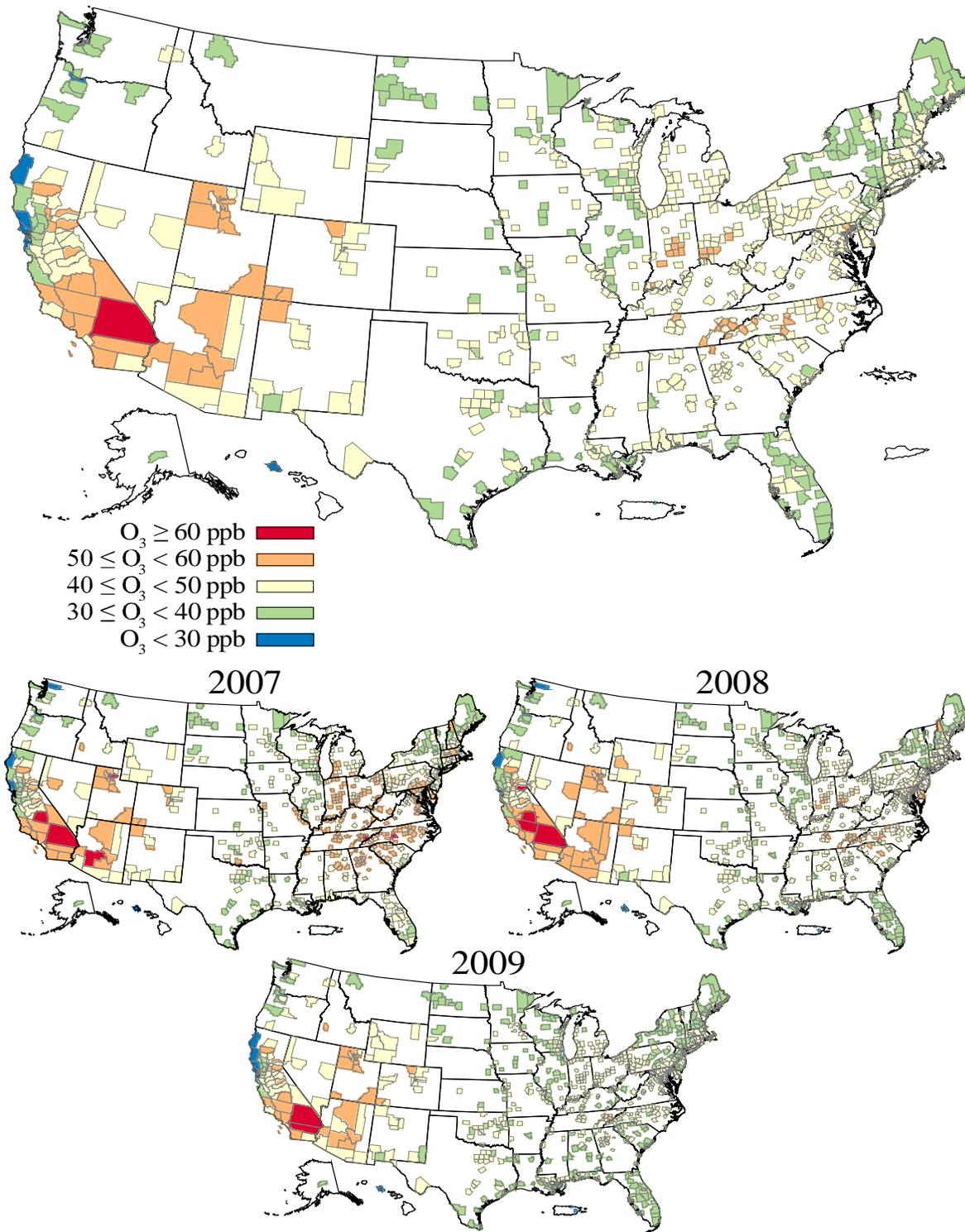


Figure 3-28 Highest monitor (by county) 3-year avg (2007-2009) of the 8-h daily max ozone concentration based on the warm-season data set (top map) with annual stratification (bottom 3 maps).

1 As shown in the top county-scale map generated from the 2007-2009 year-round data set
2 in [Figure 3-27](#), the highest 3-year avg 8-h daily max O₃ concentrations (≥ 50 ppb) occur
3 in counties in central and southern California, Arizona, Colorado and high elevation
4 counties in Tennessee. The highest year-round average concentration of 61 ppb over this
5 period comes from Site #060719002 located at an elevation of 1,244 meters in Joshua
6 Tree National Monument, San Bernardino County, CA. The lowest 3-year avg 8-h daily
7 max O₃ concentrations (<30 ppb) occur in Pacific Coast counties in northern California
8 and Washington as well as in two northeastern counties in Pennsylvania and
9 Massachusetts. The seasonally-stratified county-scale maps in [Figure 3-28](#) reinforce the
10 strong seasonality in 8-h daily max O₃ concentrations shown in [Table 3-8](#). The highest
11 wintertime concentrations (≥ 40 ppb) occur in the West with the highest 3-year
12 wintertime avg of 46 ppb calculated for Site #080690007 located at an elevation of
13 2,743 meters near Rocky Mountain National Park, Larimer County, CO. In spring and
14 summer, the concentrations increase considerably across all counties, with the highest
15 concentrations (≥ 60 ppb) occurring during the summer in 15 counties in California, 3
16 counties in Colorado and 1 county each in Nevada and Arizona. Many counties in rural
17 Wyoming, Montana, North Dakota, Maine, and along the Gulf Coast peak in the spring
18 instead of the summer. In the fall, 8-h daily max O₃ concentrations drop back down
19 below their spring and summer concentrations.

20 The top county-scale map in [Figure 3-28](#) based on the 2007-2009 warm-season data set
21 looks similar to the corresponding map in [Figure 3-27](#) based on the year-round data set.
22 The warm-season map, however, incorporates approximately twice as many monitors
23 across the U.S., providing more spatial coverage. Several counties in Utah, New Mexico,
24 Indiana, Ohio, Maryland, North Carolina, and Georgia in addition to California, Arizona,
25 Colorado and Tennessee identified above have 3-year avg (2007-2009) 8-h daily max O₃
26 concentrations ≥ 50 ppb based on the warm-season data set. The individual yearly
27 average county-maximum 8-h daily max O₃ concentrations in the lower half of
28 [Figure 3-27](#) show a general decrease in most counties from 2007 to 2009. The number of
29 counties containing a monitor reporting an annual average 8-h daily max O₃
30 concentration above 50 ppb dropped from 230 counties in 2007 to 30 counties in 2009.
31 This is consistent with the general decrease across these years shown in [Table 3-6](#) and
32 [Table 3-7](#) for the upper percentiles of the 8-h daily max O₃ concentration.

Urban-Scale Variability

33 Statistical analysis of the human health effects of airborne pollutants based on aggregate
34 population time-series data have often relied on ambient concentrations of pollutants
35 measured at one or more central monitoring sites in a given metropolitan area. The

1 validity of relying on central monitoring sites is strongly dependent on the spatial
2 variability in concentrations within a given metropolitan area. To investigate urban-scale
3 variability, 20 focus cities were selected for closer analysis of O₃ concentration
4 variability; these cities are listed in [Table 3-9](#) and were selected based on their
5 importance in O₃ epidemiology studies and on their geographic distribution across the
6 U.S. In order to provide a well-defined boundary around each city, the combined
7 statistical area (CSA) encompassing each city was used. If the city was not within a CSA,
8 the smaller core-based statistical area (CBSA) was selected. The CSAs/CBSAs are
9 defined by the [U.S. Census Bureau \(2011\)](#)¹ and have been used to establish analysis
10 regions around cities in previous ISAs for particulate matter ([U.S. EPA, 2009d](#)) and
11 carbon monoxide ([U.S. EPA, 2010c](#)).

¹A CBSA represents a county-based region surrounding an urban center of at least 10,000 people determined using 2000 census data and replaces the older Metropolitan Statistical Area (MSA) definition from 1990. The CSA represents an aggregate of adjacent CBSAs tied by specific commuting behaviors. The broader CSA definition was used when selecting monitors for the cities listed above with the exception of Phoenix and San Antonio, which are not contained within a CSA. Therefore, the smaller CBSA definition was used for these metropolitan areas.

Table 3-9 Focus cities used in this and previous assessments

| Focus City | Short Name | CSA/CBSA Name ^a | Year-Round O ₃ Monitoring Sites ^b | Warm-Season O ₃ Monitoring Sites ^c | Included in Prior ISAs ^d |
|--------------------|--------------------|-----------------------------------|---|--|---|
| Atlanta, GA | Atlanta CSA | Atlanta-Sandy Springs-Gainesville | 0 | 11 | CO, PM, SO _x , NO _x |
| Baltimore, MD | Baltimore CSA | Washington-Baltimore-northern VA | 9 | 19 | NO _x |
| Birmingham, AL | Birmingham CSA | Birmingham-Hoover-Cullman | 1 | 9 | PM |
| Boston, MA | Boston CSA | Boston-Worcester-Manchester | 3 | 18 | CO, PM, NO _x |
| Chicago, IL | Chicago CSA | Chicago-Naperville-Michigan City | 11 | 15 | PM, NO _x |
| Dallas, TX | Dallas CSA | Dallas-Fort Worth | 19 | 0 | |
| Denver, CO | Denver CSA | Denver-Aurora-Boulder | 12 | 3 | CO, PM |
| Detroit, MI | Detroit CSA | Detroit-Warren-Flint | 0 | 9 | PM |
| Houston, TX | Houston CSA | Houston-Baytown-Huntsville | 21 | 0 | CO, PM, NO _x |
| Los Angeles, CA | Los Angeles CSA | Los Angeles-Long Beach-Riverside | 47 | 3 | CO, PM, SO _x , NO _x |
| Minneapolis, MN | Minneapolis CSA | Minneapolis-St. Paul-St. Cloud | 2 | 6 | |
| New York, NY | New York CSA | New York-Newark-Bridgeport | 20 | 10 | CO, PM, SO _x , NO _x |
| Philadelphia, PA | Philadelphia CSA | Philadelphia-Camden-Vineland | 9 | 8 | PM, NO _x |
| Phoenix, AZ | Phoenix CBSA | Phoenix-Mesa-Scottsdale | 14 | 17 | CO, PM |
| Pittsburgh, PA | Pittsburgh CSA | Pittsburgh-New Castle | 2 | 12 | CO, PM |
| Salt Lake City, UT | Salt Lake City CSA | Salt Lake City-Ogden-Clearfield | 2 | 10 | |
| San Antonio, TX | San Antonio CBSA | San Antonio | 5 | 0 | |
| San Francisco, CA | San Francisco CSA | San Jose-San Francisco-Oakland | 25 | 6 | |
| Seattle, WA | Seattle CSA | Seattle-Tacoma-Olympia | 5 | 5 | CO, PM |
| St Louis, MO | St Louis CSA | St. Louis-St. Charles-Farmington | 3 | 13 | CO, PM, SO _x |

^aDefined based on 2000 Census data from the [U.S. Census Bureau \(2011\)](#).

^bThe number of sites within each CSA/CBSA with AQS monitors meeting the year-round data set inclusion criteria.

^cThe number of sites within each CSA/CBSA with AQS monitors meeting the warm-season data set inclusion criteria; the warm-season data set includes May - September data from both the warm-season and year-round monitors meeting the warm-season data set inclusion criteria.

^dBoundaries for the 2010 CO ISA ([U.S. EPA, 2010c](#)) and 2009 PM ISA ([U.S. EPA, 2009d](#)) focus cities were based on CSA/CBSA definitions; boundaries for the 2008 SO_x ISA ([U.S. EPA, 2008c](#)) and 2008 NO_x ISA ([U.S. EPA, 2008b](#)) focus cities were based on similar metropolitan statistical area (MSA) definitions from the 1990 U.S. Census.

1 The distribution of the 8-h daily max O₃ concentrations from 2007-2009 for each of the
2 20 focus cities is included in [Table 3-10](#). These city-specific distributions were extracted
3 from the warm-season data set and can be compared to the nationwide warm-season 8-h
4 daily max distribution for 2007-2009 in

5 Table 3-7 (and repeated in the first line of [Table 3-10](#) for reference). The median 8-h
6 daily max concentration in these focus cities was 41 ppb, similar to the nationwide
7 median of 42 ppb. Seattle had the lowest median (31 ppb) and Salt Lake City had the
8 highest median (53 ppb) of the 20 cities investigated. The 99th percentile of the 8-h daily
9 max concentration in the focus cities was 84 ppb; similar once again to the nationwide
10 99th percentile of 80 ppb. Seattle had the lowest 99th percentile (64 ppb) and
11 Los Angeles had the highest 99th percentile (98 ppb) of the 20 cities investigated. In
12 aggregate, the 20 focus cities selected are similar in distribution to the nationwide data
13 set, but there is substantial city-to-city variability in the individual distributions of the 8-h
14 daily max concentrations based on the warm-season data set.

15 Maps showing the location of central monitoring sites with O₃ monitors reporting to AQS
16 for each of the 20 focus cities are included as supplemental material in Section [3.9.1](#),
17 [Figure 3-76](#) through [Figure 3-95](#); examples for Atlanta, Boston and Los Angeles are
18 shown in [Figure 3-29](#) through [Figure 3-31](#). The sites are delineated in the maps as year-
19 round or warm-season based on their inclusion in the year-round data set and the warm-
20 season data set (the warm-season data set includes May-September data from both the
21 warm-season monitors and the year-round monitors meeting the warm-season data
22 inclusion criteria). The maps also include the CSA/CBSA boundary selected for monitor
23 inclusion, the location of urban areas and water bodies, the major roadway network, as
24 well as the population gravity center based on the entire CSA/CBSA and the individual
25 focus city boundaries. Population gravity center is calculated from the average longitude
26 and latitude values for the input census tract centroids and represents the mean center of
27 the population in a given area. Census tract centroids are weighted by their population
28 during this calculation.

Table 3-10 City-specific distributions of 8-h daily max ozone concentrations (ppb) from the warm-season data set (2007-2009).

| Time Period | N Monitors | N Obs | Mean | SD | Min | 1 | 5 | 10 | 25 | 50 | 75 | 90 | 95 | 98 | 99 | Max | Max Site ID ^b |
|--|------------|---------|------|----|-----|----|----|----|----|----|----|----|----|----|----|-----|--------------------------|
| 8-h daily max (2007-2009)^a | | | | | | | | | | | | | | | | | |
| Nationwide | 1,194 | 993,677 | 42 | 15 | 2 | 12 | 20 | 24 | 32 | 42 | 52 | 61 | 67 | 75 | 80 | 172 | 450210002 |
| 8-h daily max by CSA/CBSA (2007-2009)^a | | | | | | | | | | | | | | | | | |
| Atlanta CSA | 11 | 7,844 | 47 | 16 | 2 | 15 | 22 | 27 | 36 | 47 | 58 | 67 | 72 | 81 | 87 | 124 | 130890002 |
| Baltimore CSA | 28 | 20,999 | 43 | 16 | 2 | 9 | 18 | 23 | 31 | 43 | 54 | 64 | 70 | 78 | 83 | 118 | 240030014 |
| Birmingham CSA | 10 | 7,676 | 44 | 15 | 2 | 14 | 21 | 25 | 34 | 44 | 54 | 63 | 68 | 76 | 83 | 108 | 010732006 |
| Boston CSA | 21 | 12,603 | 41 | 14 | 2 | 13 | 21 | 25 | 31 | 40 | 49 | 59 | 67 | 75 | 81 | 104 | 250270015 |
| Chicago CSA | 27 | 20,764 | 37 | 14 | 2 | 9 | 15 | 19 | 27 | 37 | 47 | 57 | 62 | 69 | 74 | 108 | 170310042 |
| Dallas CSA | 19 | 19,858 | 41 | 15 | 2 | 11 | 20 | 24 | 31 | 39 | 50 | 61 | 67 | 74 | 79 | 121 | 484390075 |
| Denver CSA | 15 | 12,217 | 44 | 15 | 2 | 8 | 18 | 24 | 34 | 44 | 55 | 63 | 68 | 72 | 76 | 98 | 080590006 |
| Detroit CSA | 9 | 5,016 | 45 | 14 | 2 | 15 | 23 | 28 | 35 | 44 | 52 | 62 | 69 | 77 | 83 | 100 | 260990009 |
| Houston CSA | 21 | 22,305 | 36 | 15 | 2 | 8 | 15 | 19 | 25 | 34 | 46 | 57 | 64 | 72 | 78 | 110 | 482011034 |
| Los Angeles CSA | 49 | 49,295 | 47 | 18 | 2 | 10 | 20 | 26 | 35 | 45 | 58 | 72 | 81 | 91 | 98 | 137 | 060710005 |
| Minneapolis CSA | 8 | 5,315 | 40 | 12 | 2 | 15 | 21 | 25 | 31 | 40 | 48 | 54 | 58 | 63 | 67 | 86 | 270031002 |
| New York CSA | 21 | 26,304 | 39 | 16 | 2 | 6 | 15 | 20 | 28 | 37 | 47 | 59 | 68 | 77 | 83 | 123 | 090050005 |
| Philadelphia CSA | 14 | 12,673 | 41 | 17 | 2 | 8 | 17 | 21 | 29 | 39 | 52 | 64 | 70 | 78 | 83 | 125 | 240150003 |
| Phoenix CBSA | 22 | 26,129 | 49 | 12 | 2 | 18 | 27 | 32 | 41 | 50 | 58 | 65 | 68 | 72 | 75 | 85 | 040137021 |
| Pittsburgh CSA | 13 | 9,814 | 43 | 15 | 2 | 12 | 19 | 24 | 32 | 43 | 53 | 62 | 68 | 74 | 78 | 100 | 420050001 |
| Salt Lake City CSA | 12 | 5,146 | 51 | 14 | 2 | 8 | 23 | 32 | 44 | 53 | 61 | 67 | 71 | 77 | 80 | 96 | 490353008 |
| San Antonio CSA | 5 | 4,701 | 39 | 13 | 2 | 13 | 20 | 23 | 29 | 37 | 46 | 56 | 62 | 67 | 72 | 90 | 480290032 |
| San Francisco CSA | 31 | 28,325 | 34 | 12 | 2 | 8 | 16 | 20 | 26 | 33 | 41 | 48 | 55 | 63 | 68 | 110 | 060010007 |
| Seattle CSA | 5 | 6,148 | 31 | 12 | 2 | 4 | 12 | 17 | 23 | 31 | 39 | 46 | 51 | 59 | 64 | 91 | 530330023 |
| St Louis CSA | 19 | 11,569 | 43 | 15 | 2 | 12 | 19 | 23 | 32 | 43 | 53 | 61 | 68 | 76 | 81 | 113 | 295100086 |
| All CSAs/CBSAs listed | 360 | 314,701 | 42 | 16 | 2 | 9 | 18 | 22 | 31 | 41 | 52 | 63 | 69 | 78 | 84 | 137 | 060710005 |

^aIncludes all validated data regardless of flags or regional concurrence and therefore may differ from data used for regulatory purposes.

^bAQS Site ID corresponding to the observation in the Max column.

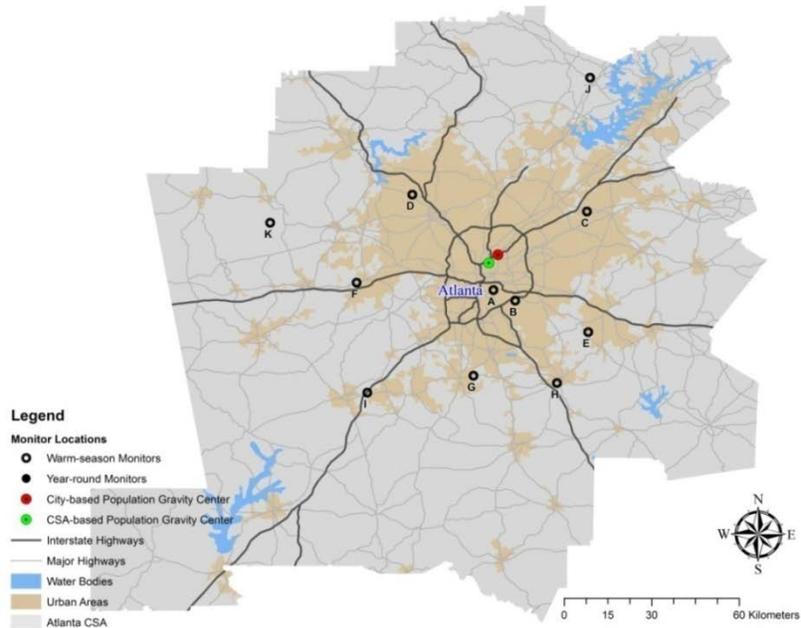


Figure 3-29 Map of the Atlanta CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

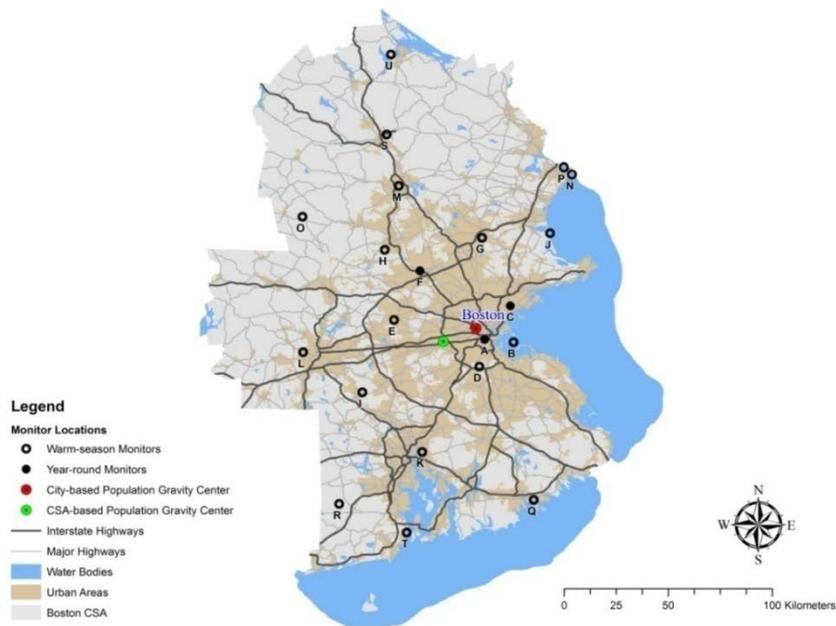


Figure 3-30 Map of the Boston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

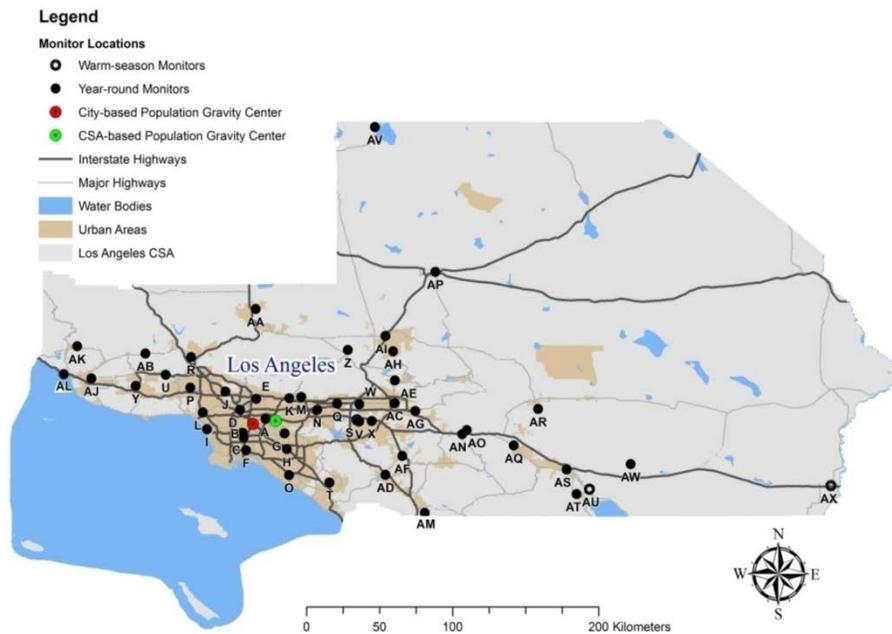


Figure 3-31 Map of the Los Angeles CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

1 The Atlanta CSA contains 11 warm-season monitors distributed evenly yet sparsely
 2 around the city center ([Figure 3-29](#)). The population gravity center for the city and the
 3 larger CSA are only separated by 4 km, indicating that the majority of the population
 4 lives within or evenly distributed around the city limits. Atlanta is landlocked with a
 5 radial network of interstate highways leading to the city center. The Boston CSA contains
 6 3-year-round and 18 warm-season monitors spread evenly throughout the CSA. Boston is
 7 a harbor city with the Atlantic Ocean to the east, resulting in the city-based population
 8 gravity center being located 17 km east of the CSA-based population gravity center. The
 9 Los Angeles CSA contains the largest number of monitors of the 20 CSA/CBSAs
 10 investigated with 47 year-round and 3 warm-season monitors. These monitors are
 11 primarily concentrated in the Los Angeles urban area with relatively few monitors
 12 extending out to the northern and eastern reaches of the CSA. These unmonitored areas
 13 are very sparsely populated, resulting in only 15 km separating the city-based and the
 14 CSA-based population gravity centers despite the vast area of the Los Angeles CSA.

15 Other CSAs/CBSAs (see [Section 3.9.1](#)) with monitors concentrated within the focus city
 16 limits include Birmingham, Chicago, Denver, Houston, Phoenix, San Antonio, and Salt
 17 Lake City. The remaining CSAs/CBSAs have monitors distributed more evenly
 18 throughout the CSA/CBSA area. Baltimore is contained within the same CSA as

1 Washington DC and suburbs, resulting in a 50-km separation (the largest of the focus
2 cities investigated) between the city-based population gravity center for Baltimore and
3 the CSA-based population gravity center for the Washington-Baltimore-Northern
4 Virginia CSA.

5 Box plots depicting the distribution of 2007-2009 warm-season 8-h daily max O₃ data
6 from each individual monitor in the 20 focus cities are included as supplemental material
7 in Section [3.9.2](#), [Figure 3-96](#) through [Figure 3-115](#); examples for Atlanta, Boston and
8 Los Angeles are shown in [Figure 3-32](#) through [Figure 3-34](#). The Atlanta CSA has little
9 spatial variability in 8-h daily max O₃ concentrations with median concentrations ranging
10 from 47 ppb at Sites I and J located far from the city center to 54 ppb at Site A located
11 closest to the city center. The variation in warm-season 8-h daily max concentrations are
12 also relatively similar across monitors with IQRs ranging from 17 ppb at Site J to 23 ppb
13 at Site B. The Boston CSA has more spatial variability in 8-h daily max O₃
14 concentrations than the Atlanta CSA with median concentrations ranging from 33 ppb at
15 Site A nearest to the city center to 46 ppb at Site L located 84 km west of the city center.
16 For monitors located within and just adjacent to the Boston city limits (Sites A-D), the O₃
17 concentrations can vary over relatively short distances owing to differing degrees of NO_x
18 titration and influence from the local topography. Like the Atlanta CSA, the variation in
19 warm-season 8-h daily max concentrations are relatively similar across monitors within
20 the Boston CSA with IQRs ranging from 15 ppb at Site U to 21 ppb at Site K. The
21 Los Angeles CSA exhibits the most variability in O₃ concentrations between monitors of
22 all the CSAs/CBSAs investigated. The median 8-h daily max O₃ concentration in the
23 Los Angeles CSA ranged from 20 ppb at Site AM in the south-central extreme of the
24 CSA to 80 ppb at Site AE near Crestline, CA in the San Bernardino National Forest just
25 north of San Bernardino, CA. These two sites are at approximately the same longitude
26 and are separated by only 85 km, but the Crestline site is downwind of the Los Angeles
27 basin, resulting in substantially higher O₃ concentrations. Site AM also contains data for
28 only 2009, which could explain some of the deviation when comparing this site with
29 others in the Los Angeles CSA. Sites AM and AE also had the lowest (8 ppb) and highest
30 (28 ppb) IQR, respectively. The remaining focus cities exhibited spatial variability
31 ranging from uniform as in the Atlanta CSA to non-uniform as observed in the
32 Los Angeles CSA (see supplemental figures in Section [3.9.2](#)).

Atlanta CSA

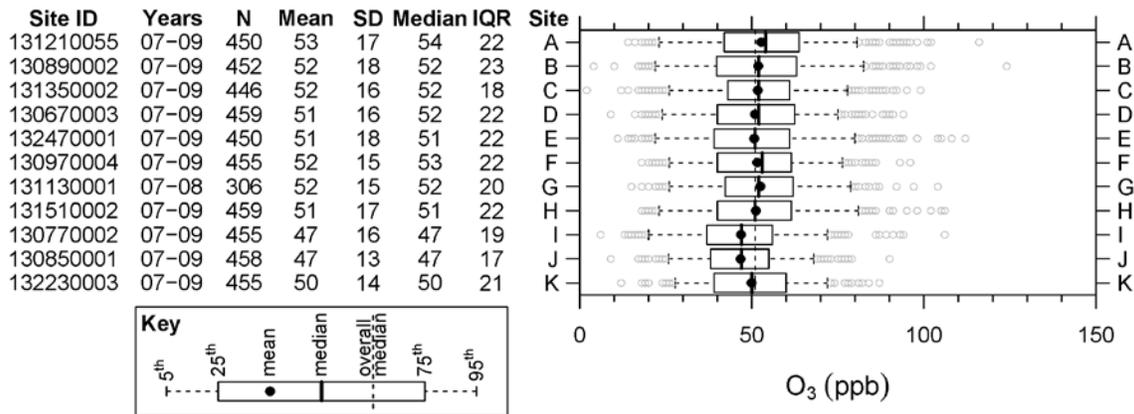


Figure 3-32 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Atlanta CSA.

Boston CSA

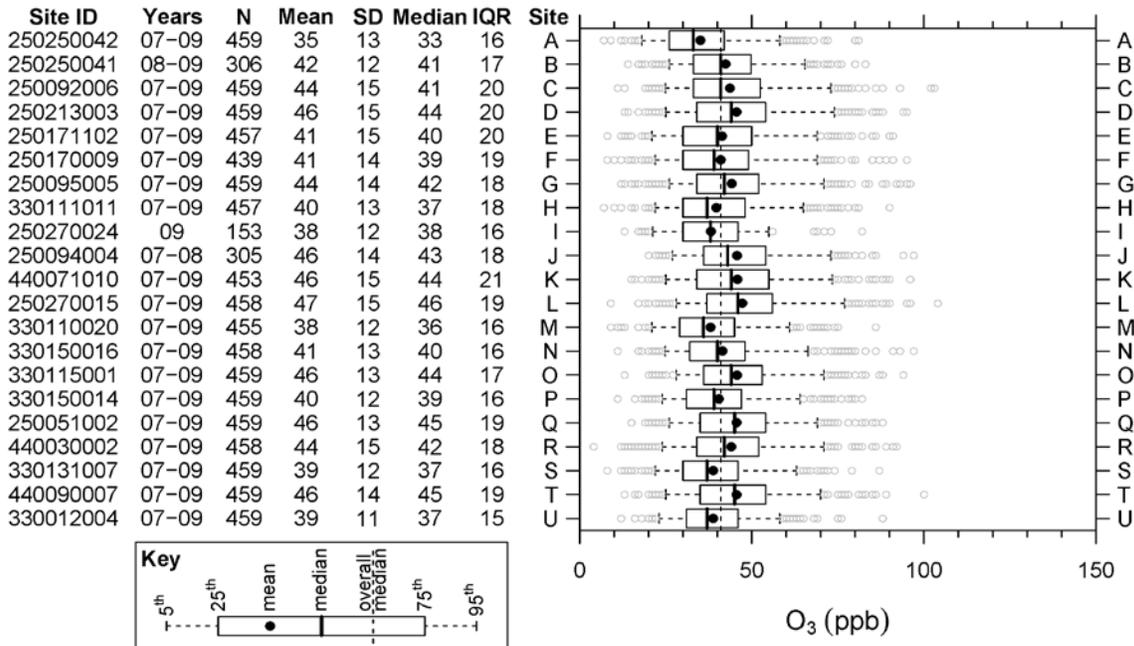


Figure 3-33 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Boston CSA.

Los Angeles CSA

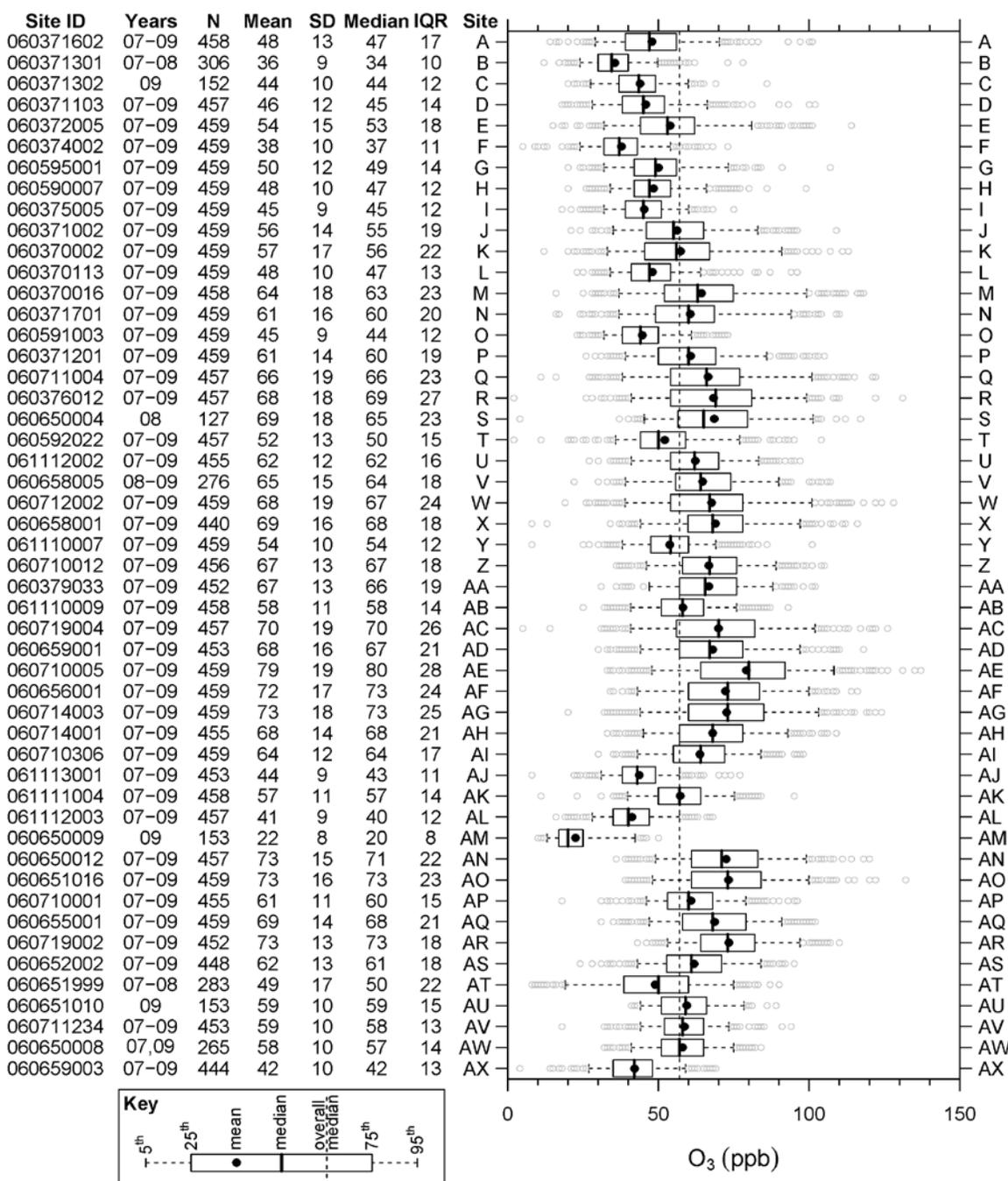


Figure 3-34 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Los Angeles CSA.

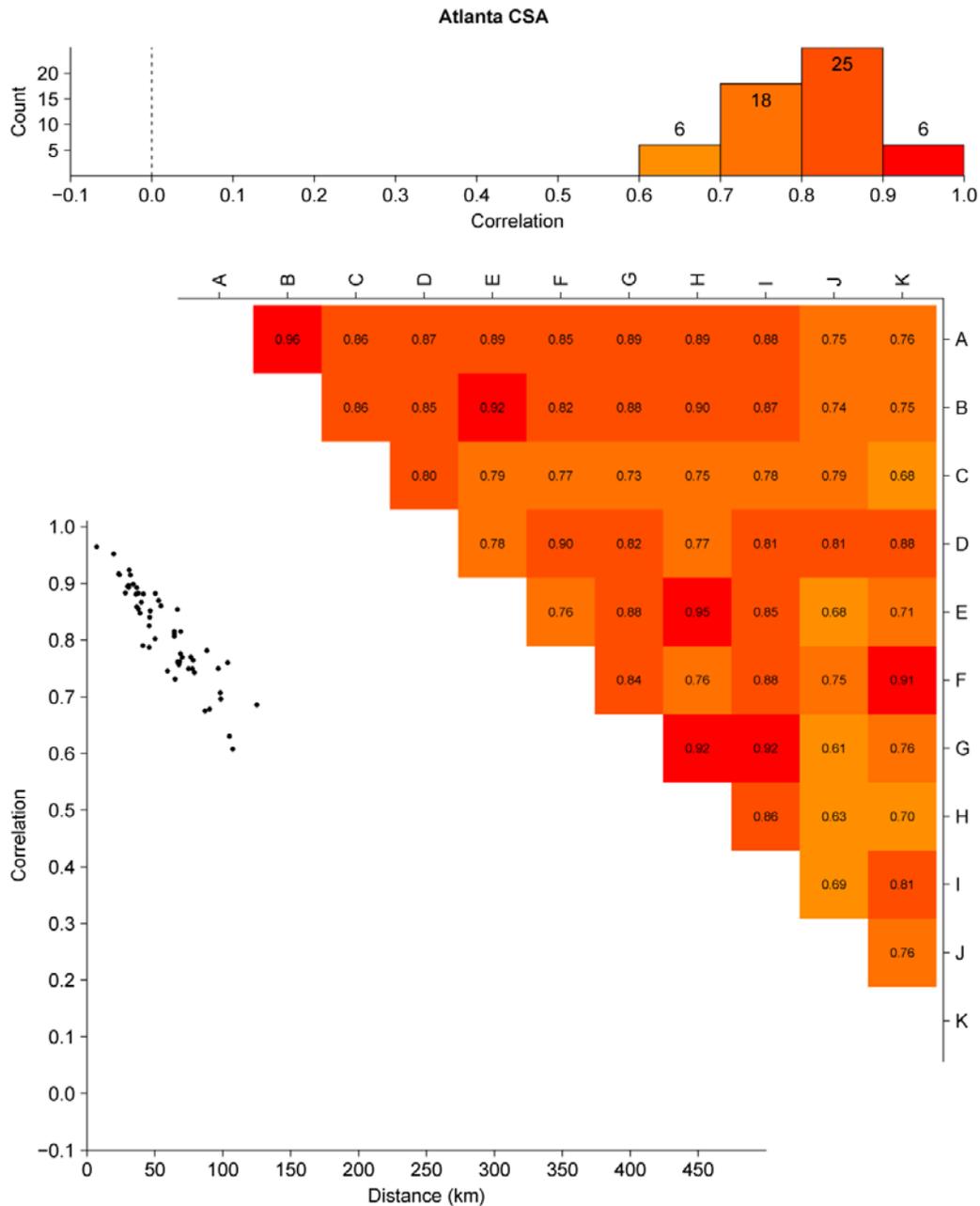
1 Pair-wise monitor comparisons were used to further evaluate spatial variability between
2 monitors within the 20 focus cities. In the particular case of ground-level O₃, central-site
3 monitoring has been justified as a regional measure of exposure mainly on the grounds
4 that correlations between concentrations at neighboring sites measured over time are
5 usually high. In areas with multiple monitoring sites, averages over the monitors have
6 often been used to characterize population exposures. However, substantial differences in
7 concentrations between monitors can exist even though concentrations measured at the
8 monitoring sites are highly correlated, thus leading to the potential for exposure
9 misclassification error. Therefore, both the Pearson correlation coefficient and the
10 coefficient of divergence (COD) were calculated for each monitor pair within the
11 CSA/CBSAs using the 8-h daily max O₃ data. The correlation provides an indication of
12 temporal linear dependence across sites while the COD provides an indication of the
13 variability in absolute concentrations across sites. The COD is defined as follows:

$$COD_{jk} = \sqrt{\frac{1}{p} \sum_{i=1}^p \left(\frac{X_{ij} - X_{ik}}{X_{ij} + X_{ik}} \right)^2}$$

Equation 3-1

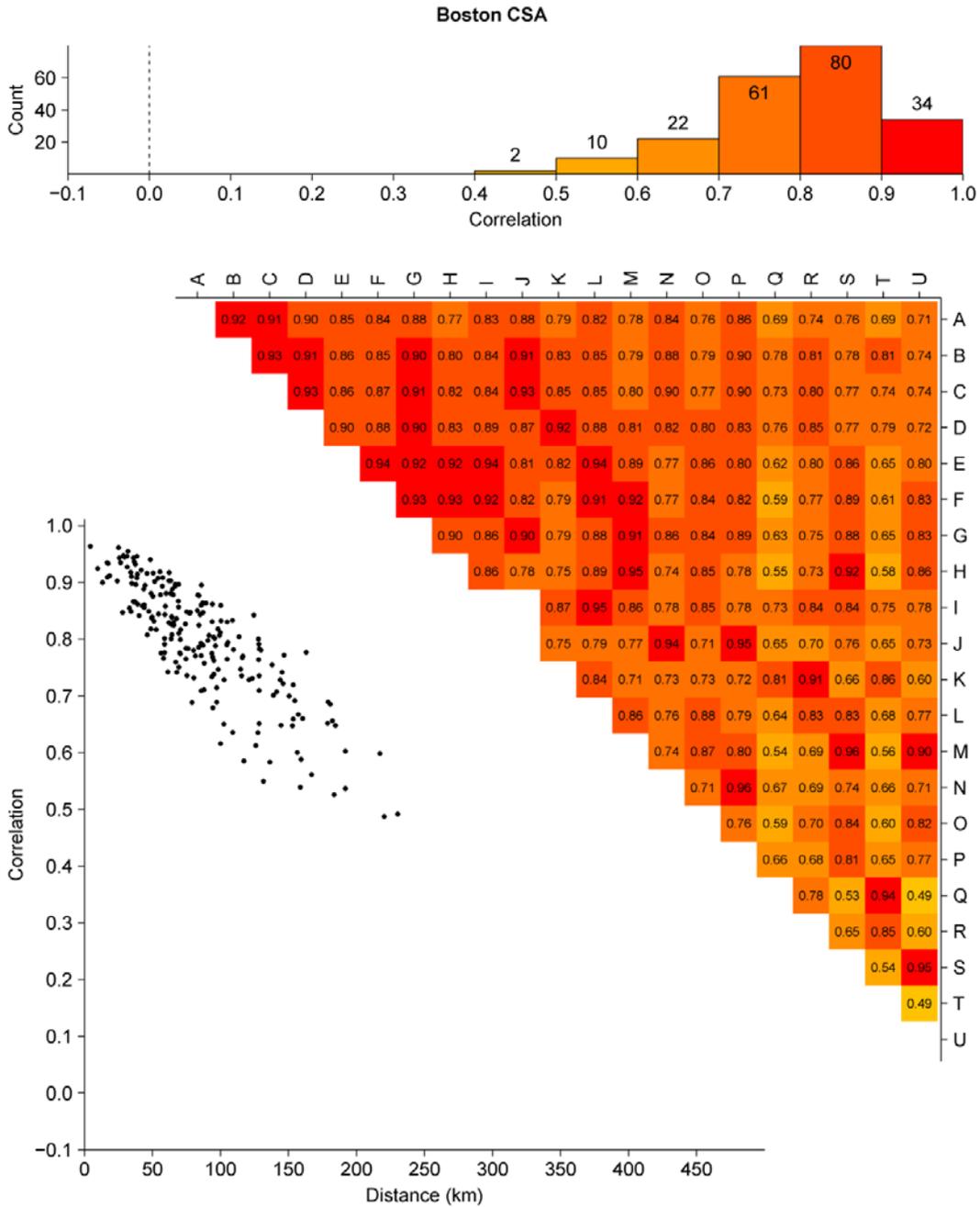
14 where X_{ij} and X_{ik} represent observed concentrations averaged over some measurement
15 averaging period i (hourly, daily, etc.) at sites j and k , and p is the number of paired
16 observations. A COD of 0 indicates there are no differences between concentrations at
17 paired sites (spatial homogeneity), while a COD approaching 1 indicates extreme spatial
18 heterogeneity. These methods for analysis of spatial variability follow those used in
19 previous ISAs for CO, PM, SO_x and NO_x as well as those used in [Pinto et al. \(2004\)](#) for
20 PM_{2.5}.

21 Histograms and contour matrices of the Pearson correlation coefficient between 8-h daily
22 max O₃ concentrations from each monitor pair are included as supplemental material in
23 Section 3.9.3, [Figure 3-116](#) through [Figure 3-135](#); examples for Atlanta, Boston and
24 Los Angeles are shown in [Figure 3-35](#) through [Figure 3-37](#). Likewise, histograms,
25 contour matrices, and scatter plots of the COD between 8-h daily max O₃ concentrations
26 from each monitor pair are included as supplemental material in Section 3.9.3,
27 [Figure 3-136](#) through [Figure 3-155](#); examples for Atlanta, Boston and Los Angeles are
28 shown in [Figure 3-38](#) through [Figure 3-40](#). These figures also contain scatter plots of
29 correlation and COD as a function of straight-line distance between monitor pairs.



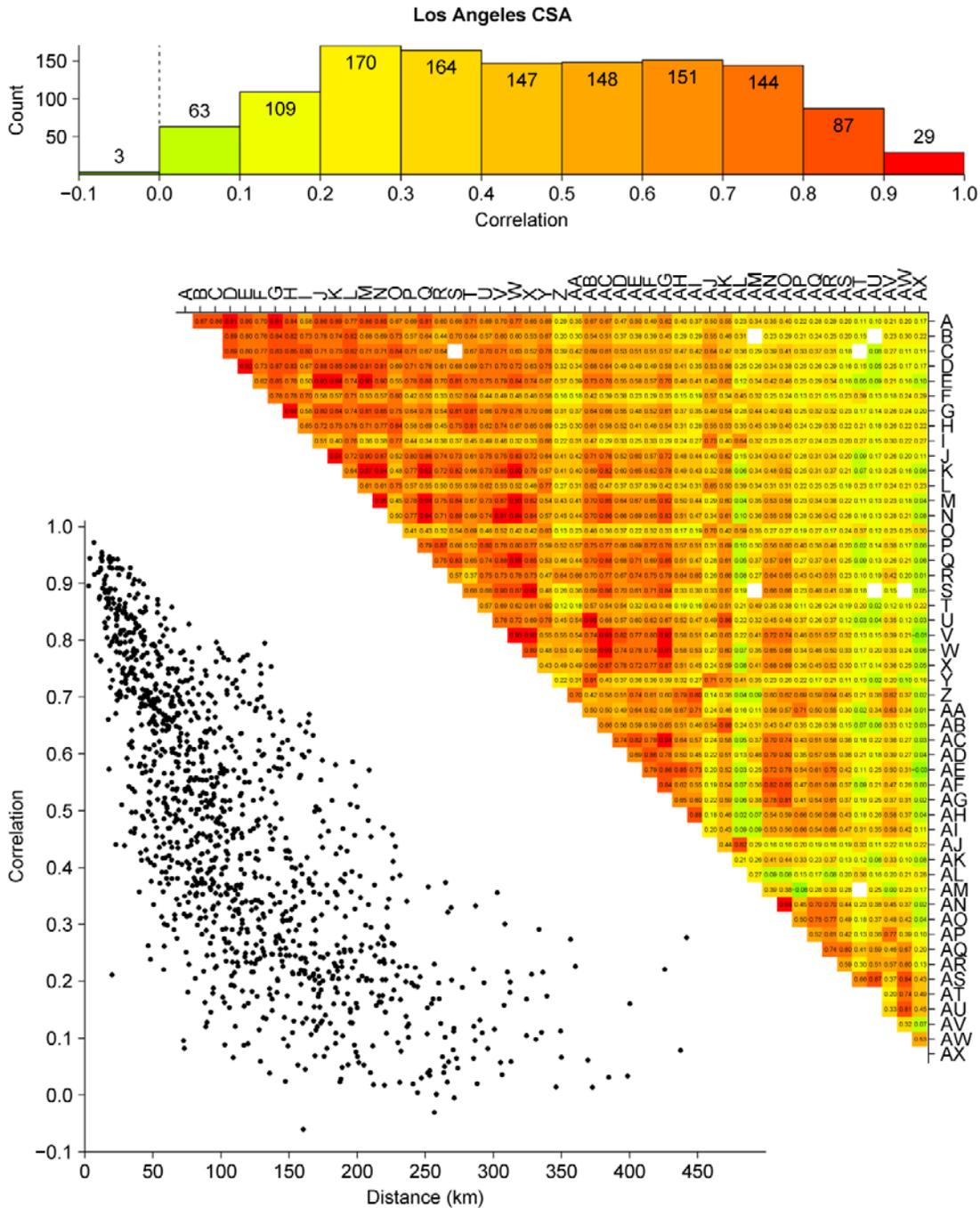
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.

Figure 3-35 Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



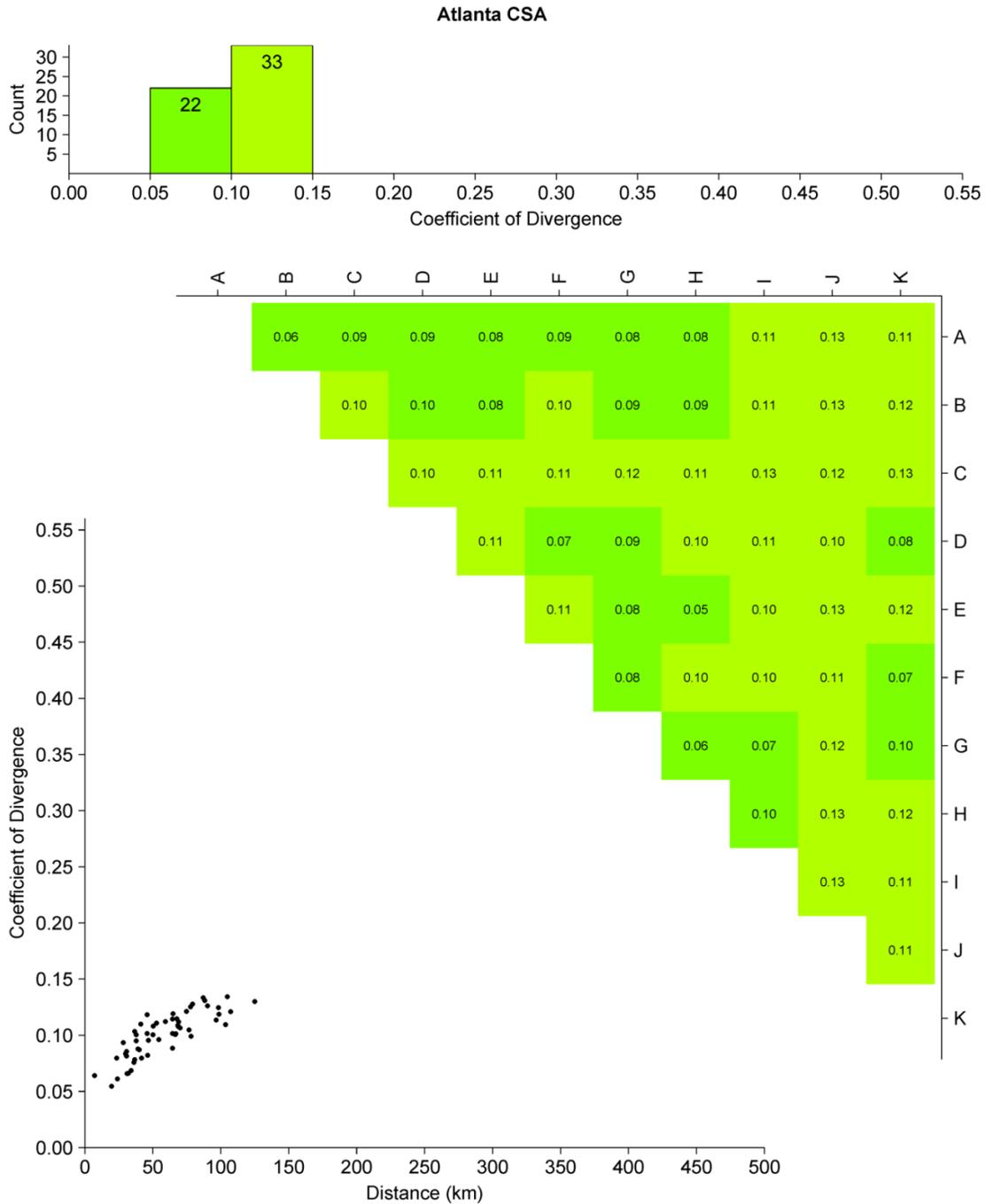
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.

Figure 3-36 Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.



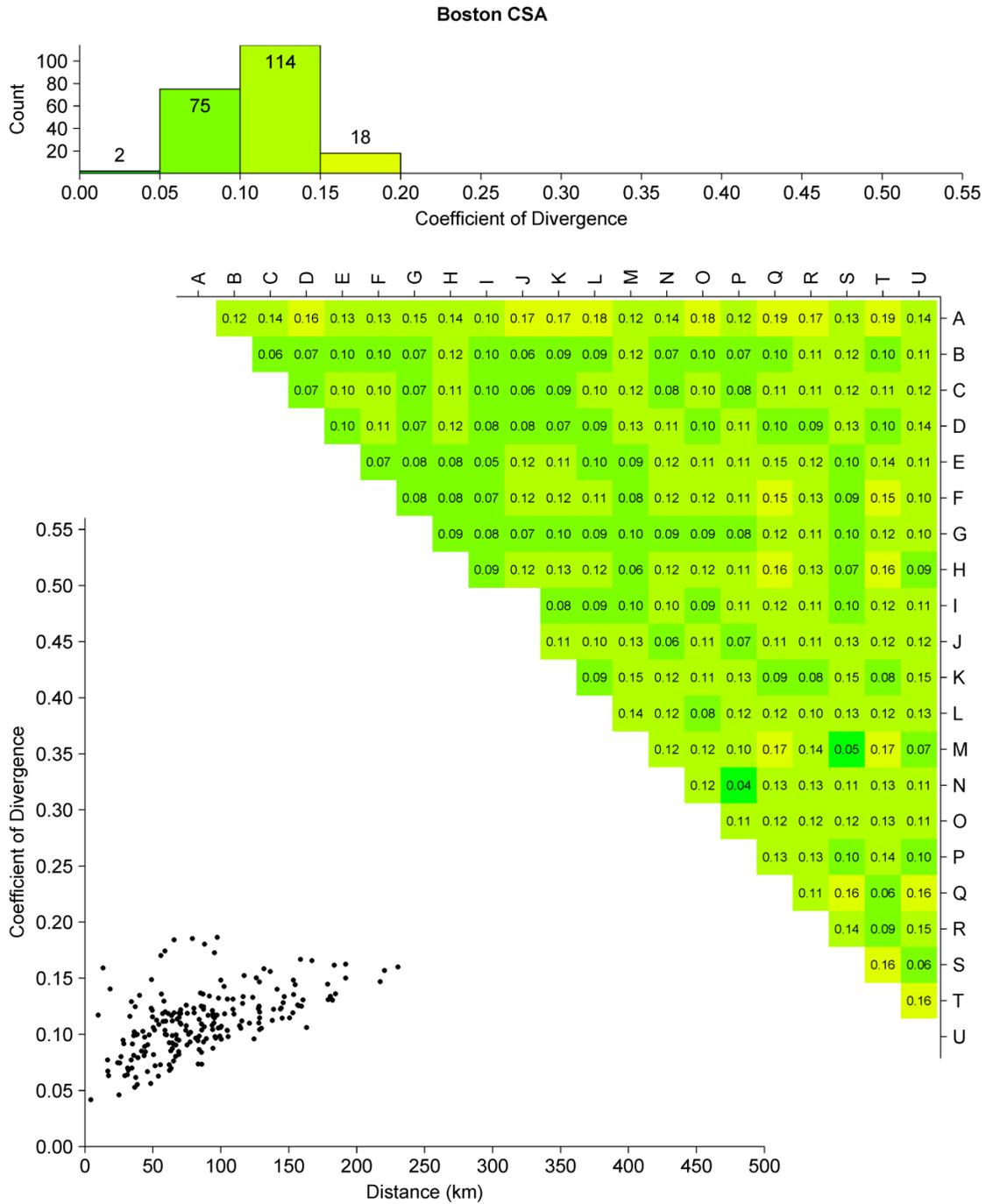
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.

Figure 3-37 Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA.



Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.

Figure 3-38 Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.

Figure 3-39 Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.

1 The monitor pairs within the Atlanta CSA ([Figure 3-35](#)) were generally well correlated
2 with correlations between 8-h daily max O₃ concentrations ranging from 0.61 to 0.96.
3 The correlations shown in the scatter plot were highest for close monitor pairs and
4 dropped off with distance in a near-linear form. At a monitor separation distance of
5 50 km or less, the correlations ranged from 0.79 to 0.96. The monitor pairs within the
6 Boston CSA ([Figure 3-36](#)) were also generally well correlated with correlations ranging
7 from 0.49 to 0.96. Again, the correlations shown in the scatter plot were highest for close
8 monitor pairs, but there was slightly more scatter in correlation as a function of distance
9 in the Boston CSA compared with the Atlanta CSA. At a monitor separation distance of
10 50 km or less, the correlations ranged from 0.81 to 0.96. The monitor pairs within the
11 Los Angeles CSA ([Figure 3-37](#)) showed a much broader range in correlations, extending
12 from -0.06 to 0.97. At a monitor separation distance of 50 km or less, the correlations
13 shown in the scatter plot ranged from 0.21 to 0.97. The negative and near-zero
14 correlations were between monitors with a relatively large separation distance (>150 km),
15 but even some of the closer monitor pairs were not very highly correlated. For example,
16 Site AL located at Emma Wood State Beach in Ventura and Site AK situated in an
17 agricultural valley surrounded by mountains 20 km inland (see map in [Figure 3-41](#)) had a
18 correlation coefficient of only 0.21 over the 2007-2009 warm-season time period. This
19 was slightly lower than the correlation between Site AL and Site AX on the Arizona
20 border, 441 km away (R = 0.28). San Francisco and Seattle ([Figure 3-133](#) and
21 [Figure 3-134](#) in Section [3.9.3](#)) also showed a broad range in pair-wise correlations, likely
22 resulting from their similar geography where background air coming in from the Pacific
23 Ocean rapidly mixes with urban pollutants such as NO_x and VOCs from coastal cities
24 and is transported downwind into diversified terrain to create spatially and temporally
25 varying O₃ concentrations.

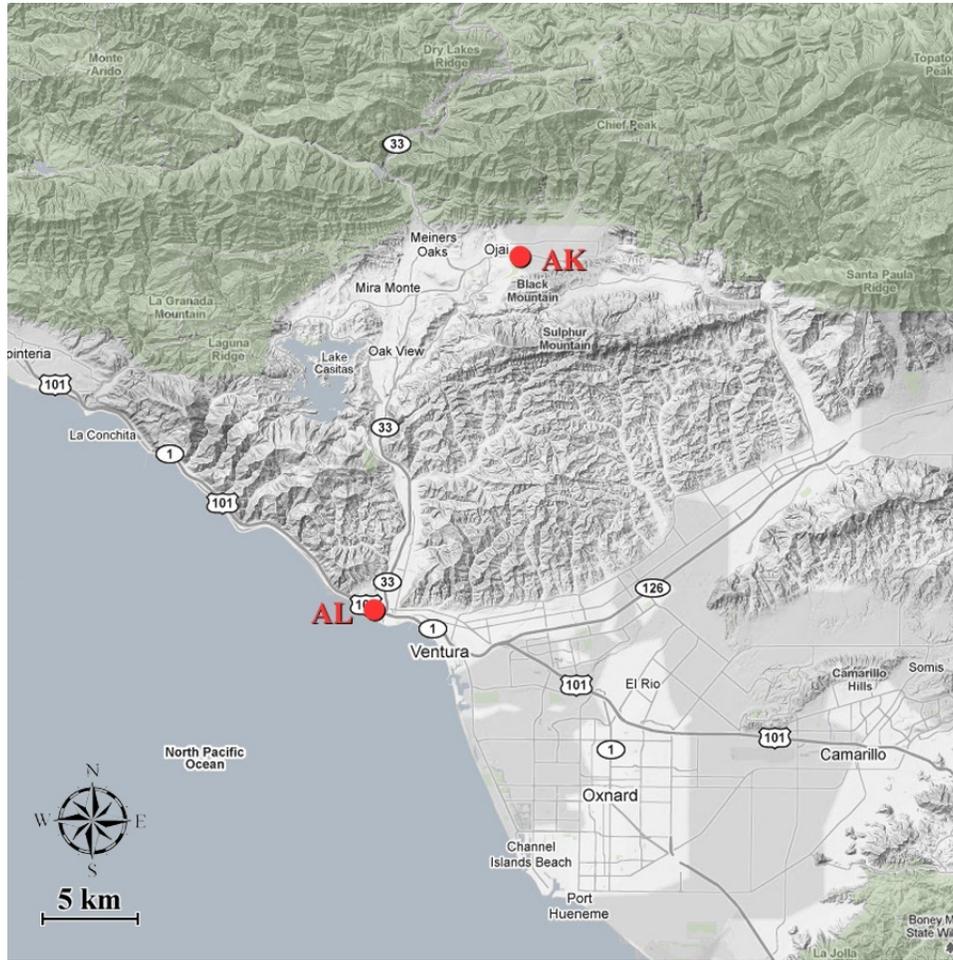


Figure 3-41 Terrain map showing the location of two nearby AQS ozone monitoring sites (red dots) along the western edge of the Los Angeles CSA. Site AL is near shore, 3 meters above sea level, while Site AK is in an agricultural valley surrounded by mountains, 262 meters above sea level.

1 The COD between 8-h daily max O₃ measured at paired monitors in all CSAs/CBSAs
 2 ([Figure 3-136](#) through [Figure 3-155](#) in Section 3.9.3) were generally low, with values
 3 similar to those shown in [Figure 3-38](#) and [Figure 3-39](#) for Atlanta and Boston. This
 4 suggests a generally uniform distribution in the 8-h daily max O₃ concentration across
 5 monitors within these cities and is consistent with the uniformity observed in the box
 6 plots (e.g., [Figure 3-32](#), [Figure 3-33](#), and [Figure 3-96](#) through [Figure 3-115](#) in
 7 Section [3.9.2](#)). Los Angeles ([Figure 3-34](#)) and San Francisco ([Figure 3-153](#) in
 8 Section [3.9.3](#)), however, had several monitor pairs with COD >0.30 indicating greater
 9 spatial heterogeneity. This is consistent with the variability observed in the box plots for
 10 these two CSAs ([Figure 3-34](#) and [Figure 3-113](#) in Section [3.9.2](#)). In particular, Site AM

1 in the Los Angeles CSA had consistently lower concentrations (median = 20 ppb,
2 IQR = 17-25 ppb) relative to other sites in the CSA (Figure 3-31), resulting in high CODs
3 with other monitors as shown in Figure 3-40. The O₃ monitor at Site AM is located on the
4 Pechanga Tribal Government Building in Temecula, CA, and began collecting data on
5 June 9, 2008. It is located in a suburban setting and is classified as a general background
6 monitor. Another close by site (site ID = 060731201) located in the Pala Reservation,
7 9.5 km south of this one (just outside the boundary of the Los Angeles CSA) reported
8 similarly low 2009 8-h daily max O₃ concentrations (median = 28 ppb, IQR = 23-32 ppb)
9 between May-June, 2009 (the only warm-season months with available data from this site
10 between 2007 and 2009).



Figure 3-42 Terrain map showing the location of four AQS ozone monitoring sites (red dots) located in or near the city limits in the center of the Boston CSA. Site characteristics range from Site A near downtown at 6 meters above sea level to Site D in a forested area on Blue Hill at 192 meters above sea level.

1 There are instances where sites in an urban area may exhibit substantial differences in
2 median concentrations, but still be moderately well correlated in time. For example, Sites
3 A and D in Boston (see terrain map in [Figure 3-42](#)) have an 11 ppb difference in median
4 8-h daily max O₃ concentration (COD = 0.16), but a high correlation (R = 0.90). In this
5 example, Site A is located in the Boston city limits at an elevation of 6 meters while Site
6 D is located 13 km to the south in a forested area on Blue Hill, the highest point in
7 Norfolk County (elevation = 192 meters). The difference in median O₃ concentration at
8 these two sites can be attributed to differing degrees of NO_x titration between the
9 neighborhood scale site (Site A) and the regional scale site (Site D) and to the influence
10 of local topography.

11 Comparison of monitoring data within the selected focus cities has demonstrated
12 considerable variability between cities in the behavior of the O₃ concentration fields.
13 Median O₃ concentrations vary more within certain urban areas than others. Likewise,
14 pair-wise monitor statistics (R and COD) are dependent on the urban area under
15 investigation. These conclusions are consistent with those drawn in the 2006 O₃ AQCD
16 ([U.S. EPA, 2006b](#)) where a subset of these focus cities were investigated using similar
17 statistics. As a result, caution should be observed in using data from a sparse network of
18 ambient O₃ monitors to approximate community-scale exposures.

Neighborhood-Scale Variability and the Near-Road Environment

19 Ozone is a secondary pollutant formed in the atmosphere from precursor emissions and
20 therefore is generally more regionally homogeneous than primary pollutants emitted from
21 stationary or mobile point sources. However, O₃ titration from primary NO emissions
22 does result in substantial localized O₃ gradients. This is evident in the near-road
23 environment where fresh NO emissions from motor vehicles titrate O₃ present in the
24 urban background air, resulting in an O₃ gradient down-wind from the roadway. Ozone
25 titration occurring in street canyons where NO emissions are continuously being
26 generated is more efficient because of inhibited transport away from the source of NO.

27 Several studies have reported O₃ concentrations that increase with increasing distance
28 from the roadway, both upwind and downwind of the road. [Beckerman et al. \(2008\)](#)
29 measured O₃ profiles in the vicinity of heavily traveled roadways with Annual Average
30 Daily Traffic (AADT) >340,000 vehicles in Toronto, Canada. Ozone was observed to
31 increase with increasing distance from the roadway, both upwind and downwind of the
32 road. This is consistent with scavenging of O₃ in the near-road environment by reaction
33 with NO to form NO₂. Upwind of the road, concentrations were >75% of the maximum
34 observed value at >100 meters from the road; downwind, concentrations were
35 approximately 60% of the maximum within 200-400 meters of the road. The O₃

1 concentration adjacent to the road on the upwind side was approximately 40% of the
2 maximum value observed at the site. Concentrations measured with Ogawa passive
3 samplers over a 1-week period ranged from 7.3-19.4 ppb with the mean at the two sites
4 ranging from 13.0-14.7 ppb. In a study of patrol cars during trooper work shifts, [Riediker](#)
5 [et al. \(2003\)](#) made simultaneous 9-h O₃ measurements inside patrol cars, at the roadside,
6 and at a centrally-located ambient monitoring site. The roadside concentrations were
7 approximately 81% of the ambient values (mean of 22.8 ppb versus 28.3 ppb). Wind
8 direction relative to the roadway was not reported.

9 [Johnson \(1995\)](#) measured O₃, NO, and CO concentrations at upwind and downwind
10 locations near a variety of roadways in Cincinnati, OH. The effects of O₃ scavenging by
11 NO were apparent in the O₃ reduction in the interval between 9 meters upwind and
12 82 meters downwind of the road. A similar effect was observed by [Rodes and Holland](#)
13 [\(1981\)](#) during an earlier study in which outdoor O₃ concentrations were monitored
14 downwind of a freeway in Los Angeles, CA. In this study, O₃ concentrations measured
15 near the roadway were approximately 20% of the concentrations measured
16 simultaneously at more distant locations judged to be unaffected by the roadway.
17 Minimal separation distances of the samplers from the roadway to eliminate measurable
18 influence were estimated to be approximately 400-500 meters for NO, NO₂, and O₃.
19 Similar results have been observed outside the U.S., for example in the city of Daegu,
20 Korea, where the yearly roadside concentrations of CO and SO₂ showed a well-defined
21 decreasing trend with distance from the roadway, whereas concentrations of NO₂ and O₃
22 exhibited the reverse trend ([Jo and Park, 2005](#)). During the peak O₃ month of May, O₃
23 concentrations in a residential neighborhood were approximately 40% higher than
24 concentrations at roadside monitors located 1 meter from the edge of multiple-lane
25 freeways.

3.6.2.2 Rural-Focused Variability and Ground-Level Vertical Gradients

26 AQS O₃ data for monitors located at several rural monitoring sites (e.g., national parks,
27 national forests, state parks, etc.) were used to investigate rural-focused O₃ concentration
28 variability in contrast with the urban-focused variability discussed in Section [3.6.2.1](#).
29 These rural monitoring sites tend to be less directly affected by anthropogenic pollution
30 sources than urban sites. However, they can be regularly affected by transport of O₃ or O₃
31 precursors from upwind urban areas, or by local anthropogenic sources within the rural
32 areas such as emissions from motor vehicles, power generation, biomass combustion, or
33 oil and gas operations. As a result, monitoring data from these rural locations are not
34 unaffected by anthropogenic emissions.

1 Six rural focus areas were selected for their geographic distribution across the U.S. as
 2 well as their unique topography and relevance to the ecological assessment in Chapter 9.
 3 [Table 3-11](#) lists the rural focus areas and provides some cursory site information along
 4 with the number of available AQS monitors reporting year-round and only during the
 5 warm-season. Accompanying box plots depicting the distribution of 2007-2009 warm-
 6 season 8-h daily max O₃ data from each individual monitor in the six rural focus areas are
 7 included in [Figure 3-43](#). This analysis was restricted to AQS monitors meeting the same
 8 data completeness criteria outlined in [Table 3-5](#) for a direct comparison with the 20 urban
 9 focus areas investigated in Section [3.6.2.1](#). Given the population-center emphasis of the
 10 AQS network, limited monitoring sites (between one and five) were available for each
 11 rural focus area. Expanded analyses of O₃ concentrations measured using the more rural-
 12 focused CASTNET monitoring network are included in Chapter 9.

Table 3-11 Rural focus areas.

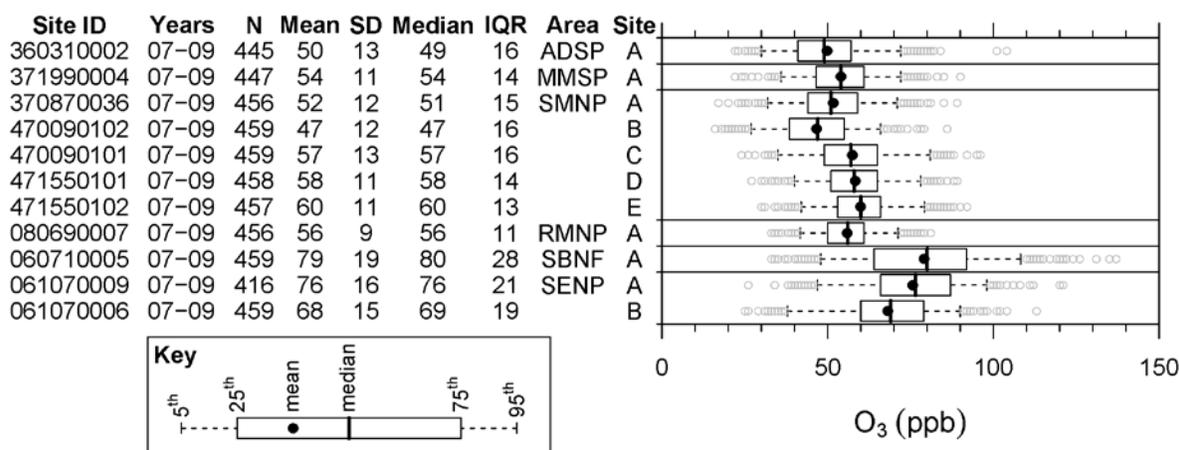
| Focus Area | Short Name | Year-Round O ₃ Monitoring Sites ^a | Warm-Season O ₃ Monitoring Sites ^b | Monitor Elevation (meters) | Site Descriptions |
|---|-------------------|---|--|----------------------------|---|
| Adirondack State Park, NY | ADSP | 1 | 0 | 1,483 | One site on the summit of Whiteface Mountain in the Adirondack Mountains |
| Mount Mitchell State Park, NC | MMSP | 0 | 1 | 1,982 | One site near the summit of Mount Mitchell (highest point in the eastern U.S.) in the Appalachian Mountains |
| Great Smoky Mountain National Park, NC-TN | SMNP | 2 | 3 | 564-2,021 | Five different locations within Great Smoky Mountain National Park in the Appalachian Mountains |
| Rocky Mountain National Park, CO | RMNP | 1 | 0 | 2,743 | One site in a valley at the foot of Longs Peak in the Rocky Mountains |
| San Bernardino National Forest, CA | SBNF ^c | 1 | 0 | 1,384 | One site in Lake Gregory Regional Park (near Crestline, CA) in the San Bernardino Mountains |
| Sequoia National Park, CA | SENP | 2 | 0 | 560-1,890 | Two contrasting sites at different elevations within Sequoia NP in the Sierra Nevada Mountains |

^aNumber of AQS monitors meeting the year-round data set inclusion criteria; the year-round data set is limited to these monitors.

^bNumber of AQS monitors meeting the warm-season data set inclusion criteria; the warm-season data set includes May-September data from both the warm-season and year-round monitors.

^cSame AQS site as Site AE in the Los Angeles CSA shown in [Figure 3-31](#).

Rural Focus Areas



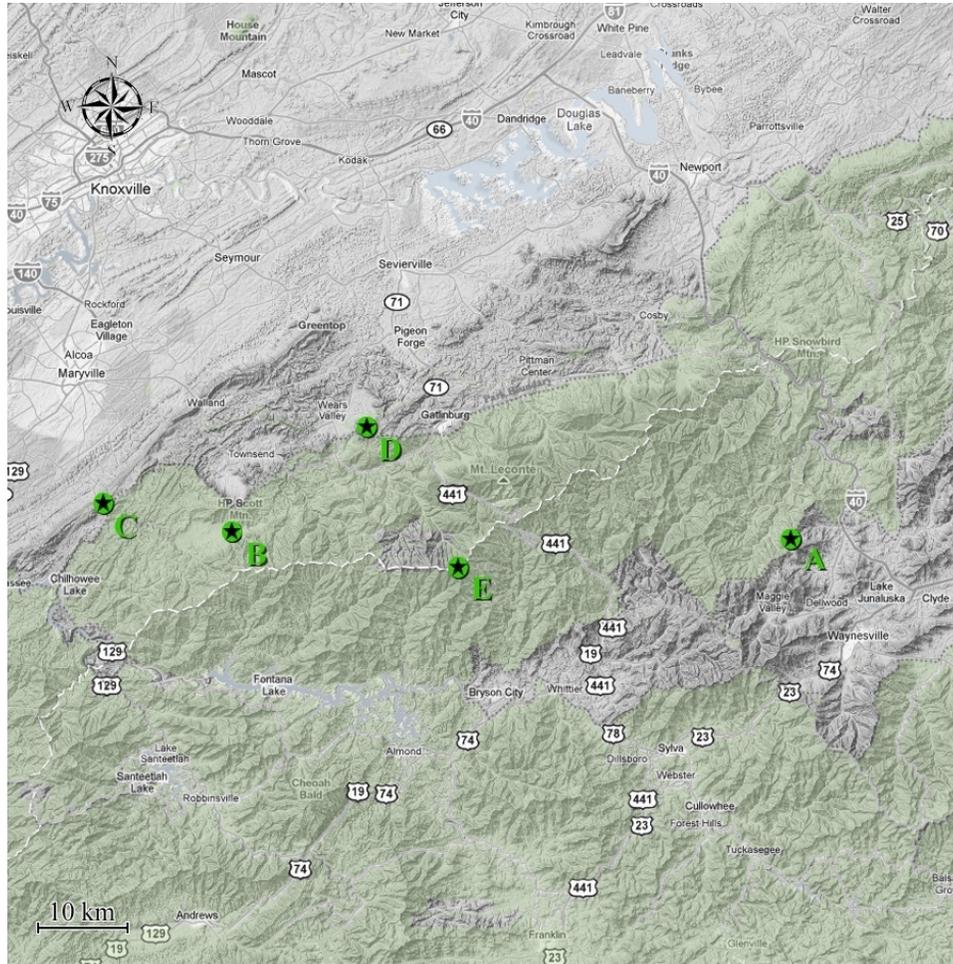
Note: includes: Adirondack State Park, NY (ADSP); Mount Mitchell State Park, NC (MMSP); Great Smoky Mountain National Park, NC-TN (SMNP); Rocky Mountain National Park, CO (RMNP); San Bernardino National Forest, CA (SBNF); and Sequoia National Park, CA (SENP).

Figure 3-43 Rural focus area site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the rural focus areas.

Eastern Rural Focus Areas

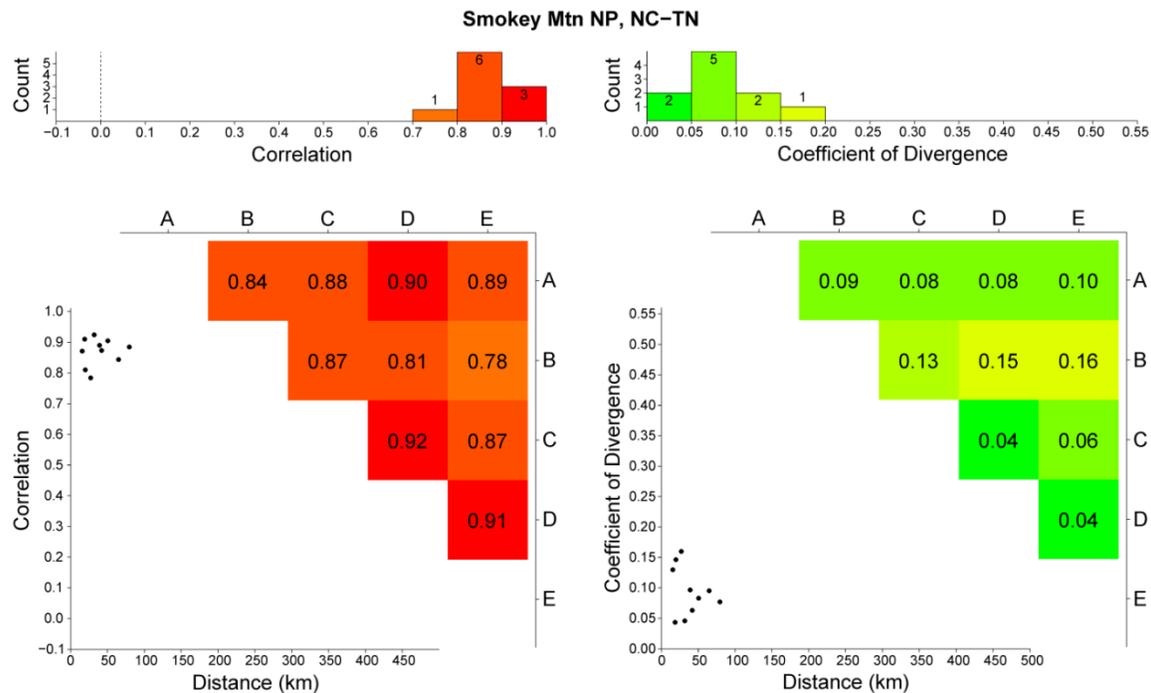
1 In the East, the distribution in warm-season 8-h daily max O₃ concentrations from the
 2 Adirondack State Park (ADSP) site on Whiteface Mountain in Upstate NY
 3 (median = 49 ppb) (Figure 3-43) was among the lowest of the rural focus monitors
 4 investigated, but was still higher than concentration distributions measured in the Boston
 5 CSA (medians ranging from 33 to 46 ppb) (Figure 3-33) located 320 km to the southeast.
 6 The ADSP AQS site was included in an analysis for the 2006 O₃ AQCD (U.S. EPA,
 7 2006b) and had the lowest year-round median hourly O₃ concentration of the rural
 8 forested sites investigated (including Yellowstone NP, the Great Smoky Mountains NP,
 9 and Shenandoah NP). For the Appalachian Mountain monitors in Mount Mitchell State
 10 Park, NC (MMSP) and Great Smoky Mountain National Park, NC-TN (SMNP), there
 11 was a fair amount of variability in concentration distribution. Within SMNP, the median
 12 warm-season 8-h daily max O₃ concentration ranged from 47 ppb at the lowest elevation
 13 site (elevation = 564 meters; site ID = 470090102) to 60 ppb at the highest elevation site
 14 (elevation = 2,021 meters; site ID = 471550102); these sites are shown on the terrain map
 15 in Figure 3-44. The warm-season median 8-h daily max O₃ concentration gradient
 16 between these two sites located 26.2 km apart in SMNP was 0.9 ppb per 100 meters
 17 elevation gain.

1 Data from the five sites within SMNP allowed for further investigation of spatial
2 variability within the park; [Figure 3-45](#) contains histograms, contour plots and scatter
3 plots as a function of distance for the pair-wise correlation and COD (defined in
4 [Equation 3-1](#)) for SMNP. The correlations between the five sites ranged from 0.78 to
5 0.92 and the CODs ranged from 0.04 to 0.16. The plots of correlation and COD as a
6 function of distance between SMNP monitor pairs in [Figure 3-45](#) show a large degree of
7 spatial variability between monitors over relatively short distances. A host of factors may
8 contribute to these variations, including proximity to local O₃ precursor emissions,
9 variations in boundary-layer influences, meteorology and stratospheric intrusion as a
10 function of elevation, and differences in wind patterns and transport behavior due to local
11 topography.



Note: The lowest elevation site (Site B) is 564 meters above sea level, while the highest elevation site (Site E) is 2,021 meters above sea level.

Figure 3-44 Terrain map showing the location of five AQS ozone monitoring sites (green/black stars) in Great Smoky Mountain National Park, NC-TN (SMNP).



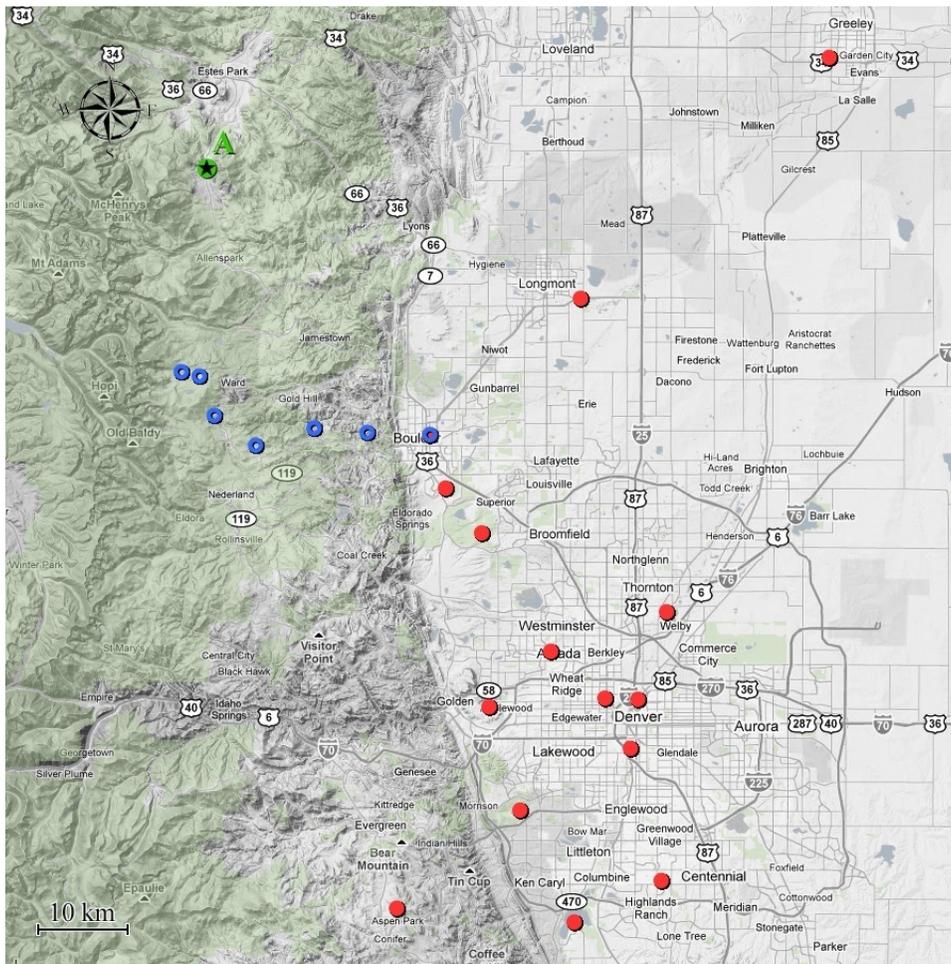
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histograms includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations and CODs.

Figure 3-45 Pair-wise monitor correlations (left) and coefficients of divergence (COD, right) expressed as a histogram (top), contour matrix (middle) and scatter plot vs. distance between monitors (bottom) for Great Smoky Mountain National Park, NC-TN (SMNP).

Western Rural Focus Areas

1 The Rocky Mountain National Park (RMNP) site in Colorado at 2,743 meters in
 2 elevation had a warm-season 8-h daily max O₃ concentration distribution
 3 (median = 56 ppb, IQR = 11 ppb) (Figure 3-43) that is comparable to the distributions at
 4 sites in the Denver CSA located 75 km southeast at elevations around 1,600 meters
 5 (medians ranging from 41 to 59 ppb, IQRs ranging from 10 to 16 ppb; see Figure 3-102
 6 in Section 3.9.1). In nearby Boulder County, CO, a 1-year time-series (Sep 2007-Aug
 7 2008) of ambient surface-level O₃ measurements was collected by Brodin et al. (2010)
 8 along an elevation gradient ranging from 1,608 meters to 3,528 meters. The 7 sites used
 9 in this study are shown in Figure 3-46 along with the RMNP site and the 15 Denver CSA
 10 sites. In fall, winter, and spring, they observed a clear monotonic increase in O₃
 11 concentration with elevation, with a rate of increase in the mean O₃ concentration of
 12 1.5 ppb per 100 meters elevation gain during winter. In summer, the O₃ gradient was
 13 similar in magnitude over the seven-site transect (1.3 ppb per 100 meters), but much less

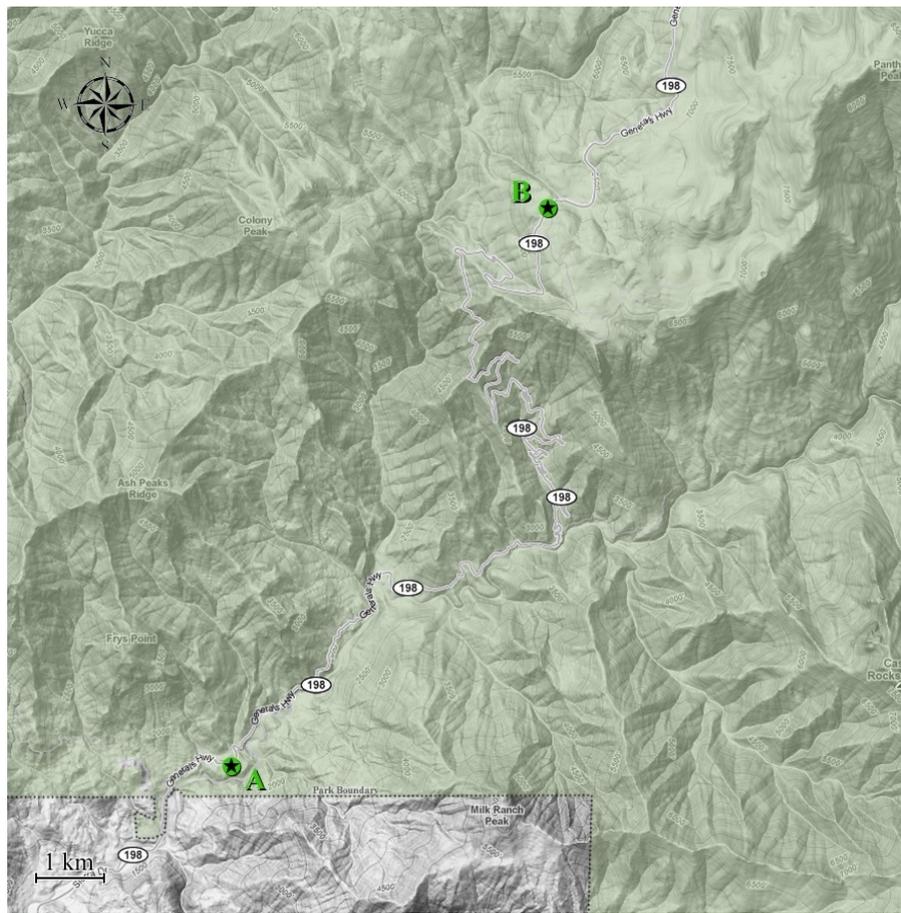
1 monotonic; the majority of the vertical gradient occurred between the lowest two sites
2 (4.5 ppb per 100 meters) and between the highest two sites (5.5 ppb per 100 meters), with
3 the middle five sites all having approximately equal median O₃ concentrations. Ozone
4 concentrations at the lowest site in Boulder were influenced by NO titration as evidenced
5 by traffic-related diel cycles in O₃ concentrations, but the remaining six sites were located
6 at elevation in more rural/remote settings and illustrate a positive surface-level O₃
7 elevation gradient similar to that seen in SMNP and typical of areas under less direct
8 influence of boundary layer pollution.



Note: Elevations range from approximately 1,600 meters above sea level in Denver and Boulder to 3,528 meters above sea level at the highest mountainous site.

Figure 3-46 Terrain map showing the location of the AQS ozone monitoring site in Rocky Mountain National Park, CO (black/green star) and the Denver CSA (red dots) along with ozone monitoring sites used in the [Brodin et al. \(2010\)](#) study (blue circles).

1 The three sites in California—one in San Bernardino National Forest (SBNF) and two in
2 Sequoia National Park (SENP)—had the highest distribution of 8-h daily max O₃
3 concentrations of the selected rural focus area monitors included in [Figure 3-43](#). The
4 SBNF site had a warm-season 8-h daily max O₃ concentration mean of 80 ppb and a
5 maximum of 137 ppb measured on July 1, 2007. This site is located in Crestline, CA,
6 90 km down-wind of Los Angeles in the San Bernardino Mountains. This site was
7 included in the Los Angeles CSA shown in [Figure 3-31](#) (Site AE) and had the highest
8 median 8-h daily max O₃ concentration of any AQS site in the Los Angeles CSA during
9 this time period ([Figure 3-34](#)). This site was also included in an analysis performed for
10 the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) where similarly high O₃ concentrations were
11 observed using 2004 year-round hourly observations.



Note: The lower site (site ID = 061070009) is 560 meters above sea level and the higher site (site ID = 061070006) is 1,890 meters above sea level.

12 **Figure 3-47 Terrain map showing the location of two AQS ozone monitoring sites (black/green stars) in Sequoia National Park, CA.**

1 The two sites in SENP are located 9.7 km apart at contrasting elevations as is illustrated
2 in the terrain map in [Figure 3-47](#). The correlation in 8-h daily max O₃ between these two
3 sites was 0.86 and the COD was 0.09, which are within the range in correlations and
4 CODs for SMNP ([Figure 3-45](#)). The distribution of 8-h daily max O₃ concentrations at
5 the lower elevation site (elevation = 560 meters; site ID = 061070009) is shifted slightly
6 higher with a median of 76 ppb compared to the higher elevation site
7 (elevation = 1,890 meters; site ID = 061070006) with a median of 69 ppb. The lower
8 elevation site is located at the entrance to the park and is at a low enough elevation to be
9 influenced by boundary layer pollution coming upwind from Fresno and the San Joaquin
10 Valley. The higher elevation site is in the free troposphere above the planetary boundary
11 layer and is less influenced by such pollution. This gives rise to a negative average
12 surface-level elevation gradient of -0.5 ppb per 100 meters elevation gain in SENP,
13 illustrating the location-specific complexities inherent to high-altitude surface-level O₃
14 concentrations.

15 Since O₃ produced from emissions in urban areas is transported to more rural downwind
16 locations, elevated O₃ concentrations can occur at considerable distances from urban
17 centers. In addition, major sources of O₃ precursors such as highways, power plants,
18 biomass combustion, and oil and gas operations are commonly found in rural areas,
19 adding to the O₃ in these areas. Due to lower chemical scavenging in non-urban areas, O₃
20 tends to persist longer in rural than in urban areas which tends to lead to higher
21 cumulative exposures in rural areas influenced by anthropogenic precursor emissions.
22 The persistently high O₃ concentrations observed at many of these rural sites investigated
23 here indicate that cumulative exposures for humans and vegetation in rural areas can be
24 substantial and often higher than cumulative exposures in urban areas.

3.6.3 Temporal Variability

3.6.3.1 Multiyear Trends

25 As reported in the 2010 National Air Quality Status and Trends report ([U.S. EPA,](#)
26 [2010e](#)), nation-wide surface level O₃ concentrations in the U.S. have declined gradually
27 over the last decade. [Figure 3-48](#) shows the downward trend in the annual 4th highest 8-h
28 daily max O₃ concentration from 870 surface level monitors across the U.S. [Figure 3-49](#)
29 shows a similar trend in the annual second highest 1-h daily max O₃ concentration from
30 875 surface level monitors. The median annual 4th highest 8-h daily max dropped from
31 88 ppb in 1998 to 71 ppb in 2010. Likewise, the median annual second highest 1-h daily
32 max dropped from 109 ppb in 1998 to 86 ppb in 2010. The large decreases in 2003 and

1 2004 in both figures coincides with NO_x emissions reductions resulting from
2 implementation of the NO_x State Implementation Plan (SIP) Call rule, which began in
3 2003 and was fully implemented in 2004. This rule was designed to reduce NO_x
4 emissions from power plants and other large combustion sources in the eastern U.S.
5 Reductions in mobile NO_x emissions nationwide from the implementation of recent
6 vehicle and fuel standards could also be adding to the gradual decline in nationwide
7 surface level O₃ concentrations ([Dallmann and Harley, 2010](#)).

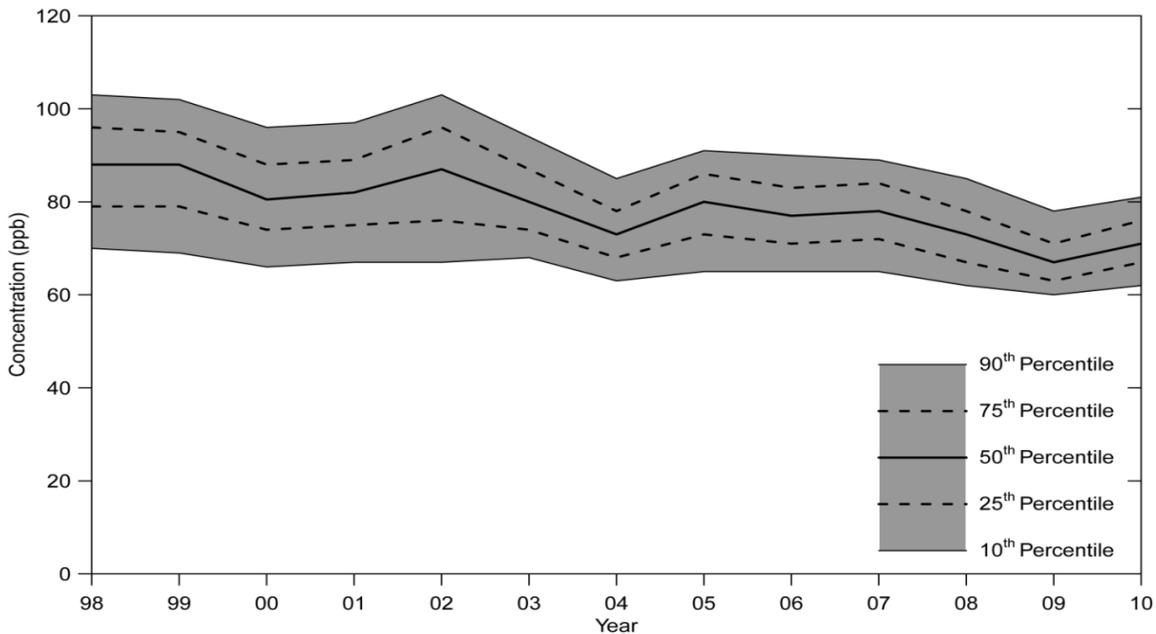


Figure 3-48 National 8-h daily max ozone trend and distribution across 870 U.S. ozone monitors, 1998-2010 (annual 4th highest 8-h daily max ozone concentrations in ppm).

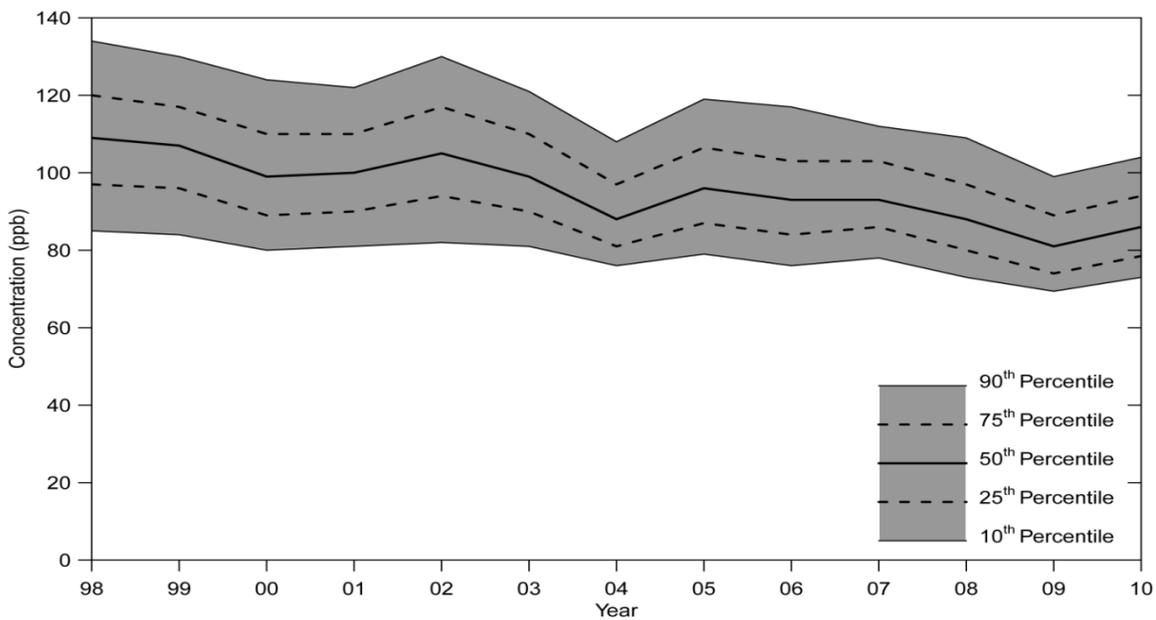


Figure 3-49 National 1-h daily max ozone trend and distribution across 875 U.S. ozone monitors, 1998-2010 (annual second highest 1-h daily max ozone concentrations in ppm).

1 The distributional percentiles (10th, 25th, 75th, and 90th) displayed in [Figure 3-48](#) and
 2 [Figure 3-49](#) reveal a gradual tightening of the O₃ concentration distribution observed
 3 across monitors. For the annual 4th highest 8-h daily max O₃ concentration, the IQR
 4 decreased from 17 ppb in 1998 to 9 ppb in 2010. Likewise, for the annual second highest
 5 1-h daily max O₃ concentration, the IQR decreased from 23 ppb in 1998 to 16 ppb in
 6 2010. A similar tightening was observed for the wider percentiles (90th-10th) for both
 7 averaging times.

8 Weather can have a strong influence on the O₃ trends shown in [Figure 3-48](#) and
 9 [Figure 3-49](#). The number of hot, dry days can substantially alter the number of high O₃
 10 days in any given year, even if O₃ forming emissions do not change. To better evaluate
 11 the progress and effectiveness of emissions reduction programs, EPA uses a statistical
 12 model to estimate the influence of atypical weather on O₃ formation ([U.S. EPA, 2010e](#)).
 13 After adjusting for the influence of weather, the downward trend in surface level national
 14 8-h daily max O₃ concentrations between 2001 and 2008 increased slightly from an 8%
 15 reduction prior to adjustment for weather to an 11% reduction after adjustment for
 16 weather ([U.S. EPA, 2010e](#)).

17 A regional breakdown of the trend in O₃ concentrations for the 8-hour and 1-hour metrics
 18 is included in [Figure 3-50](#) and [Figure 3-51](#), respectively. In general, the trends are region-

1 specific with a substantial amount of year-to-year variability. The reduction in NO_x and
 2 O₃ during the 2003-2004 timeframe is particularly evident in the North Central and
 3 Northeastern U.S. where the NO_x SIP Call was focused ([U.S. EPA, 2010e](#)). The western
 4 region (including Alaska and Hawaii but excluding California) started out with the lowest
 5 annual O₃ concentration in 1998 and exhibits the least amount of reduction when
 6 compared to 2010 concentrations (11% reduction in the average annual 4th highest 8-h
 7 daily max and 13% reduction in the average annual second highest 1-h daily max). In
 8 contrast, California—which has some of the highest concentrations of the identified
 9 regions—shows a larger downward trend in O₃ concentrations over the same time period
 10 (19% reduction in the average annual 4th highest 8-h daily max and 22% reduction in the
 11 average annual second highest 1-h daily max).

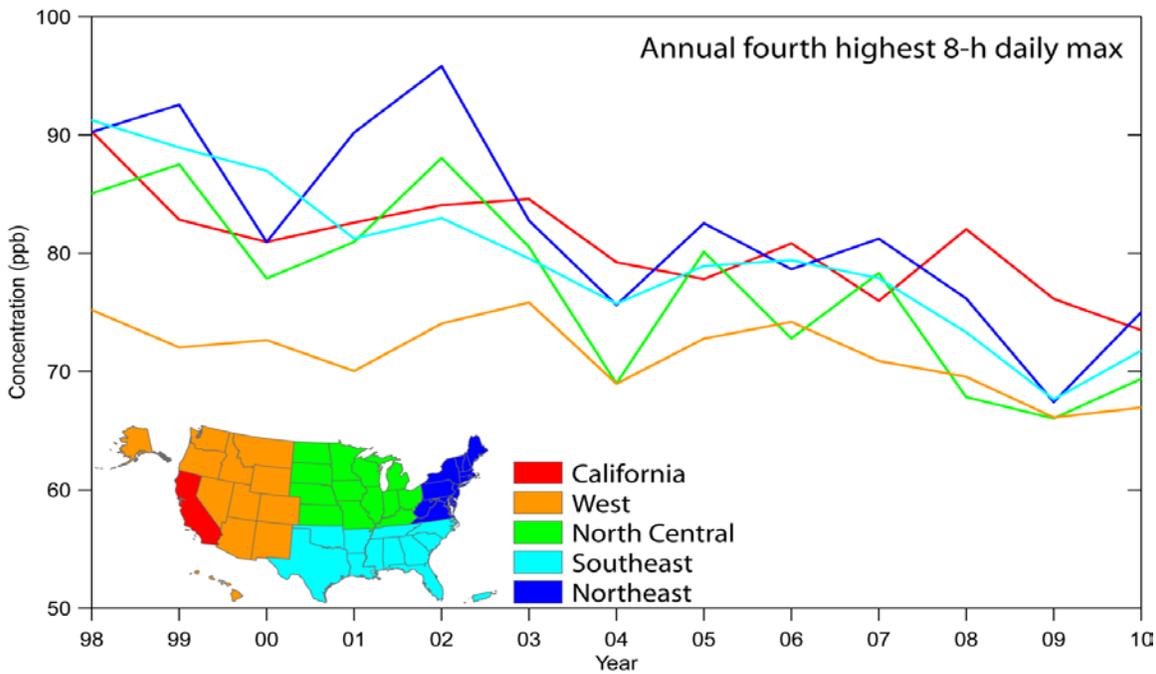


Figure 3-50 Trend in 8-h daily max ozone by region, 1998-2010 (annual 4th highest 8-h daily max ozone concentrations in ppm).

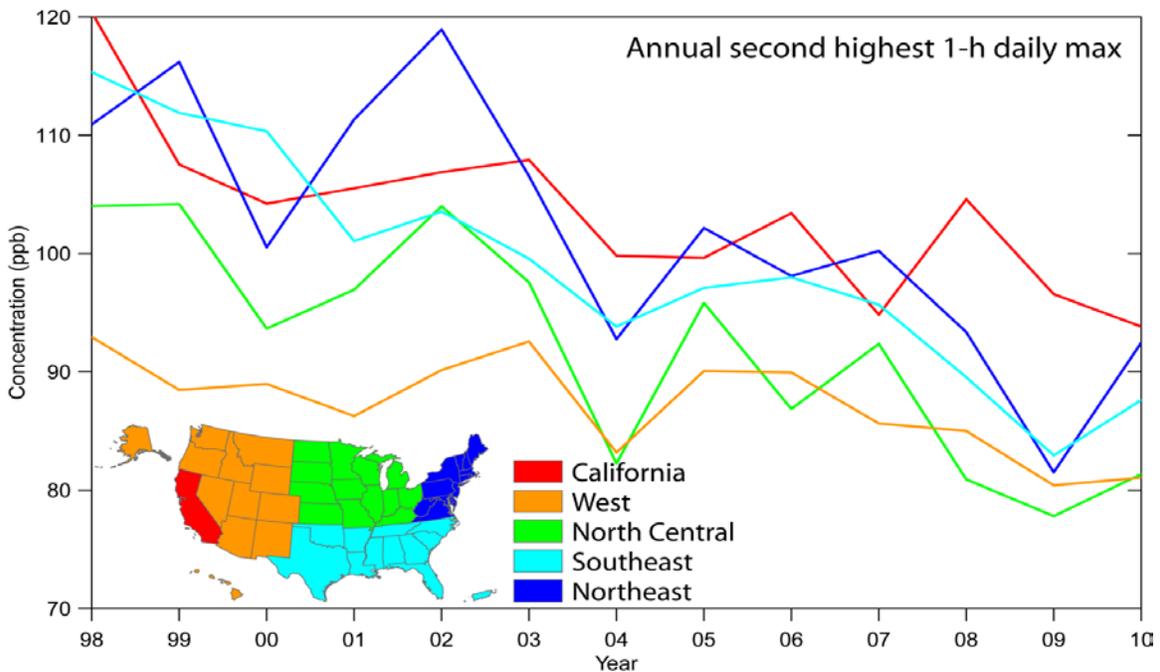


Figure 3-51 Trend in 1-h daily max ozone by region, 1998-2010 (annual second highest 1-h daily max ozone concentrations in ppm).

1 Narrowing the focus to changes in O₃ concentrations at the individual monitor level,
 2 [Figure 3-52](#) displays the 8-h O₃ design value (4th highest 8-h daily max O₃ concentration
 3 occurring within a three-year period) for all available monitors for the 2008-2010 period
 4 ([Figure 3-52A](#)) as well as the change in this design value between the 2001-2003 period
 5 and the 2008-2010 period ([Figure 3-52B](#)). [Figure 3-53](#) displays analogous information for
 6 a 1-h O₃ design value (4th highest 1-h daily max O₃ concentration occurring within a
 7 three-year period). As can be seen in both figures, the majority of monitors recorded a
 8 decrease in design values when comparing the 2001-2003 period to the 2008-2010
 9 period. Specifically, 699 of 853 sites (82%) included in [Figure 3-52B](#) for the 8-h design
 10 value and 747 of 869 sites (86%) included in [Figure 3-53B](#) for the 1-h design value
 11 reported a decrease of at least 6 ppb in the respective design values. The highest density
 12 of monitors reporting decreases occurs in the Northeast. Only 8 sites (1%) reported an
 13 increase of more than 5 ppb in the 8-h design value and only 16 sites (2%) reported an
 14 increase of more than 5 ppb in the 1-h design value. These sites reporting an increase
 15 between the 2001-2003 and the 2008-2010 periods were located primarily in the West.

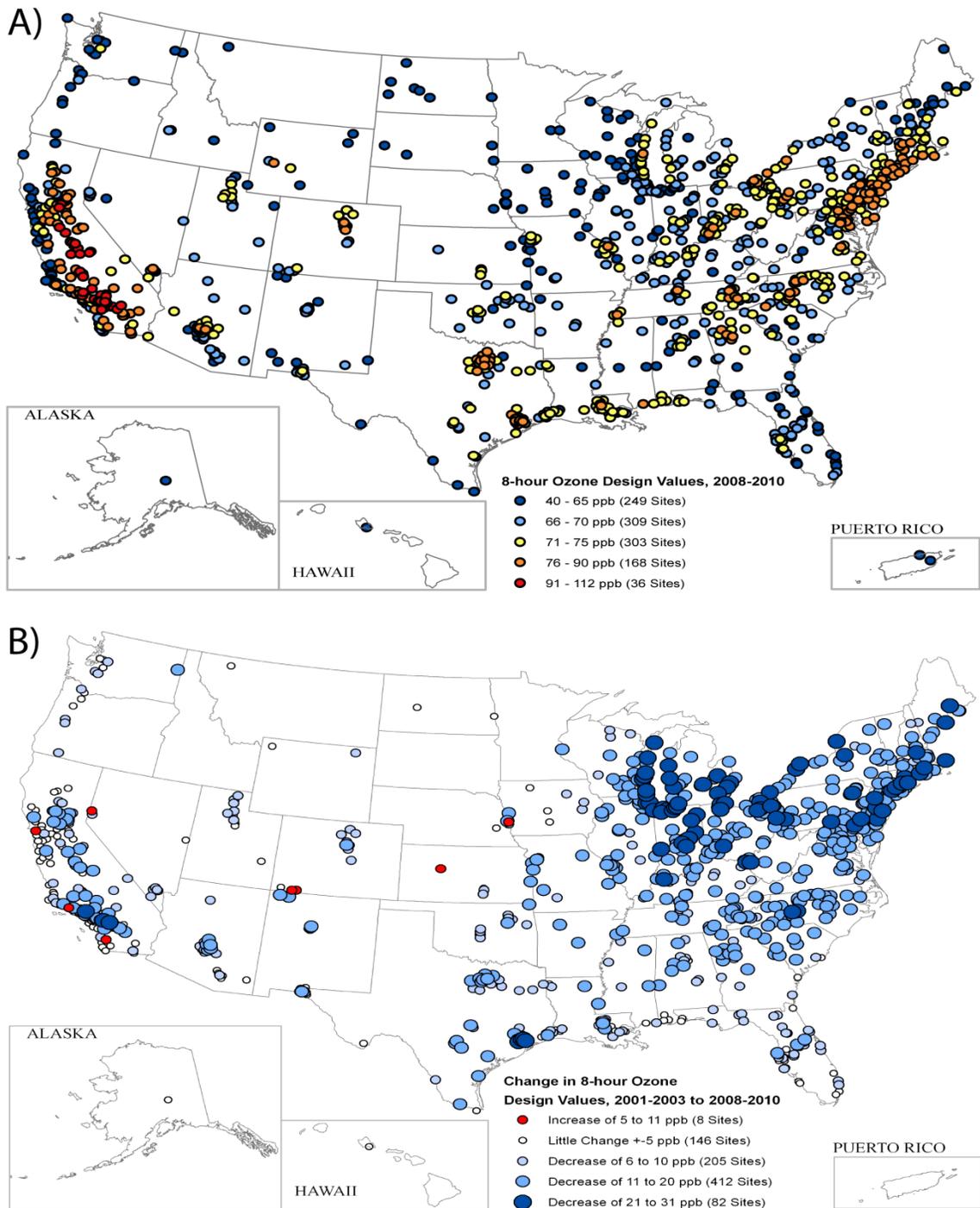


Figure 3-52 Individual monitor 8-h daily max ozone design values displayed A) for the 2008-2010 period and B) as the change since the 2001-2003 period.

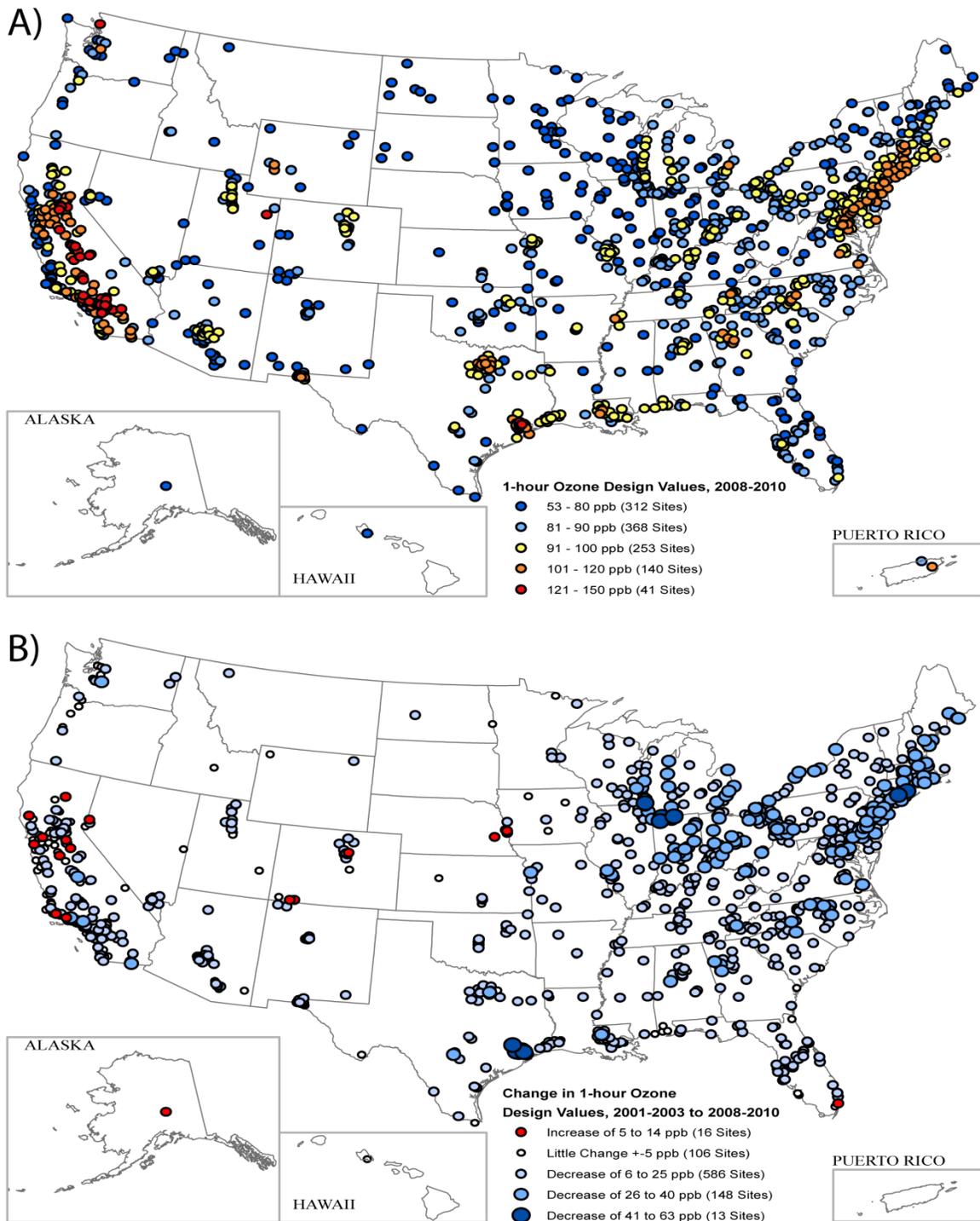


Figure 3-53 Individual monitor 1-h daily max ozone design values displayed A) for the 2008-2010 period and B) as the change since the 2001-2003 period.

1 Similar findings were reported for regional trends in the 4th highest 8-h daily max O₃
2 concentration between 2001 and 2008 in the 2010 National Air Quality Status and Trends
3 report ([U.S. EPA, 2010e](#)). Individual sites that showed the greatest reduction in O₃
4 between 2001 and 2008 were in or near the following metropolitan areas: Anderson, IN;
5 Chambersburg, PA; Chicago, IL; Cleveland, OH; Houston, TX; Michigan City, IN;
6 Milwaukee, WI; New York, NY; Racine, WI; Watertown, NY; and parts of Los Angeles,
7 CA. Individual sites that showed an increase in O₃ over this time period and had
8 measured concentrations above the O₃ standard¹ during the 2006-2008 time period were
9 located in or near the following metropolitan areas: Atlanta, GA; Baton Rouge, LA;
10 Birmingham, AL; Denver, CO; El Centro, CA; San Diego, CA; Seattle, WA; and parts of
11 Los Angeles, CA.

12 [Pegues et al. \(2012\)](#) investigated changes in 3-year average 8-h daily max O₃ design
13 values between 2003 and 2009 and found reductions at the majority of sites across the
14 U.S.; consistent with the findings in this section and in the 2010 National Air Quality
15 Status and Trends report ([U.S. EPA, 2010e](#)). Furthermore, they compared trends in O₃
16 design values between areas that were or were not classified as nonattainment of the
17 84 ppb O₃ standard in the 2004 designations. Monitors designated nonattainment
18 achieved O₃ design value reductions of 13.3 ppb on average while monitors designated in
19 attainment achieved reductions of 7.0 ppb on average.

20 Looking further back in time, [Leibensperger et al. \(2008\)](#) included an analysis of June-
21 August 8-h daily max O₃ trends from 1980-2006 using AQS data from over 2000 sites in
22 the contiguous U.S. They created an index for “pollution days” representing days when
23 the 8-h daily max O₃ concentration was greater than 84 ppb. The observed trend in
24 summertime O₃ pollution days over this 27 year period decreased at an average rate of -
25 0.84 days/year. The authors used several methods to deconstruct this trend into a
26 component coming from reductions in O₃ precursor emissions (-1.50 days/year) and a
27 component coming from climate change (+0.63 days/year). The climate change impact is
28 a result of decreases in frequency of mid-latitude cyclones which serve to ventilate
29 surface air over the U.S. {Leibensperger, 2008, 611799@@author-year} conclude that
30 the reduction in frequency of mid-latitude cyclones over the 1980-2006 time period has
31 offset almost half of the air quality gains in the Northeastern U.S. that should have been
32 achieved from reductions of anthropogenic emissions alone over that period.

33 Averaging time can have an impact on perceived trends in surface level O₃
34 concentrations. [Lefohn et al. \(2008\)](#) investigated the impact of using different exposure
35 indices on trends in surface level O₃ concentrations in the U.S. by comparing the annual
36 second highest 1-h average concentration, the annual 4th highest daily max 8-h average

¹ On September 16, 2009, EPA announced it would reconsider the 2008 O₃ NAAQS, which, at the time, included primary and secondary standards of 0.075 ppm (8-h daily max).

1 concentration, and the seasonally corrected 24-h W126 cumulative exposure index.
2 Between 1980 and 2005, most of the urban and rural sites across the U.S. included in this
3 study showed decreasing or zero trend for all three of these metrics. However, the
4 magnitude of this trend varied greatly by exposure index. The largest downward trend in
5 the 1-h and 8-h metrics listed above were observed in Southern California (>2%/yr
6 downward trend) but the W126 cumulative exposure metric showed large (>2%/yr)
7 downward trends in many locations across the U.S. including Southern California, the
8 Midwest and Northeast. By contrasting the 1980 – 2005 trends with more recent 1990 –
9 2005 trends, [Lefohn et al. \(2008\)](#) reported that a large number of sites (44%, 35% and
10 25% of sites for the 1-h, 8-h and W126 metrics, respectively) shifted from a negative
11 trend to no trend. These shifts in trends were attributed to slow changes in mid-level
12 concentrations (i.e., 60-90 ppb) following a more rapid change in peak concentrations in
13 the early years. A similar conclusion was drawn from nationwide O₃ data between 1980 –
14 2008 ([Lefohn et al., 2010b](#)), suggesting a shift in the O₃ distribution over this time period.

15 In contrast to the mostly urban observations included in the [Pegues et al. \(2012\)](#) study
16 above, several studies focusing on rural western monitors have reported positive trends in
17 O₃ concentrations over the last few decades. [Jaffe and Ray \(2007\)](#) investigated daytime
18 (10 a.m. – 6 p.m. local time) O₃ concentrations at rural sites in the northern and western
19 U.S. between 1987-2004. They found significantly positive trends in seven of the eleven
20 sites selected ranging from 0.19 ppb/yr in Gothic, CO to 0.51 ppb/yr in Rocky Mountain
21 NP, CO (mean trend of 0.26 ppb/yr at these seven sites). No significant trend was
22 observed for the two sites in Alaska and one site each in Wyoming and Montana.
23 Seasonal analyses were conducted on the sites having the longest records in Rocky
24 Mountain NP, Yellowstone, NP and Lassen NP and positive trends were found for all
25 seasons at all sites. As noted in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)), caution should be
26 exercised in using trends calculated at national parks to infer contributions from distant
27 sources either inside or outside of North America because of the influence of regional
28 pollution (see Section [3.4](#) for a discussion of background O₃ concentrations and
29 international transport).

30 Trends in baseline O₃ concentrations, defined as O₃ concentrations at a given site in the
31 absence of strong local influences, were estimated by region and season in the U.S. in
32 [Chan and Vet \(2010\)](#). The temperature-adjusted decadal (1997-2006) trends in estimated
33 baseline O₃ varied substantially by region and season. In the Pacific coastal regions, the
34 trends increased in all seasons except fall, but none of the trends were statistically
35 significant. In the eastern U.S., negative trends were observed in all seasons with the
36 exception of (1) insignificant positive trends in northeast Maine in summer, fall and
37 winter; (2) significant positive trends in the Midwest in winter; and 3) significant positive
38 trends at one site in Vermont in the summer. The density of sites in the central and

1 western U.S. were much lower than the coastal and eastern areas, but in general all sites
2 showed trends that tended to be negative in the spring and fall but positive in the summer
3 and winter.

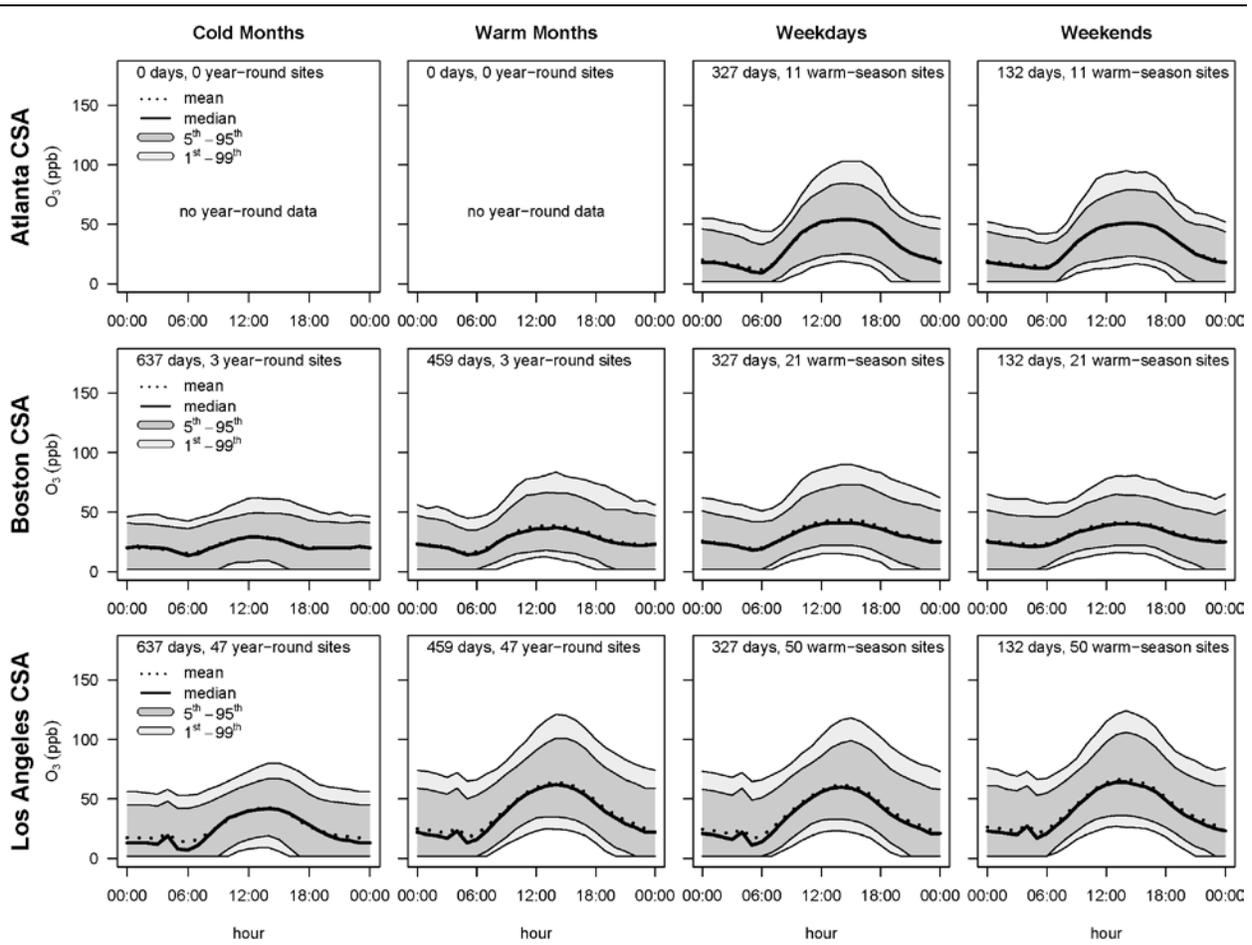
4 Positive trends in marine boundary layer O₃ concentrations at several sites on the Pacific
5 Coast have been reported by other sources in the literature. [Parrish et al. \(2009\)](#) used
6 observations from multiple coastal sites in California and Washington and reported a
7 positive annual mean trend of 0.34 ± 0.09 ppb/yr between the mid-1980s and 2007 (exact
8 dates varied by site depending on available data). A seasonal stratification of the data at
9 these sites showed the largest positive trend in the spring (0.46 ± 0.13 ppb/yr) with a
10 smaller and non-significant positive trend during fall (0.12 ± 0.14 ppb/yr). These results
11 agree with positive trends in springtime O₃ mixing ratios reported in an earlier study
12 ([Jaffe et al., 2003](#)). Positive trends in O₃ measurements in the free troposphere above
13 western North America at altitudes of 3-8 km (above sea level) during April and May of
14 1995 to 2008 were reported by [Cooper et al. \(2010\)](#) and discussed in Section [3.4.2](#) as they
15 relate to intercontinental transport. Comparable trends were observed in the median as
16 well as 5th, 33rd, 67th, and 95th percentiles of observations. Note, however, that these
17 results relate to O₃ trends above ground level and not to surface O₃.

18 Extending back to the 19th Century, [Volz and Kley \(1988\)](#) report a series of historic O₃
19 measurements from Europe. Comparing these with more contemporary measurements,
20 [Parrish et al. \(2009\)](#) report a 2 to 3 fold increase in boundary layer O₃ mixing ratios over
21 the last 130 years with no indication of stabilization in recent years. Other long-term
22 observations of global trends in the burden of tropospheric O₃ as they relate to climate
23 change are discussed in Chapter [10](#), Section [10.3.3.1](#).

3.6.3.2 Hourly Variations

24 Ozone concentrations frequently possess a strong degree of diel variability resulting from
25 daily patterns in temperature, sunlight, and precursor emissions. Other factors, such as the
26 relative importance of transport versus local photochemical production and loss rates, the
27 timing for entrainment of air from the nocturnal residual boundary layer, and the diurnal
28 variability in mixing layer height also play a role in daily O₃ patterns. The 2006 O₃
29 AQCD ([U.S. EPA, 2006b](#)) looked at composite urban diel variations from April to
30 October 2000 to 2004 and found 1-h maxima to occur in mid-afternoon and 1-h minima
31 to occur in early morning. On a national basis, however, there was a high degree of
32 spread in these times and caution was raised in extrapolating results from one city to
33 another in determining the time of day for O₃ maxima and minima.

1 Urban diel variability in O₃ concentrations was investigated for the 20 focus cities listed
 2 in [Table 3-9](#) using 1-h avg O₃ data from AQS. The year-round data set described in
 3 [Table 3-5](#) was used to compare diel patterns during cold months (October - April) and
 4 warm months (May - September) between 2007 and 2009. The warm-season data set,
 5 also described in [Table 3-5](#), was used to compare weekday and weekend diel patterns.
 6 [Figure 3-156](#) through [Figure 3-160](#) in the supplemental material in Section 3.9.4 show
 7 these patterns for each of the 20 cities; examples for Atlanta, Boston and Los Angeles are
 8 shown in [Figure 3-54](#).



Note: Uses the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half). Atlanta had no year-round monitors available for the cold month/warm month comparison.

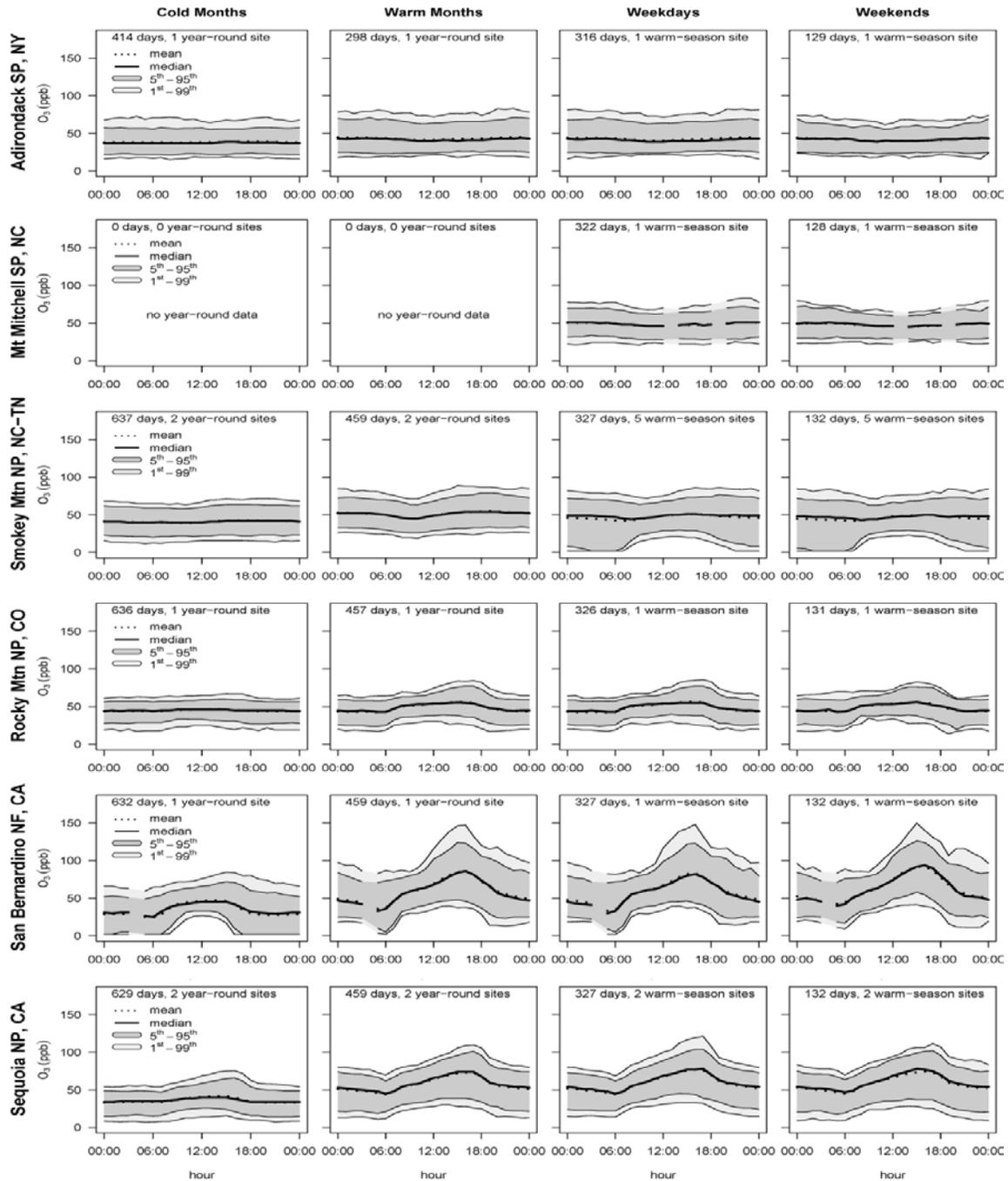
Figure 3-54 Diel patterns in 1-h avg ozone for Atlanta, Boston and Los Angeles between 2007 and 2009.

1 In general, all the urban areas showed 1-h daily max concentrations occurring typically in
2 the early afternoon. In all cities, these afternoon peaks were more pronounced in the
3 warm months than in the cold months. However, a small peak was still present during the
4 cold months. During warm months, the difference between the median daily extrema
5 varied considerably by city. For example, in Los Angeles, the median 1-h daily min
6 (10 ppb) at ~5:00 a.m. was 50 ppb less than the median 1-h daily max (60 ppb) at ~2:00
7 p.m. By contrast, in Boston, the median 1-h daily min (13 ppb) occurred at the same time,
8 but was only 25 ppb less than the median 1-h daily max (38 ppb). Cities with large daily
9 swings (>40 ppb) in median 1-h O₃ concentrations included Atlanta, Birmingham,
10 Los Angeles, Phoenix, Pittsburgh, and Salt Lake City ([Figure 3-156](#) through [Figure 3-160](#)
11 in Section [3.9.4](#)). Cities with small daily swings (<25 ppb) in median 1-h O₃
12 concentrations included Boston, Minneapolis, San Francisco and Seattle ([Figure 3-156](#)
13 through [Figure 3-160](#) in Section [3.9.4](#)). These results are very similar to those found in
14 the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) where many of these same urban areas were
15 investigated. This supports the conclusions drawn in the previous O₃ review that diel
16 patterns in O₃ have remained stable over the last 20 years, with times of occurrence of the
17 daily maxima varying by no more than an hour from year to year.

18 Using the warm-season data, there was little difference in the median diel profiles for
19 weekdays compared with weekends across all urban areas. This result stresses the
20 complexity of O₃ formation and the importance of meteorology, entrainment, biogenic
21 precursor emissions, and transport in addition to anthropogenic precursor emissions.
22 There was, however, a subtle deviation between weekdays and weekends in the lower
23 percentiles (1st and 5th) of the distribution. The lower end of the distribution tended to be
24 lower on weekdays relative to weekends. This is consistent with analyses in the 2006 O₃
25 AQCD ([U.S. EPA, 2006b](#)) and is a result of lower traffic volumes on weekends relative
26 to weekdays, leading to less NO emissions and O₃ titration on the weekends.

27 Seasonal and site-to-site variations in diel patterns within a subset of the urban focus
28 areas presented here were investigated in the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). In
29 northern cities, there was substantial seasonal variability in the diel patterns with higher
30 extreme values in the O₃ distribution during the warm season than during the cold season.
31 In southern cities, the seasonal differences in extreme O₃ concentrations were much
32 smaller, and some of the highest O₃ concentrations in the Houston CSA were found
33 outside of summer. The general pattern that emerged from investigating site-to-site
34 variability within the urban areas was that peaks in 1-h avg O₃ concentrations are higher
35 and tend to occur later in the day at downwind sites relative to sites located in the urban
36 core. Differences between sites were not only related to the distance between them, but
37 also depend on the presence or absence of nearby O₃ sources or sinks.

1 Rural diel variability in O₃ concentrations was investigated for the six rural focus areas
2 listed in [Table 3-11](#) using 1-h avg O₃ data from AQS. As with the urban analysis, the
3 year-round data set described in [Table 3-5](#) was used to compare diel patterns during cold
4 months (October - April) and warm months (May - September) between 2007 and 2009.
5 The warm-season data set, also described in [Table 3-5](#), was used to compare weekday
6 and weekend diel patterns. [Figure 3-55](#) shows the diel patterns for each of the rural areas
7 investigated.



Note: Uses the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half). Mt. Mitchell SP, NC had no year-round monitors available for the cold month/warm month comparison.

Figure 3-55 Diel patterns in 1-h avg ozone for six rural focus areas between 2007 and 2009.

1 There was considerable variability in the diel patterns observed in the six rural focus
2 areas. The selected mountainous eastern sites in ADSP, MMSP, and SMNP exhibited a
3 generally flat profile with little hourly variability in the median concentration and the
4 upper percentiles. In SMNP, there was some diel variability in the lower percentiles, with
5 higher values during the daylight hours in the warm season data. This behavior was not
6 present in the data coming from the two year-round monitors located at lower elevation
7 sites (Sites C and Site D; see map in [Figure 3-44](#)), however, possibly resulting from
8 differing impacts from local sources within SMNP. For the western rural areas, there was
9 a clear diel pattern to the hourly O₃ data with a peak in concentration in the afternoon
10 similar to those seen in the urban areas in [Figure 3-54](#) and [Figure 3-156](#) through
11 [Figure 3-160](#) in Section 3.9.4. This was especially obvious at the SBNF site which sits
12 90 km east of Los Angeles in the San Bernardino Mountains at an elevation of
13 1,384 meters. This site was located here to monitor O₃ transported downwind from major
14 urban areas in the South Coast Air Basin. It had the highest 2007-2009 median 8-h daily
15 max O₃ concentration of any AQS site in the Los Angeles CSA (see [Figure 3-34](#)), and is
16 clearly impacted by the upwind urban plume which has sufficient time and sunlight to
17 form O₃ from precursor emissions and concentrate the O₃ in the shallow boundary layer
18 present at this elevation.

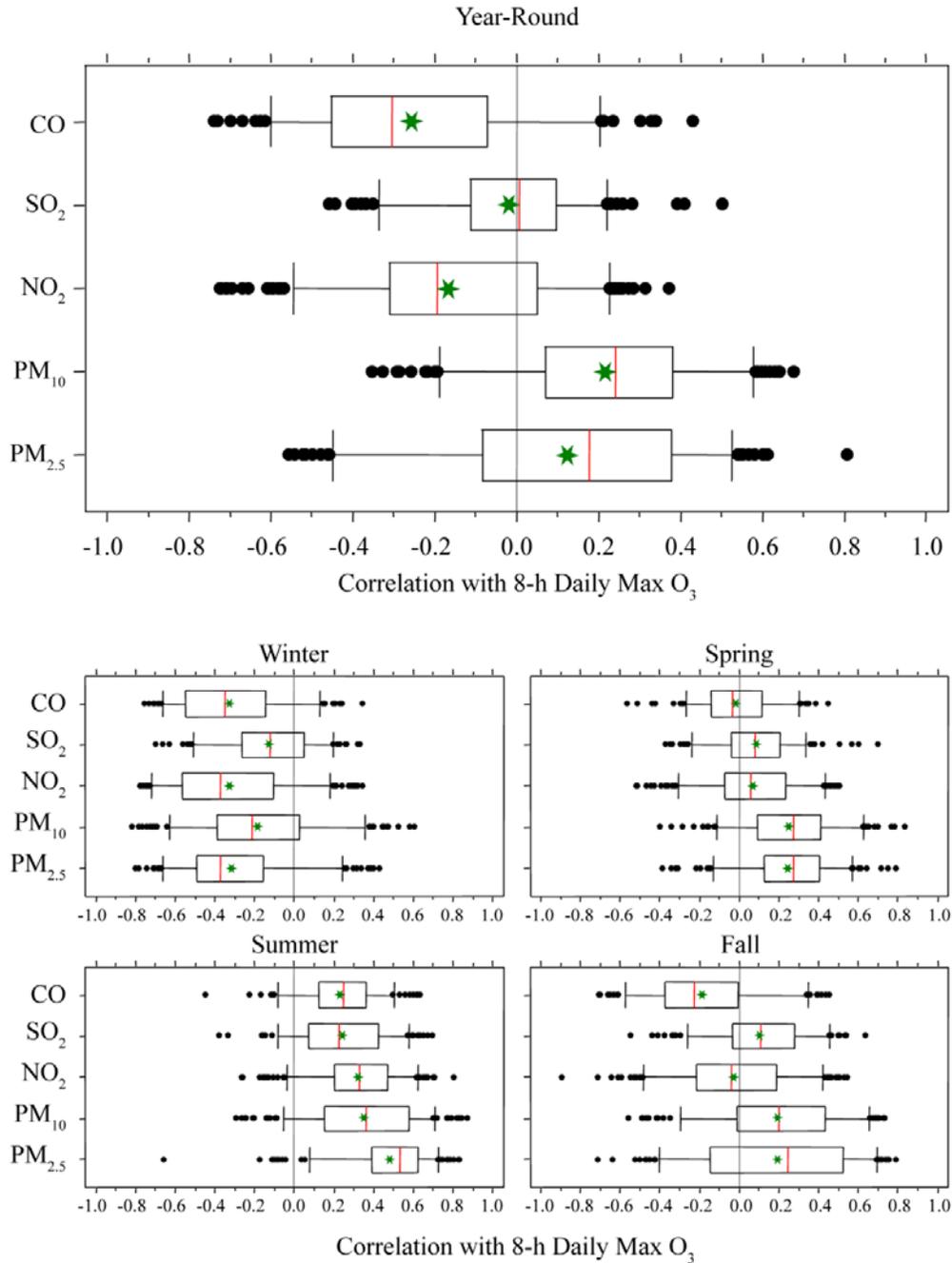
19 As with the urban analysis, there was little difference observed in the weekday and
20 weekend diel profiles using the warm-season data, even down at the lower percentiles in
21 the distribution. This is consistent with the regional nature of tropospheric O₃. Using the
22 year-round data, there was an upward shift in the distribution going from the cold months
23 to the warm months, and in some instances the general shape of the distribution changed
24 considerably as was seen in several urban sites.

3.6.4 Associations with Co-pollutants

25 Correlations between O₃ and other criteria pollutants are discussed in this section. Since
26 O₃ is a secondary pollutant formed in the atmosphere from precursor emissions, its
27 correlation with primary pollutants such as CO and NO_x can vary substantially by
28 location. Furthermore, O₃ formation is strongly influenced by meteorology, entrainment,
29 and transport of both O₃ and O₃ precursors, resulting in a broad range in correlations with
30 other pollutants which can vary substantially with season. This section focuses on
31 correlations between O₃ and other criteria pollutants measured at the mostly urban AQS
32 sites: a more detailed discussion of O₃ and O₃-precursor relationships is included in
33 Section 3.2.4. To investigate correlations with co-pollutants, 8-h daily max O₃ from the
34 year-round and warm-season data sets ([Table 3-6](#) and

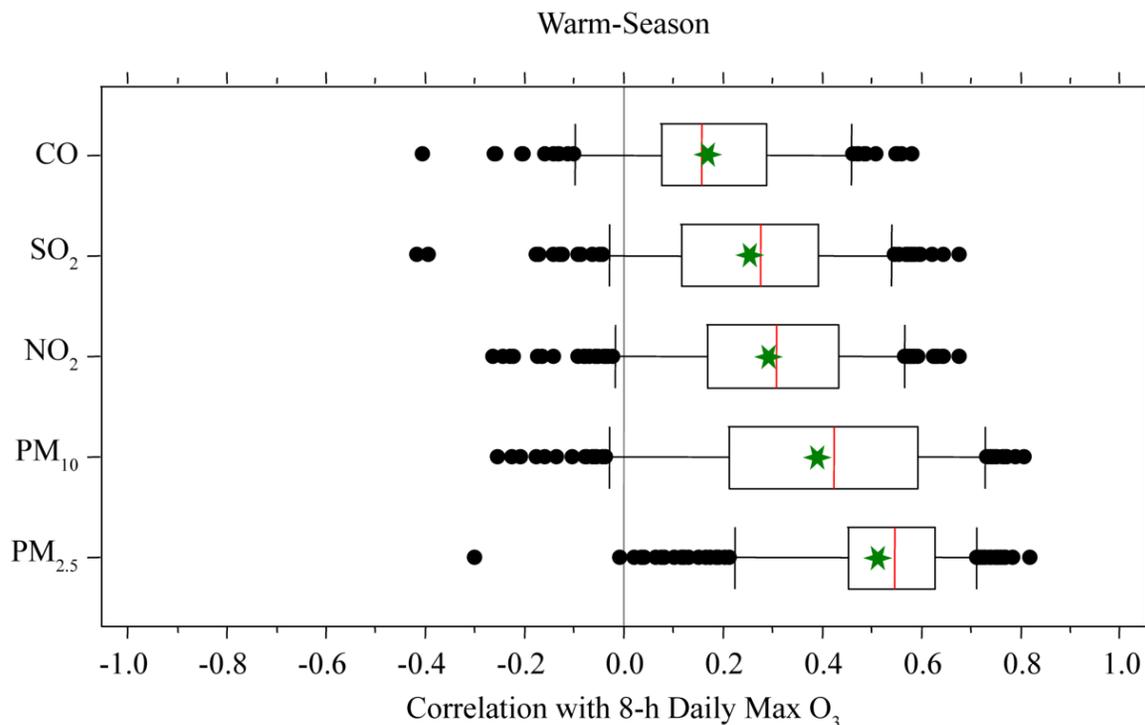
1 Table 3-7) were compared with co-located 24-h avg CO, SO₂, NO₂, PM_{2.5} and PM₁₀
2 obtained from AQS for 2007-2009. [Figure 3-56](#) and [Figure 3-57](#) contain co-pollutant box
3 plots of the correlation between co-located monitors for the year-round data set and the
4 warm-season data set, respectively.

5 The year-round 8-h daily max O₃ data ([Figure 3-56](#)) had a very wide range in correlations
6 with all the 24-h avg co-pollutants. A clearer pattern emerged when the data were
7 stratified by season (bottom four plots in [Figure 3-56](#)) with mostly negative correlations
8 in the winter and mostly positive correlations in the summer for all co-pollutants. In
9 summer, the IQR in correlations is positive for all co-pollutants. However, the median
10 seasonal correlations are still modest at best with the highest positive correlation at 0.52
11 for PM_{2.5} in the summer and the highest negative correlation at -0.38 for PM_{2.5} in the
12 winter. Spring and fall lie in between with spring having a slightly narrower distribution
13 than fall for all copollutants. The warm-season 8-h daily max O₃ data ([Figure 3-57](#))
14 shows a very similar distribution to the summer stratification of the year-round data due
15 to their overlap in time periods (May-Sept and Jun-Aug, respectively).



Note: Year round (Top figure), and with seasonal stratification (Bottom four figures). Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers) and extremes (black circles).

Figure 3-56 Distribution of Pearson correlation coefficients for comparison of 8-h daily max ozone from the year-round data set with co-located 24-h avg CO, SO₂, NO₂, PM₁₀ and PM_{2.5} from AQS, 2007-2009.



Note: Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers), and extremes (black circles).

Figure 3-57 Distribution of Pearson correlation coefficients for comparison of 8-h daily max ozone from the warm-season (May-Sept) data set with co-located 24-h avg CO, SO₂, NO₂, PM₁₀ and PM_{2.5} from AQS, 2007-2009.

1 The seasonal fluctuations in correlations present in [Figure 3-56](#) result in part from the
 2 mixture of primary and secondary sources for the co-pollutants. For example, O₃ is a
 3 secondary pollutant whereas PM_{2.5} has both primary and secondary origins and these two
 4 pollutants show the largest summertime/wintertime swing in correlation distributions.
 5 This situation arises because the secondary component to PM_{2.5} is larger during the
 6 summer and is formed in conditions conducive to secondary O₃ formation. This results in
 7 positive correlations between O₃ and PM_{2.5} during the summer. During the winter,
 8 photochemical production of O₃ is much smaller than during summer and O₃ comes
 9 mainly from aloft, i.e., the free troposphere (see Section [3.4.1.1](#) for further details). In
 10 addition, concentrations of PM_{2.5} are much lower aloft. On relatively clean days, this can
 11 lead to high concentrations of O₃ and lower concentrations of primary pollutants such as
 12 PM_{2.5} or NO. On relatively dirty days with elevated NO and PM_{2.5}, the intruding O₃ is
 13 readily titrated by NO in the boundary layer. These processes result in negative
 14 correlations between O₃ and PM_{2.5} during the winter.

3.7 Chapter Summary

1 This section contains a summary of the major topics included in this chapter on the
2 atmospheric chemistry and ambient concentrations of tropospheric O₃ and other related
3 photochemical oxidants. This chapter has built upon information previously reported in
4 the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) and includes updated material on: (1) physical
5 and chemical processes of O₃ formation and removal; (2) atmospheric modeling;
6 (3) background O₃ concentrations; (4) monitoring techniques and networks; and
7 (5) ambient concentrations.

3.7.1 Physical and Chemical Processes

8 Ozone in the troposphere is a secondary pollutant; it is formed by photochemical
9 reactions of precursor gases and is not directly emitted from specific sources. Ozone
10 precursor gases originate from both anthropogenic and natural source categories. Ozone
11 attributed to anthropogenic sources is formed in the atmosphere by photochemical
12 reactions involving sunlight and precursor pollutants including VOCs, NO_x, and CO.
13 Ozone attributed to natural sources is formed through similar photochemical reactions
14 involving natural emissions of precursor pollutants from vegetation, microbes, animals,
15 biomass burning, lightning, and geogenic sources. The distinction between natural and
16 anthropogenic sources of O₃ precursors is often difficult to make in practice, as human
17 activities affect directly or indirectly emissions from what would have been considered
18 natural sources during the preindustrial era. The formation of O₃, other oxidants, and
19 oxidation products from these precursors is a complex, nonlinear function of many
20 factors including: (1) the intensity and spectral distribution of sunlight reaching the lower
21 troposphere; (2) atmospheric mixing; (3) concentrations of precursors in the ambient air
22 and the rates of chemical reactions of these precursors; and (4) processing on cloud and
23 aerosol particles.

24 Ozone is present not only in polluted urban atmospheres but throughout the troposphere,
25 even in remote areas of the globe. The same basic processes involving sunlight-driven
26 reactions of NO_x, VOCs and CO contribute to O₃ formation throughout the troposphere.
27 These processes also lead to the formation of other photochemical products, such as
28 PAN, nitric acid, and sulfuric acid, and to other compounds, such as formaldehyde and
29 other carbonyl compounds. In urban areas, NO_x, VOCs and CO are all important for O₃
30 formation. In non-urban vegetated areas, biogenic VOCs emitted from vegetation tend to
31 be the most important precursor to O₃ formation. In the remote troposphere, methane–
32 structurally the simplest VOC–and CO are the main carbon-containing precursors to O₃

1 formation. Ozone is subsequently removed from the troposphere through a number of gas
2 phase reactions and deposition to surfaces.

3 Convective processes and turbulence transport O₃ and other pollutants both upward and
4 downward throughout the planetary boundary layer and the free troposphere. In many
5 areas of the U.S., O₃ and its precursors can be transported over long distances, aided by
6 vertical mixing. The transport of pollutants downwind of major urban centers is
7 characterized by the development of urban plumes. Meteorological conditions, small-
8 scale circulation patterns, localized chemistry, and mountain barriers can influence
9 mixing on a smaller scale, resulting in frequent heterogeneous O₃ concentrations across
10 individual urban areas.

3.7.2 Atmospheric Modeling

11 CTMs have been widely used to compute the interactions among atmospheric pollutants
12 and their transformation products, and the transport and deposition of pollutants. They
13 have also been widely used to improve basic understanding of atmospheric chemical
14 processes and to develop control strategies. The domains of CTMs extend from a few
15 hundred kilometers on a side to the entire globe.

16 Most major regional (i.e., sub-continental) scale air-related modeling efforts at EPA rely
17 on the CMAQ modeling system. The horizontal domain for CMAQ typically extends
18 over North America with efforts underway to extend it over the entire Northern
19 Hemisphere. The upper boundary for CMAQ is typically set at 100 hPa, which is located
20 on average at an altitude of ~16 km. CMAQ is most often driven by the MM5 mesoscale
21 meteorological model, though it may be driven by other meteorological models including
22 the WRF model and the RAMS. Other major air quality systems used for regional scale
23 applications include CAMx and WRF/Chem.

24 Fine scale resolution is necessary to resolve features which can affect pollutant
25 concentrations such as urban heat island circulation; sea breezes; mountain and valley
26 breezes; and the nocturnal low-level jet. Horizontal domains are typically modeled by
27 nesting a finer grid model within a larger domain model of coarser resolution. Caution
28 must be exercised in using nested models because certain parameterizations like those for
29 convection might be valid on a relatively coarse grid scale but may not be valid on finer
30 scales and because incompatibilities can occur at the model boundaries. The use of finer
31 resolution in CTMs will require advanced parameterizations of meteorological processes
32 such as boundary layer fluxes, deep convection, and clouds, and necessitate finer-scale
33 inventories of land use, source locations, and emission inventories.

1 Because of the large number of chemical species and reactions that are involved in the
2 oxidation of realistic mixtures of anthropogenic and biogenic hydrocarbons, condensed
3 mechanisms must be used to simplify atmospheric models. These mechanisms can be
4 tested by comparison with smog chamber data. However, the existing chemical
5 mechanisms often neglect many important processes such as the formation and
6 subsequent reactions of long-lived carbonyl compounds, the incorporation of the most
7 recent information about intermediate compounds, and heterogeneous reactions involving
8 cloud droplets and aerosol particles. As a result, models such as CMAQ have had
9 difficulties with capturing the regional nature of O₃ episodes, in part because of
10 uncertainty in the chemical pathways converting NO_x to isoprene nitrates and recycling
11 of NO_x.

12 Errors in photochemical modeling arise from meteorological, chemical, and emissions
13 inputs to the model. Algorithms must be used for simulating meteorological processes
14 that occur on spatial scales smaller than the model's grid spacing and for calculating the
15 dependence of emissions on meteorology and time. Large uncertainties exist in the
16 mechanism for oxidizing compounds of importance for atmospheric chemistry such as
17 isoprene. Appreciable errors in emissions can occur if inappropriate assumptions are used
18 in these parameterizations.

19 The performance of CTMs must be evaluated by comparison with field data as part of a
20 cycle of model evaluations and subsequent improvements. Discrepancies between model
21 predictions and observations can be used to point out gaps in current understanding of
22 atmospheric chemistry and to spur improvements in parameterizations of atmospheric
23 chemical and physical processes.

3.7.3 Background Concentrations

24 Because the mean tropospheric lifetime of O₃ is on the order of a few weeks, O₃ can be
25 transported from continent to continent. The degree of influence from intercontinental
26 transport varies greatly by location and time. For instance, high elevation sites are most
27 susceptible to the intercontinental transport of pollution, particularly during spring.
28 However, because the atmospheric chemistry of O₃ is quite complex and can be highly
29 non-linear in environments close to sources of precursors, isolating the influence of
30 intercontinental transport of O₃ and O₃ precursors on urban air quality is particularly
31 problematic.

32 A number of recent studies indicate that natural sources such as wildfires and
33 stratospheric intrusions and the intercontinental transport of pollution can significantly
34 affect O₃ air quality in the United States. Two major modeling/field studies that focused

1 on discerning the contributions of Asian emissions to air quality in California were the
2 IONS-2010 and the CalNex studies conducted in May through June of 2010. Modeling
3 and observational components of these studies found evidence for substantive
4 contributions from stratospheric intrusions and Eurasian pollution to boundary layer O₃.
5 In particular, one modeling study found evidence of Asian contributions of 8 -15 ppb in
6 surface air during strong transport events in southern California. These contributions are
7 in addition to contributions from dominant local pollution sources. Their results suggest
8 that the influence of background sources on high O₃ concentrations at the surface is not
9 always confined to high elevation sites. It is not clear to what extent the contributions
10 inferred by these studies are likely to be found in other years, during other seasons, or in
11 other locations. To gain a broader perspective and to isolate the influence of natural or
12 transported O₃, estimates from CTMs must be used. This is because observations within
13 the U.S.—even at relatively remote monitoring sites—are impacted by transport from
14 anthropogenic source regions within the U.S. borders.

15 In the context of a review of the NAAQS, it is useful to define background O₃
16 concentrations in a way that distinguishes between concentrations that result from
17 precursor emissions that are relatively less controllable from those that are relatively
18 more controllable through U.S. policies. For this assessment, three definitions of
19 background O₃ concentrations are considered, including (1) NA background (simulated
20 O₃ concentrations that would exist in the absence of anthropogenic emissions from the
21 U.S., Canada and Mexico), (2) U.S. background (simulated O₃ concentrations that would
22 exist in the absence of anthropogenic emissions from the U.S.), and (3) natural
23 background (simulated O₃ concentrations in the absence of all anthropogenic emissions
24 globally). Each definition of background O₃ includes contributions resulting from
25 emissions from natural sources (e.g., stratospheric intrusion, wildfires, biogenic methane
26 and more short-lived VOC emissions) throughout the globe. There is no chemical
27 difference between background O₃ and O₃ attributable to U.S. or North American
28 anthropogenic sources. However, to inform policy considerations regarding the current or
29 potential alternative standards, it is useful to understand how total O₃ concentrations can
30 be attributed to different sources.

31 Since background O₃ concentrations as defined above are a construct that cannot be
32 directly measured, the range of background O₃ concentrations is estimated using CTMs.
33 For the current assessment, recently published results from [Zhang et al. \(2011\)](#) using the
34 GEOS-Chem model at 0.5° × 0.667° (~50 km × 50 km) horizontal resolution and [Emery
35 et al. \(2012\)](#) using a GEOS-Chem/CAMx model (hereafter referred to as CAMx) at finer
36 horizontal resolution (12 km × 12 km) were used. Results from these models represent
37 the latest estimates for background O₃ concentrations documented in the peer-reviewed
38 literature.

1 The main results from these modeling efforts can be summarized as follows. Simulated
2 regional and seasonal means of base-case O₃ using both models generally agree to within
3 a few ppb with observations for most of the U.S. However, neither model is currently
4 capable of simulating day specific base-case O₃ concentrations within reasonable bounds.
5 Both models show background concentrations vary spatially and temporally. NA
6 background concentrations are generally higher in spring than in summer across the U.S.
7 Simulated mean NA background concentrations are highest in the Intermountain West
8 (i.e., at high altitude) in spring and in the Southwest in summer. Lowest estimates of NA
9 background occur in the East in the spring and the Northeast in summer. NA background
10 concentrations tend to increase with total (i.e., base case) O₃ concentrations at high
11 elevation, but that tendency is not as clear at low elevations. Comparison of NA
12 background and natural background indicate that methane is a major contributor to NA
13 background O₃, accounting for slightly less than half of the increase in background since
14 the pre-industrial era; and whose relative contribution is projected to grow in the future.
15 U.S. background concentrations are on average 2.6 ppb higher than NA background
16 concentrations during spring and 2.7 ppb during summer across the U.S. with highest
17 increases above NA background over the Northern Tier of New York State (19.1 ppb
18 higher than NA background) in summer. High values for U.S. background are also found
19 in other areas bordering Canada and Mexico. Contributions to background O₃ can be
20 episodic or non-episodic; high background concentrations are driven primarily by the
21 episodic events such as stratospheric intrusions and wildfires. The most pronounced
22 differences between these model results and observations are at the upper end of the
23 concentration distribution, particularly at high elevations. In general, these model
24 simulations provide a consistent representation of average background concentrations
25 over seasons and broad spatial areas, but are not able to capture background
26 concentrations at finer spatial (i.e., urban) and temporal (i.e., specific day) scales.

27 Note that the calculations of background concentrations presented in this chapter were
28 formulated to answer the question, “what would O₃ concentrations be if there were no
29 anthropogenic sources”. This is different from asking, “how much of the O₃ measured or
30 simulated in a given area is due to background contributions”. Because of potentially
31 strong non-linearities—particularly in many urban areas—these estimates by themselves
32 should not be used to answer the second question posed above. The extent of these non-
33 linearities will generally depend on location and time, the strength of concentrated
34 sources, and the nature of the chemical regime. Further work is needed on how these
35 estimates of background concentrations can be used to help determine the contributions
36 of background sources of O₃ to urban concentrations.

3.7.4 Monitoring

1 The FRM for O₃ measurement is the CLM and is based on the detection of
2 chemiluminescence resulting from the reaction of O₃ with ethylene gas. Almost all of the
3 SLAMS that reported data to AQS from 2005 to 2009 used UV absorption photometer
4 FEMs and greater than 96% of O₃ monitors met precision and bias goals during this
5 period.

6 State and local monitoring agencies operate O₃ monitors at various locations depending
7 on the area size and typical peak concentrations (expressed in percentages below, or near
8 the O₃ NAAQS). SLAMS make up the ambient air quality monitoring sites that are
9 primarily needed for NAAQS comparisons and include PAMS, NCore, and all other State
10 or locally-operated stations except for the monitors designated as SPMs.

11 In 2010, there were 1250 SLAMS O₃ monitors reporting values to the EPA AQS
12 database. Since O₃ levels decrease appreciably in the colder parts of the year in many
13 areas, O₃ is required to be monitored at SLAMS monitoring sites only during the “ozone
14 season” which varies by state. PAMS provides more comprehensive data on O₃ in areas
15 classified as serious, severe, or extreme nonattainment for O₃. There were a total of 119
16 PAMS reporting values to the EPA AQS database in 2009. NCore is a new multipollutant
17 monitoring network currently being implemented to meet multiple monitoring objectives.
18 Each state is required to operate at least one NCore site and the network will consist of
19 about 60 urban and 20 rural sites nationwide.

20 CASTNET is a regional monitoring network established to assess trends in acidic
21 deposition and also provides concentration measurements of O₃. CASTNET O₃ monitors
22 operate year round and are primarily located in rural areas. At the beginning of 2010,
23 there were 80 CASTNET sites located in, or near, rural areas. The NPS also operates a
24 POMS network. The POMS couples the small, low-power O₃ monitor with a data logger,
25 meteorological measurements, and solar power in a self contained system for monitoring
26 in remote locations. Twenty NPS POMS reported O₃ data to AQS in 2010. A map of the
27 current and proposed rural NCore sites, along with the CASTNET, and the NPS POMS
28 sites was shown in [Figure 3-22](#).

29 Satellite observations for O₃ are growing as a resource for many purposes, including
30 model evaluation, assessing emissions reductions, pollutant transport, and air quality
31 management. Satellite retrievals are conducted using the solar backscatter or thermal
32 infrared emission spectra and a variety of algorithms. Most satellite measurement systems
33 have been developed for measurement of the total O₃ column. Mathematical techniques
34 have been developed and must be applied to derive information from these systems about
35 tropospheric O₃.

3.7.5 Ambient Concentrations

1 Ozone is the only photochemical oxidant other than NO₂ that is routinely monitored and
2 for which a comprehensive database exists. Other photochemical oxidants are typically
3 only measured during special field studies. Therefore, the concentration analyses
4 contained in this chapter have been limited to widely available O₃ data obtained directly
5 from AQS for the period from 2007 to 2009.

6 The median 24-h avg, 8-h daily max, and 1-h daily max O₃ concentrations across all U.S.
7 sites reporting data to AQS between 2007 and 2009 were 29, 40, and 44 ppb,
8 respectively. Representing the upper end of the distribution, the 99th percentiles of these
9 same metrics across all sites were 60, 80, and 94 ppb, respectively.

10 To investigate urban-scale O₃ variability, 20 focus cities were selected for closer analysis;
11 these cities were selected based on their importance in O₃ epidemiologic studies and on
12 their geographic distribution across the U.S. Several of these cities had relatively little
13 spatial variability in 8-h daily max O₃ concentrations (e.g., inter-monitor correlations
14 ranging from 0.61 to 0.96 in Atlanta) while other cities exhibited considerably more
15 variability in O₃ concentrations (e.g., inter-monitor correlations ranging from -0.06 to
16 0.97 for Los Angeles). The negative and near-zero correlations in Los Angeles were
17 between monitors with a relatively large separation distance (>150 km), but even some of
18 the closer monitor pairs were not very highly correlated. Similar to the correlation, the
19 coefficient of divergence was found to be highly dependent on the urban area under
20 investigation. As a result, caution should be observed in using data from a sparse network
21 of ambient O₃ monitors to approximate community-scale exposures.

22 To investigate rural-focused O₃ variability using AQS data, all monitors located within
23 six rural monitoring areas were examined. These rural monitoring sites are impacted by
24 transport of O₃ or O₃ precursors from upwind urban areas, and by local anthropogenic
25 emissions within the rural areas such as emissions from motor vehicles, power
26 generation, biomass combustion, or oil and gas operations. As a result, monitoring data
27 from these rural locations are not unaffected by anthropogenic emissions. The rural area
28 investigated with the largest number of available AQS monitors was Great Smoky
29 Mountain National Park in NC and TN where the median warm-season 8-h daily max O₃
30 concentration ranged from 47 ppb at the lowest elevation site (elevation = 564 meters;
31 site ID = 470090102) to 60 ppb at the highest elevation site (elevation = 2,021 meters;
32 site ID = 471550102), with correlations between the 5 sites ranging from 0.78 to 0.92 and
33 CODs ranging from 0.04 to 0.16. A host of factors may contribute to variations observed
34 at these rural sites, including proximity to local O₃ precursor emissions, variations in
35 boundary-layer influences, meteorology and stratospheric intrusion as a function of

1 elevation, and differences in wind patterns and transport behavior due to local
2 topography.

3 Since O₃ produced from emissions in urban areas is transported to more rural downwind
4 locations, elevated O₃ concentrations can occur at considerable distances from urban
5 centers. In addition, major sources of O₃ precursors such as highways, power plants,
6 biomass combustion, and oil and gas operations are commonly found in rural areas,
7 adding to the O₃ in these areas. Due to lower chemical scavenging in non-urban areas, O₃
8 tends to persist longer in rural than in urban areas which tends to lead to higher
9 cumulative exposures in rural areas influenced by anthropogenic precursor emissions.
10 The persistently high O₃ concentrations observed at many of these rural sites investigated
11 here indicate that cumulative exposures for humans and vegetation in rural areas can be
12 substantial and often higher than cumulative exposures to O₃ in urban areas.

13 Nation-wide surface level O₃ concentrations in the U.S. have declined gradually over the
14 last decade. A noticeable decrease in O₃ concentrations between 2003 and 2004,
15 particularly in the eastern U.S., coincided with NO_x emissions reductions resulting from
16 implementation of the NO_x SIP Call rule, which began in 2003 and was fully
17 implemented in 2004. This rule was designed to reduce NO_x emissions from power
18 plants and other large combustion sources in the eastern U.S. Downward trends in O₃
19 concentrations in the western U.S. have not been as substantial and several individual
20 monitors have reported increases in O₃ concentrations when 2001-2003 design values are
21 compared with 2008-2010 design values. In contrast to the downward regional trends in
22 surface-level O₃ concentrations in the U.S., global scale observations have indicated a
23 general rise in O₃ by a factor of 2 or more since pre-industrial times, as discussed in
24 Chapter 10, Section 10.3.3.1. Several observational studies investigating O₃
25 concentrations in the marine layer off the Pacific Coast of the U.S. have reported a steady
26 rise in O₃ concentrations over the last few decades.

27 Urban O₃ concentrations show a strong degree of diel variability resulting from daily
28 patterns in temperature, sunlight, and precursor emissions. Other factors, such as the
29 relative importance of transport versus local photochemical production and loss rates, the
30 timing for entrainment of air from the nocturnal residual boundary layer, and the diurnal
31 variability in mixing layer height also play a role in daily O₃ patterns. Urban diel
32 variations investigated in this assessment show no substantial change in patterns since the
33 2006 O₃ AQCD ([U.S. EPA, 2006b](#)). The 1-h max concentrations tend to occur in mid-
34 afternoon and 1-h min concentrations tend to occur in early morning, with more
35 pronounced peaks in the warm months relative to the cold months. There is city-to-city
36 variability in these times, however, and caution is raised in extrapolating results from one
37 city to another in determining the time of day for O₃ maxima and minima.

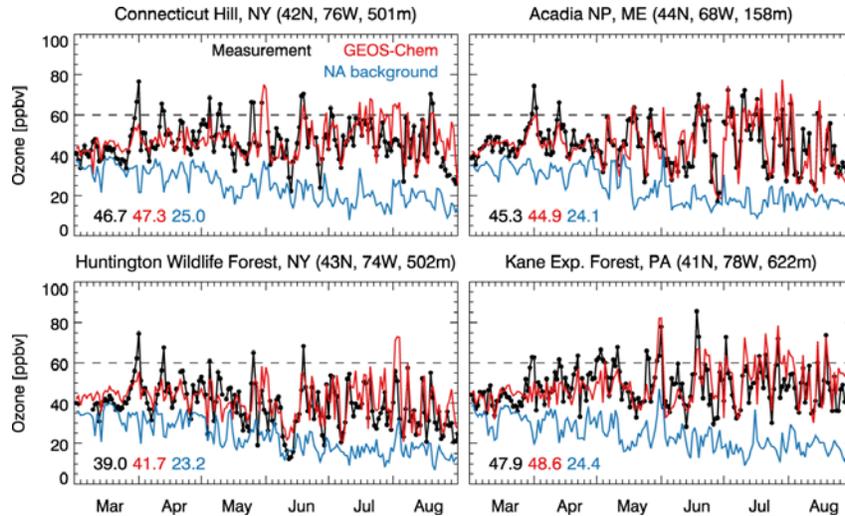
1 Rural O₃ concentrations show a varying degree of diel variability depending on their
2 location relative to larger urban areas. Three rural areas investigated in the east showed
3 relatively little diel variability, reflecting the regional nature of O₃ in the east. In contrast,
4 three rural areas investigated in the west did display diel variability resulting from their
5 proximity to fresh urban emissions. These six areas investigated were selected as
6 illustrative examples and do not represent all rural areas in the U.S.

7 Since O₃ is a secondary pollutant formed in the atmosphere from precursor emissions, its
8 correlation with primary pollutants such as CO and NO_x can vary substantially by
9 location. Furthermore, O₃ formation is strongly influenced by meteorology, entrainment,
10 and transport of both O₃ and O₃ precursors, resulting in a broad range in correlations with
11 other pollutants which can vary substantially with season. In the co-pollutant analyses
12 shown in [Figure 3-56](#), the year-round 8-h daily max O₃ data exhibited a very wide range
13 in correlations with all the criteria pollutants. A clearer pattern emerged when the data are
14 stratified by season with mostly negative correlations in the winter and mostly positive
15 correlations in the summer for all co-pollutants. The median seasonal correlations are
16 modest at best with the highest positive correlation at 0.52 for PM_{2.5} in the summer and
17 the highest negative correlation at -0.38 for PM_{2.5} in the winter. Therefore, statistical
18 analyses that may be sensitive to correlations between co-pollutants need to take
19 seasonality into consideration, particularly when O₃ is being investigated.

3.8 Supplemental Information on Ozone Model Predictions

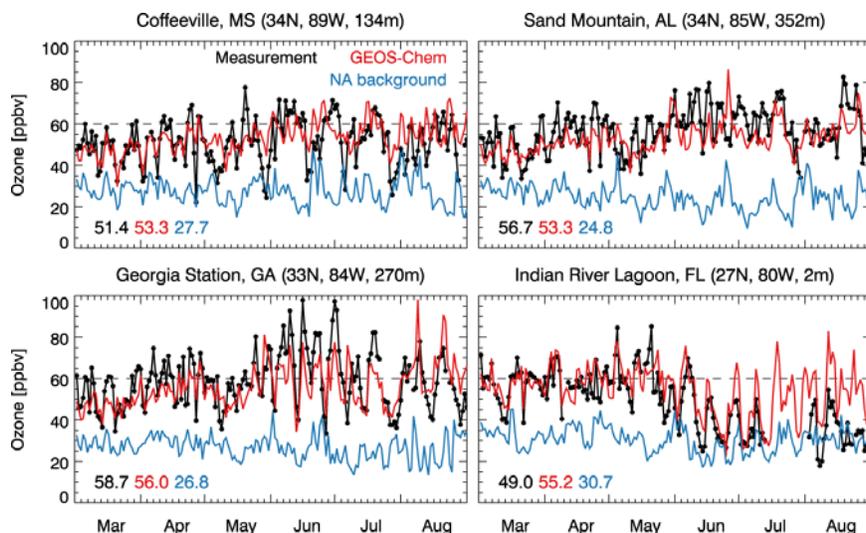
20 This section contains supplemental comparisons between GEOS-Chem simulations of
21 MDA8 O₃ concentrations with observations for 2006 from [Zhang et al. \(2011\)](#) and [Emery
22 et al. \(2012\)](#). Further details on these simulations can be found in Section [3.4.3](#).
23 [Figure 3-58](#) through [Figure 3-64](#) show GEOS-Chem predictions for the base model
24 (i.e., model including all anthropogenic and natural sources; labeled as GEOS-Chem in
25 the figure) and the NA background model (i.e., model including natural sources
26 everywhere in the world and anthropogenic sources outside the U.S., Canada, and
27 Mexico; labeled as NA background in the figure) along with measurements obtained
28 from selected CASTNET sites (labeled as Measurement in the figure). [Figure 3-65](#) shows
29 a comparison of GEOS-Chem output with measurements at Mt. Bachelor, OR from
30 March-August, 2006. [Figure 3-66](#) shows a comparison of vertical profiles (mean ± 1
31 standard deviation) calculated by GEOS-Chem with ozonesondes launched at Trinidad
32 Head, CA and Boulder, CO. [Figure 3-67](#) and [Figure 3-68](#) show a comparison of AM3
33 simulations of individual stratospheric intrusions during May-June 2010. [Figure 3-69](#)
34 through [Figure 3-74](#) show box plots for measurements at CASTNET sites, GEOS-Chem
35 predictions from [Zhang et al. \(2011\)](#) and CAMx predictions from [Emery et al. \(2012\)](#) for

1 both the base case and NA background. [Figure 3-75](#) shows time series of AM3
2 simulations at approximately $2^\circ \times 2^\circ$ at Gothic CO for 2006.



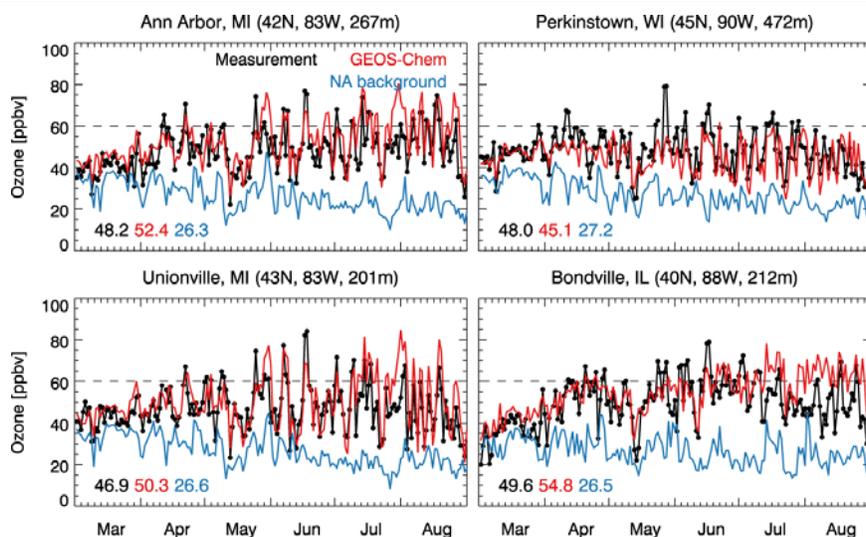
Source: [Zhang et al. \(2011\)](#).

Figure 3-58 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Northeast with GEOS-Chem predictions for the base case and for the North American background case during March-August, 2006.



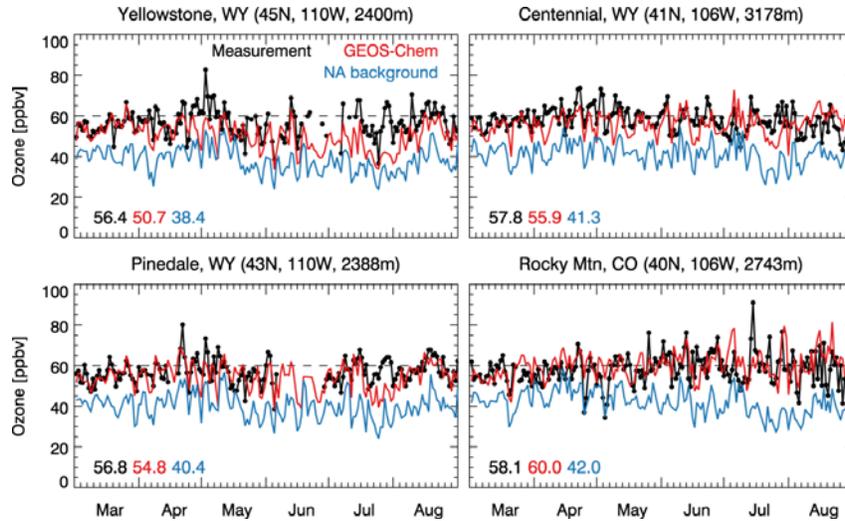
Source: [Zhang et al. \(2011\)](#).

Figure 3-59 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Southeast with GEOS-Chem predictions for the base case and for the North American background case during March-August, 2006.



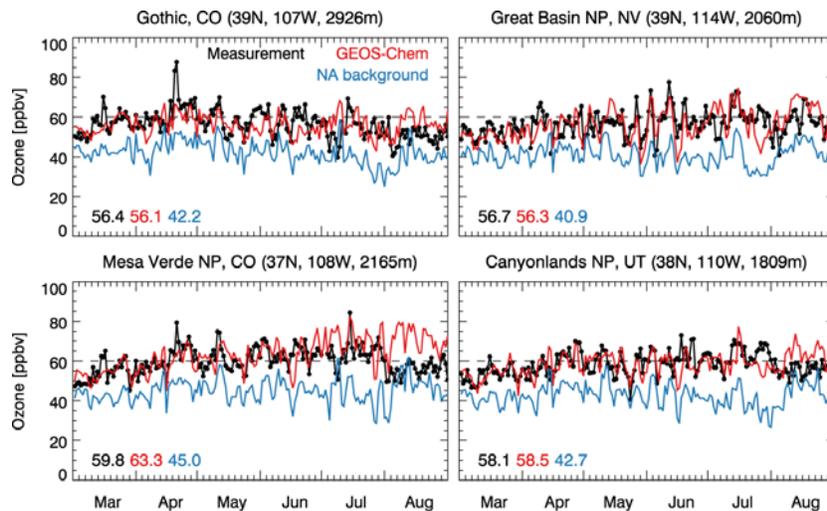
Source: [Zhang et al. \(2011\)](#).

Figure 3-60 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Upper Midwest with GEOS-Chem predictions for the base case and for the North American background case during March-August, 2006.



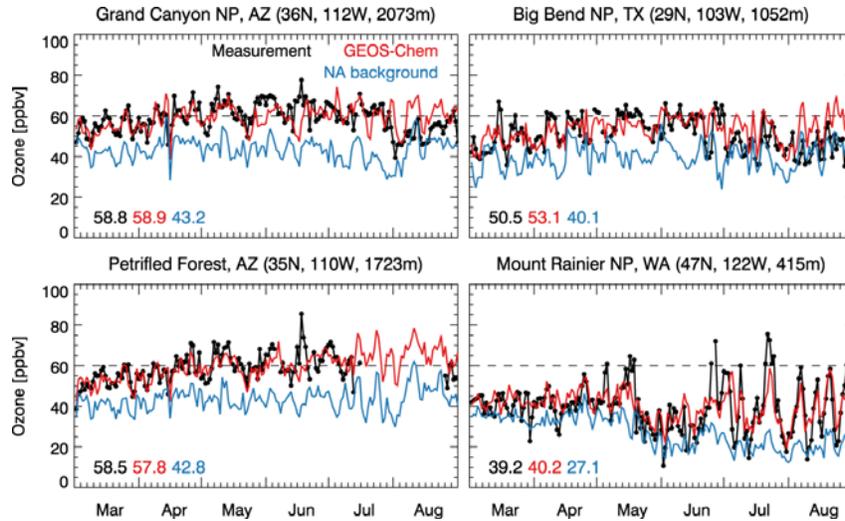
Source: [Zhang et al. \(2011\)](#).

Figure 3-61 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Intermountain West with GEOS-Chem predictions for the base case and the North American background case during March-August, 2006.



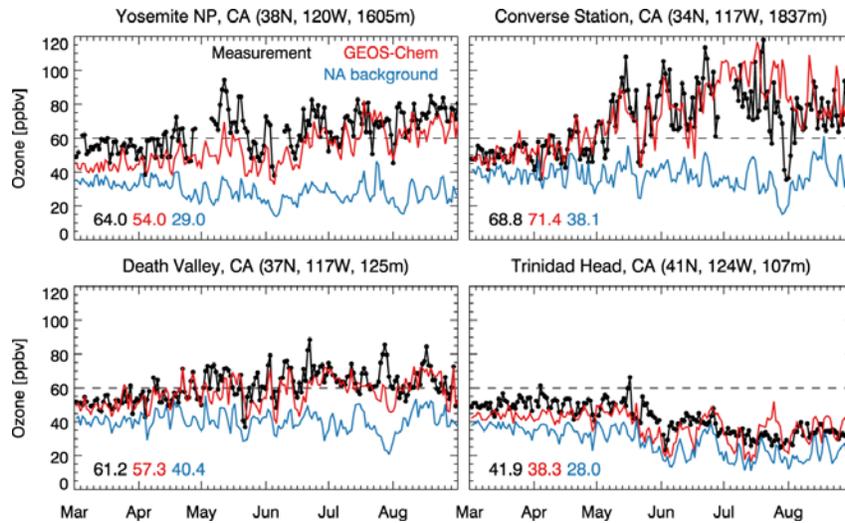
Source: [Zhang et al. \(2011\)](#).

Figure 3-62 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the Intermountain West with GEOS-Chem predictions for the base case and the North American background case during March-August, 2006.



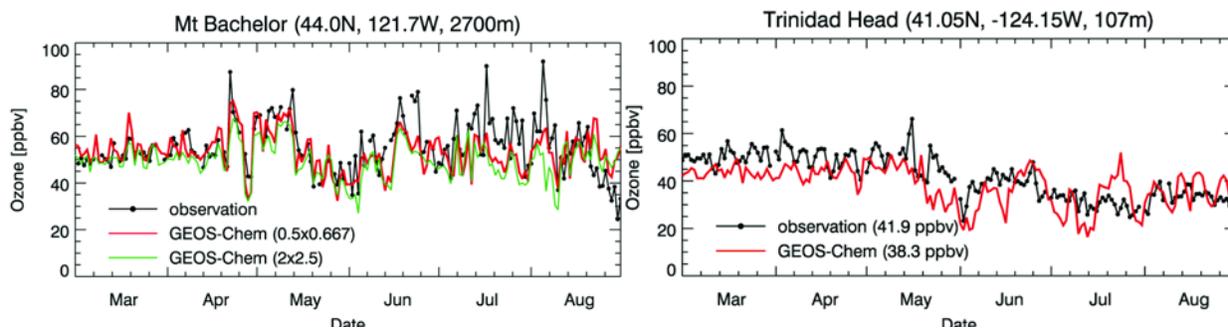
Source: [Zhang et al. \(2011\)](#).

Figure 3-63 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at four CASTNET sites in the West with GEOS-Chem predictions for the base case and the North American background case during March-August, 2006.



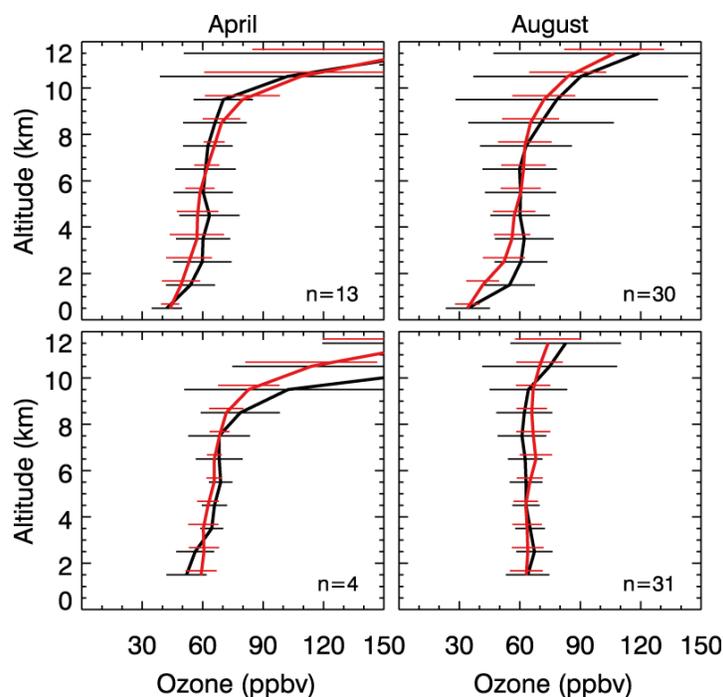
Source: [Zhang et al. \(2011\)](#).

Figure 3-64 Comparison of time series of measurements of daily maximum 8-hour average ozone concentrations at three CASTNET sites and the Trinidad Head site in California with GEOS-Chem predictions for the base case and the North American background case during March-August, 2006.



Source: [Zhang et al. \(2011\)](#).

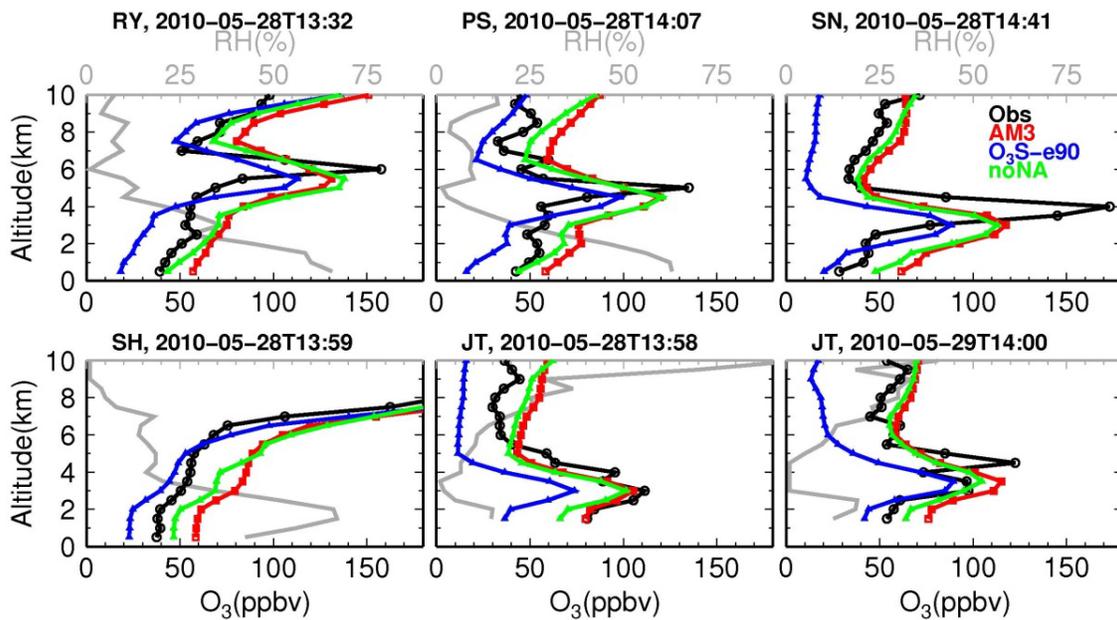
Figure 3-65 Comparison of daily maximum 8-h average ozone predicted using GEOS-Chem at $0.5^\circ \times 0.667^\circ$ (and $2^\circ \times 2.5^\circ$ resolution; left figure only) with measurements at Mount Bachelor, OR (left); and at Trinidad Head, CA (right) from March to August 2006.



Note: The letter 'n' refers to the number of ozonesonde profiles, and the model was sampled on the same days as the ozonesonde launches. As can be seen from the figure, variability in both model and measurements increases with altitude, but variability in the model results is much smaller at high altitudes than seen in the observations at both sites.

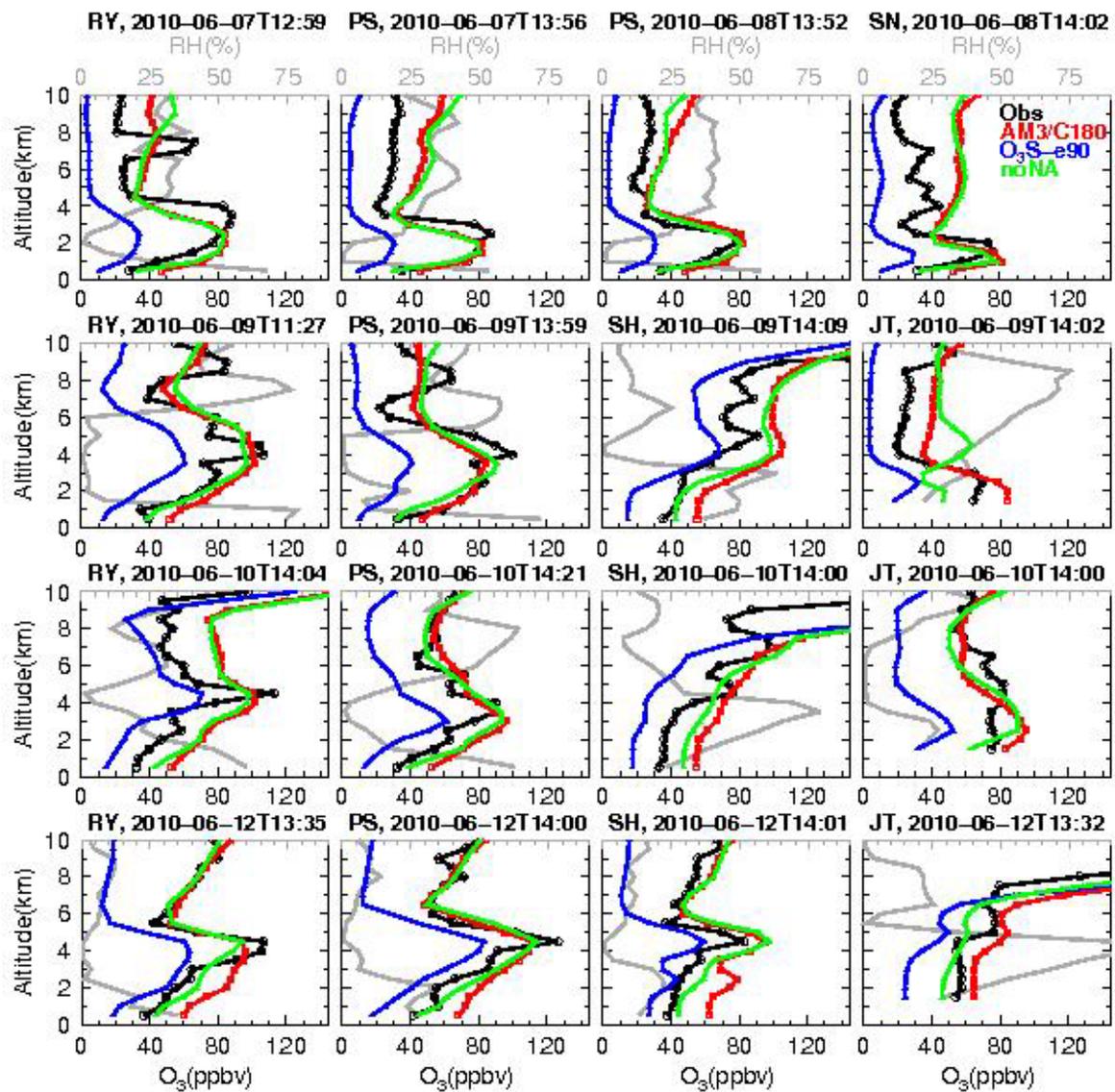
Source: [Zhang et al. \(2011\)](#).

Figure 3-66 Comparison of monthly mean (± 1 standard deviation) ozone calculated GEOS-Chem (in red) with ozonesondes (in black) at Trinidad Head, CA (top) and Boulder, CO (bottom) during April and August 2006.



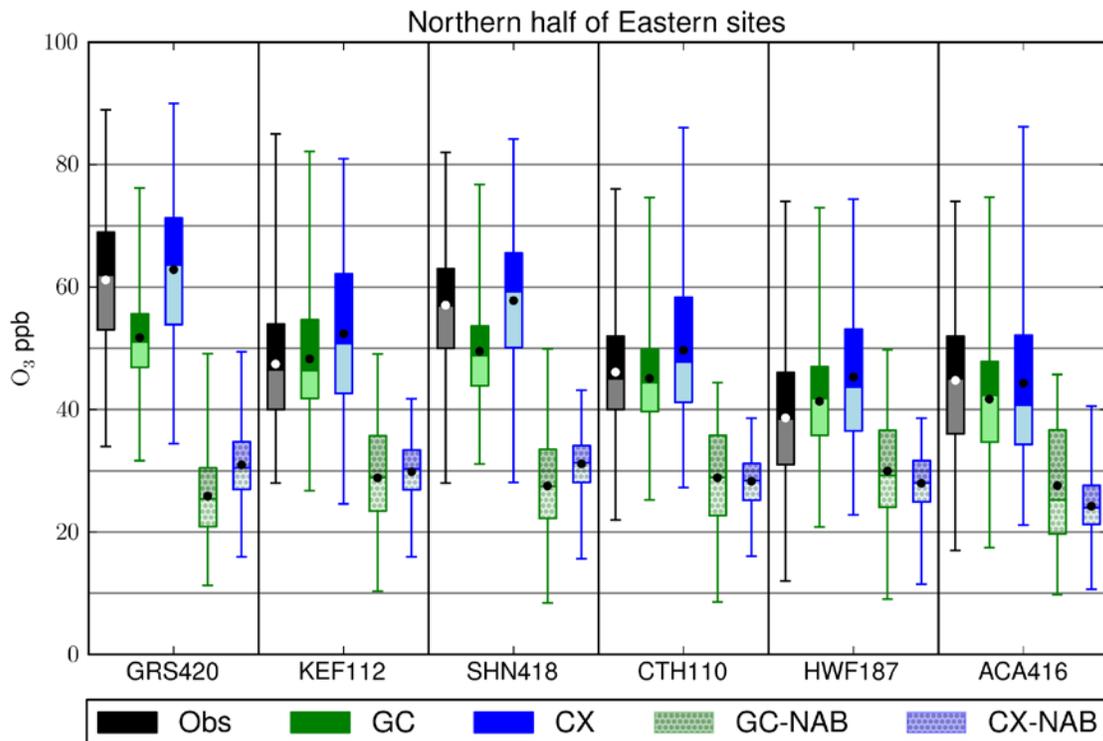
Note: Shows ozone profiles at multiple sites as observed (black) by ozonesondes and simulated (red) by the GFDL AM3 model at $\sim 50 \times 50$ km resolution. Also shown are observed relative humidity (gray) and AM3 estimates of ozone concentrations in the absence of North American anthropogenic emissions (green) and the stratospheric contribution (blue). Model results have been interpolated to sonde pressure and averaged over 0.5-km altitude bins.

Figure 3-67 A deep stratospheric ozone intrusion over California on May 28-29, 2010.



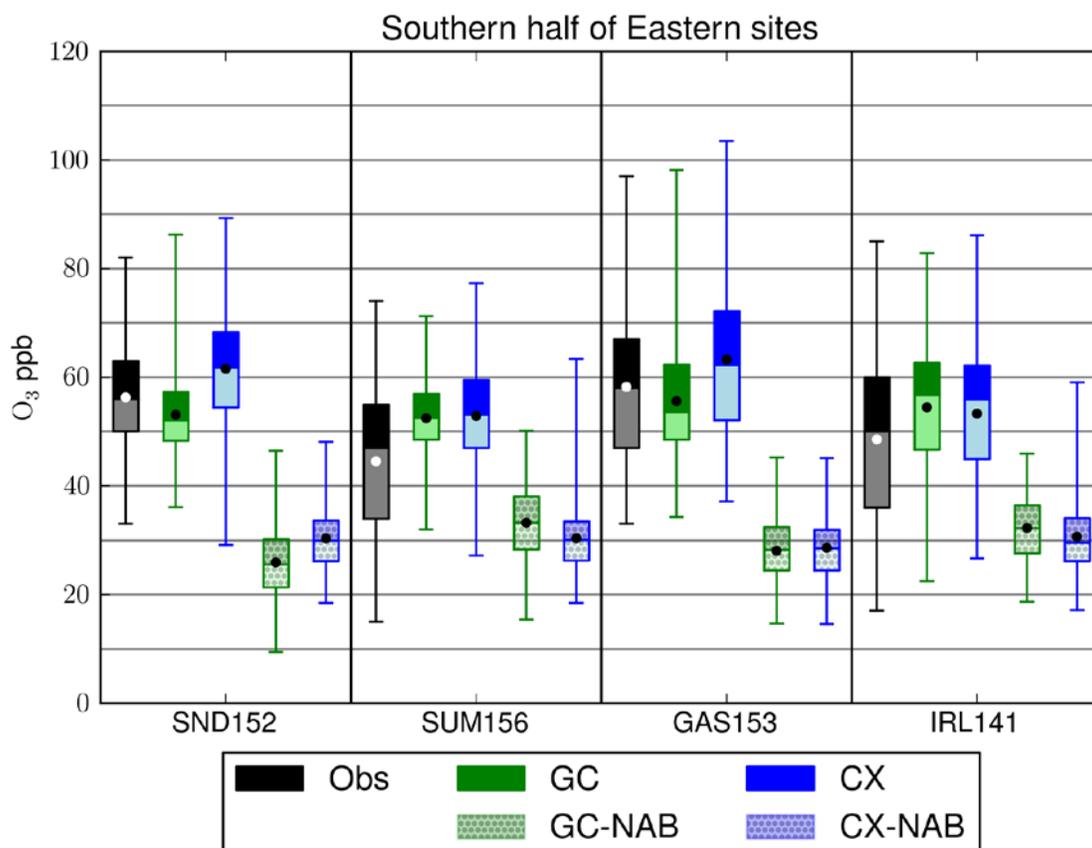
Note: Shows ozone profiles at multiple sites as observed (black) by ozonesondes and simulated (red) by the GFDL AM3 model at $\sim 50 \times 50$ km resolution. Also shown are observed relative humidity (gray) and AM3 estimates of ozone concentrations in the absence of North American anthropogenic emissions (green) and the stratospheric contribution (blue). Model results have been interpolated to sonde pressure and averaged over 0.5-km altitude bins.

Figure 3-68 A deep stratospheric ozone intrusion over California on June 7-12, 2010.



Note: Stippled boxes indicate North American background. GRS = Great Smoky NP; KEF = Kane Exp. Forest; SHN = Shenandoah NP; CTH = Connecticut Hill; HWF = Huntington Wildlife Forest; ACA = Acadia NP.
Source: Adapted from [Emery et al. \(2012\)](#) and [Zhang et al. \(2011\)](#).

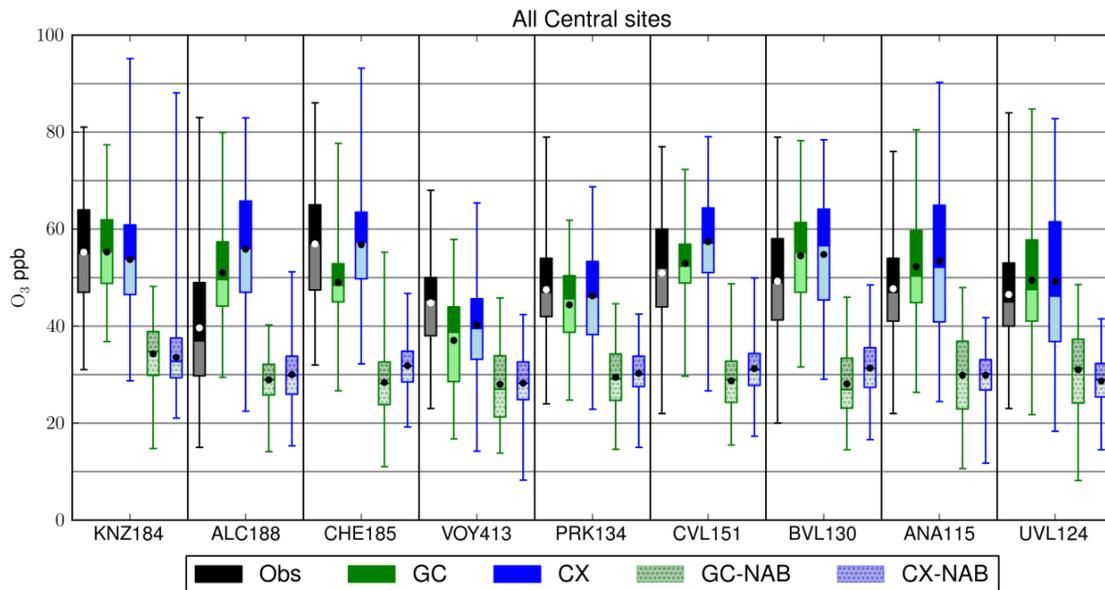
Figure 3-69 Box plots showing maximum, interquartile range and minimum ozone concentrations measured at CASTNET sites (black) in the Northeast and predictions from GEOS-Chem at ~50 × 50 km resolution (green) and CAMx at 12 × 12 km resolution (blue) for May-August 2006.



Note: Stippled boxes indicate North American background. SND = Sand Mountain; SUM = Sumatra; GAS = Georgia Station; IRL = Indian River Lagoon.

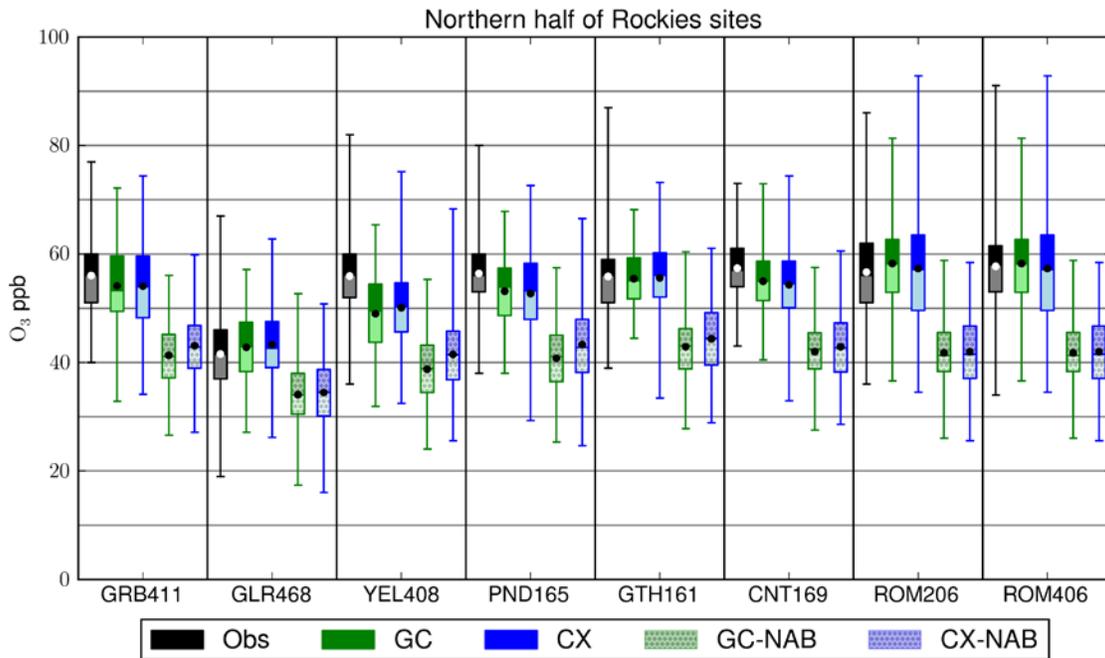
Source: Adapted from [Emery et al. \(2012\)](#) and [Zhang et al. \(2011\)](#).

Figure 3-70 Box plots showing maximum, interquartile range and minimum ozone concentrations measured at CASTNET sites (black) in the Southeast and predictions from GEOS-Chem at $\sim 50 \times 50$ km resolution (green) and CAMx at 12×12 km resolution (blue) for May-August 2006.



Note: Stippled boxes indicate North American background. KNZ = Konza Prairie; ALC = Alabama-Coushatta; CHE = Cherokee Nation; VOY = Voyageurs NP; PRK = Perkinstown; CVL = Coffeerville; BVL = Bondsville; ANA = Ann Arbor; UVL = Unionville.
 Source: Adapted from [Emery et al. \(2012\)](#) and [Zhang et al. \(2011\)](#).

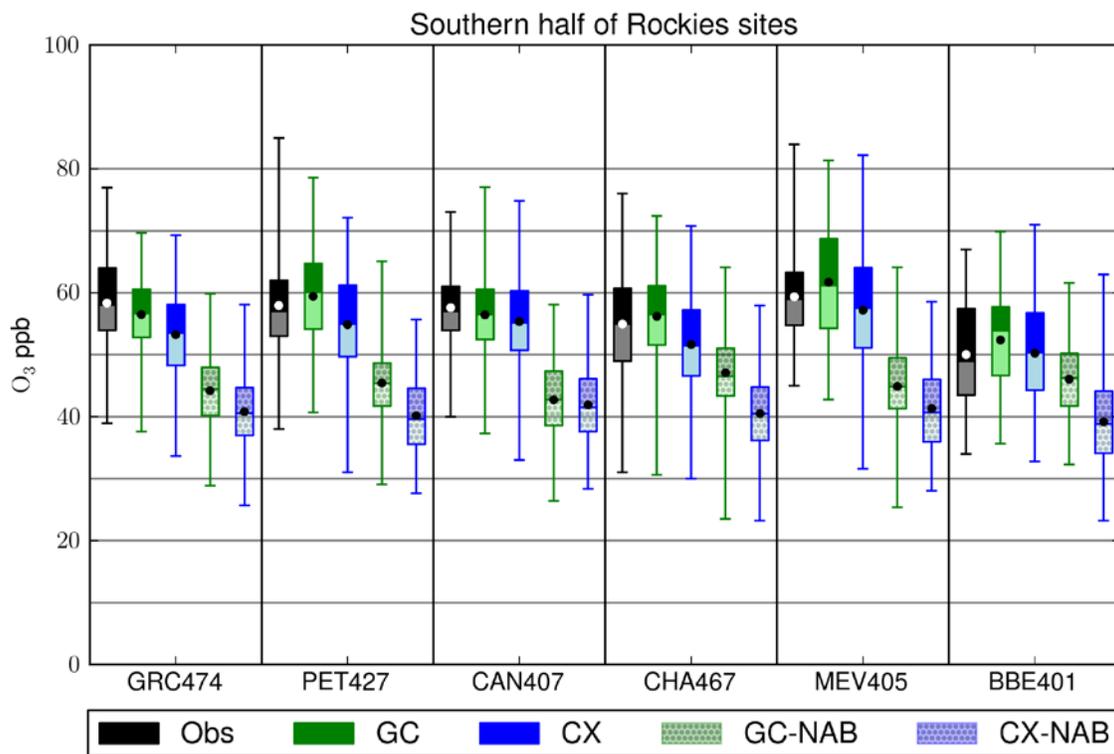
Figure 3-71 Box plots showing maximum, interquartile range and minimum ozone concentrations measured at CASTNET sites (black) in the Central U.S. and predictions from GEOS-Chem at $\sim 50 \times 50$ km resolution (green) and CAMx at 12×12 km resolution (blue) for May-August 2006.



Note: Stippled boxes indicate North American background. GRB = Great Basin NP; GLR = Glacier NP; YEL = Yellowstone NP; PND = Pinedale; GTH = Gothic; CNT = Centennial; ROM = Rocky Mountain NP (co-located sites).

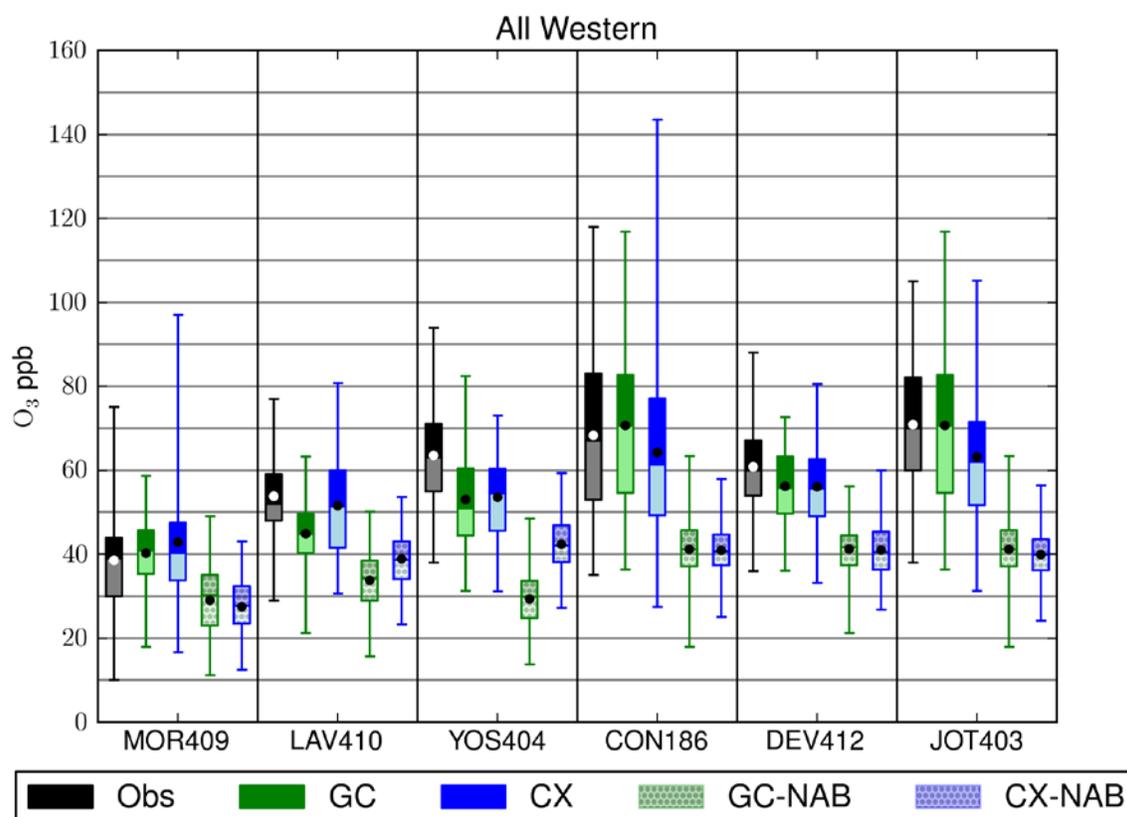
Source: Adapted from [Emery et al. \(2012\)](#) and [Zhang et al. \(2011\)](#).

Figure 3-72 Box plots showing maximum, interquartile range and minimum ozone concentrations measured at CASTNET sites (black) in the Northern Rockies and predictions from GEOS-Chem at ~50 x 50 km resolution (green) and CAMx at 12 x 12 km resolution (blue) for May-August 2006.



Note: Stippled boxes indicate North American background. GRC = Grand Canyon NP; PET = Petrified Forest; CAN = Canyonlands NP; CHA = Chiricahua NM; MEV = Mesa Verde NP; BBE = Big Bend NP.
 Source: Adapted from [Emery et al. \(2012\)](#) and [Zhang et al. \(2011\)](#).

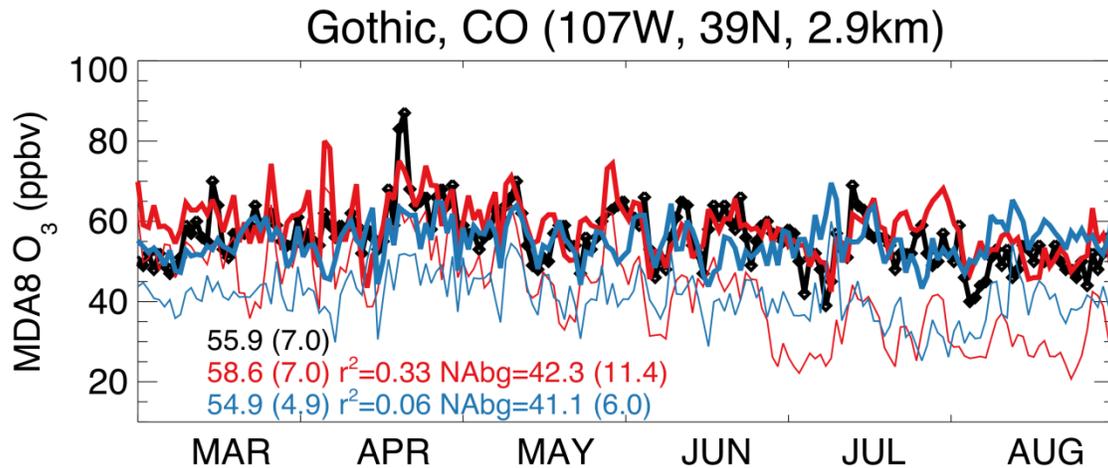
Figure 3-73 Box plots showing maximum, interquartile range and minimum ozone concentrations measured at CASTNET sites (black) in the Southern Rockies and predictions from GEOS-Chem at ~50 x 50 km resolution (green) and CAMx at 12 x 12 km resolution (blue) for May-August 2006.



Note: Stippled boxes indicate North American background. MOR = Mount Ranier NP; LAV = Lassen Volcanic NP; YOS = Yosemite NP; CON = Converse Station; DEV = Death Valley NM; JOT = Joshua Tree NM.

Source: Adapted from [Emery et al. \(2012\)](#) and [Zhang et al. \(2011\)](#).

Figure 3-74 Box plots showing maximum, interquartile range and minimum ozone concentrations measured at CASTNET sites (black) in the West and predictions from GEOS-Chem at $\sim 50 \times 50$ km resolution (green) and CAMx at 12×12 km resolution (blue) for May-August 2006.



Note: Observed (black) and simulated by the GEOS-Chem (blue; horizontal resolution is $0.5^\circ \times 0.667^\circ$) and AM3 (red; horizontal resolution is approximately $2^\circ \times 2^\circ$) global models. Also shown are the model estimates for North American background (thin lines); the spike in mid-April likely corresponds to a stratospheric intrusion. The model correlations with observations, average (over the entire March through August period) total O_3 and North American background (NAbg) O_3 estimates, and their standard deviations (shown in parentheses) are presented in the lower left.

Figure 3-75 Daily maximum 8-hour average (MDA8) ozone in surface air at Gothic, CO for March through August 2006.

3.9 Supplemental Figures of Observed Ambient Ozone Concentrations

3.9.1 Ozone Monitor Maps for the Urban Focus Cities

1 This section contains supplemental maps showing the location of O_3 monitors reporting
 2 to AQS for each of the 20 urban focus cities introduced in Section 3.6.2.1. The monitors
 3 are delineated in the maps as year-round or warm-season based on their inclusion in the
 4 year-round data set and the warm-season data set discussed in Section 3.6.2.1. The maps
 5 also include the CSA/CBSA boundary selected for monitor inclusion, the location of
 6 urban areas and water bodies, the major roadway network, as well as the population
 7 gravity center based on the entire CSA/CBSA and the individual focus city boundaries.
 8 Population gravity center is calculated from the average longitude and latitude values for
 9 the input census tract centroids and represents the mean center of the population in a
 10 given area. Census tract centroids are weighted by their population during this
 11 calculation.

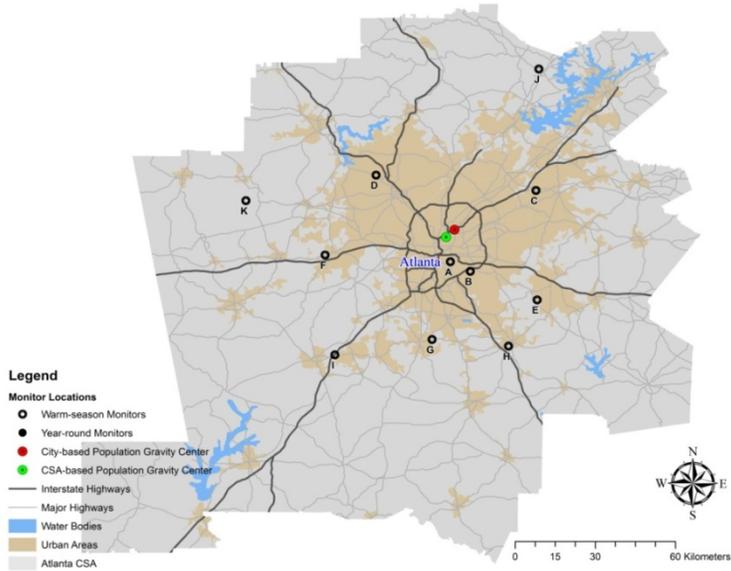


Figure 3-76 Map of the Atlanta CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

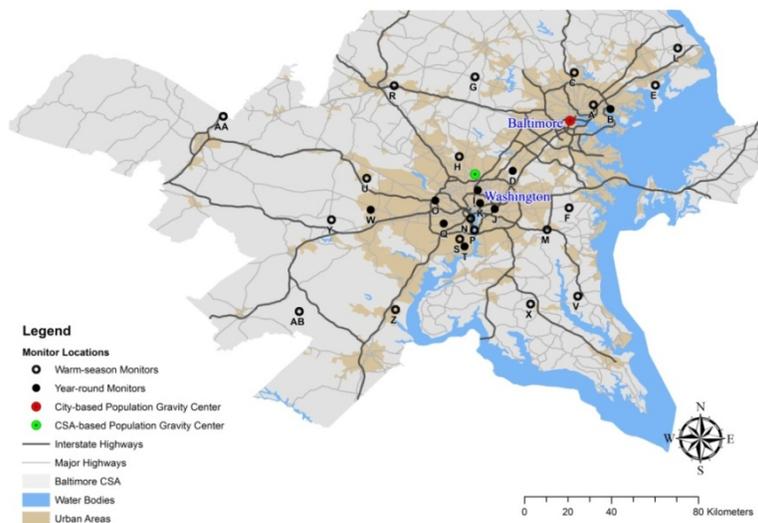


Figure 3-77 Map of the Baltimore CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

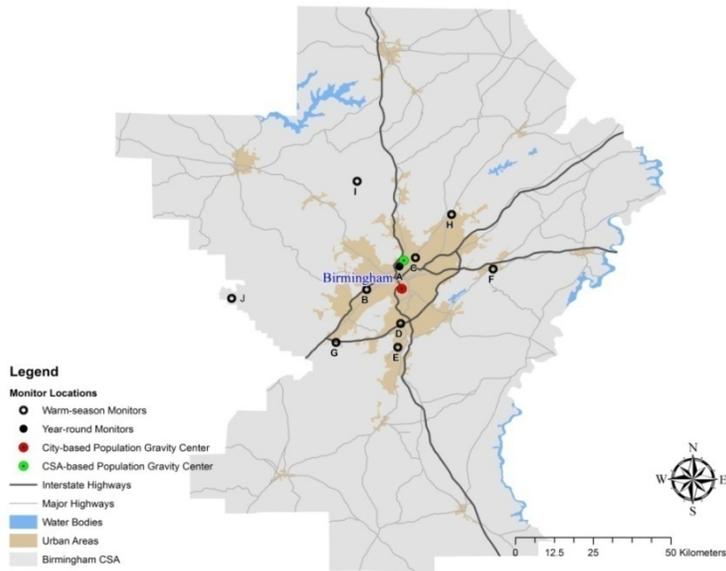


Figure 3-78 Map of the Birmingham CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.



Figure 3-79 Map of the Boston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

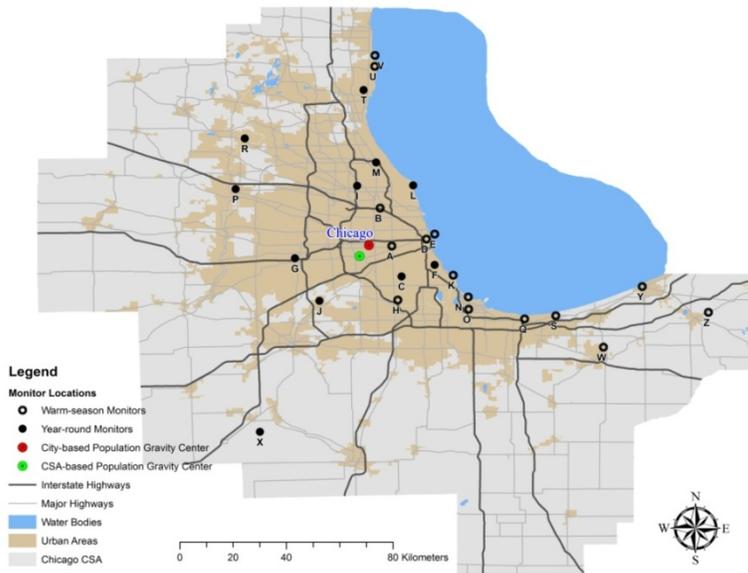


Figure 3-80 Map of the Chicago CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

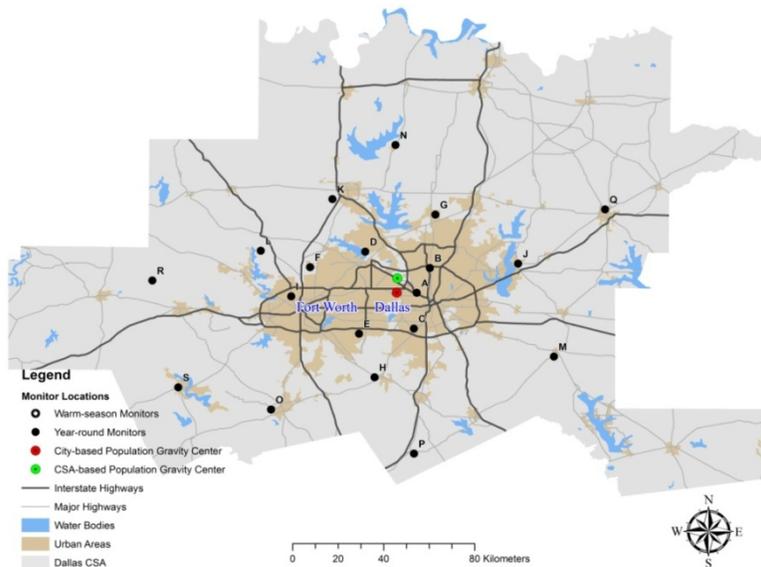


Figure 3-81 Map of the Dallas CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

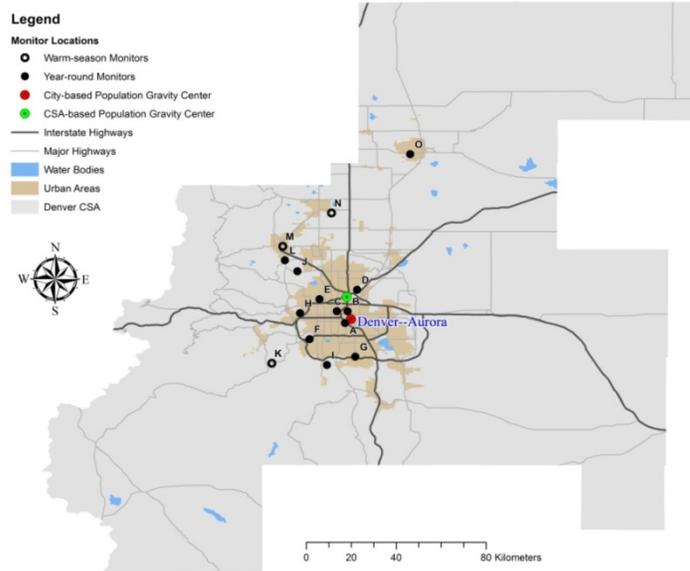


Figure 3-82 Map of the Denver CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

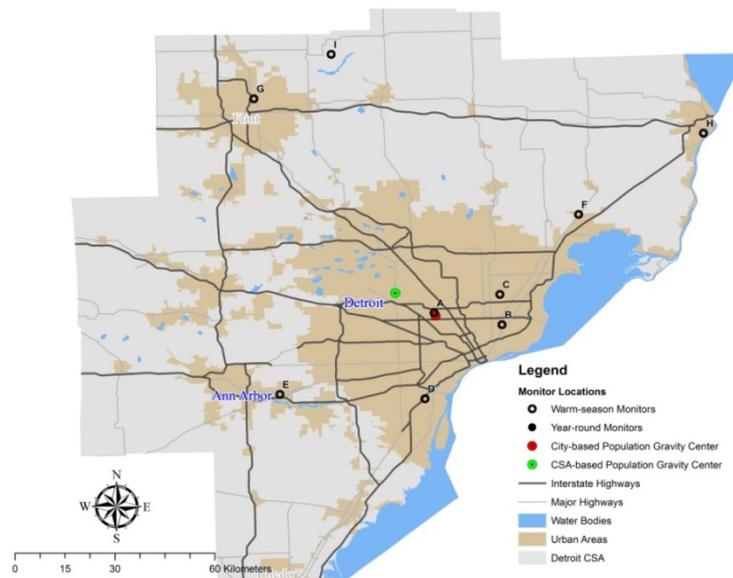


Figure 3-83 Map of the Detroit CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

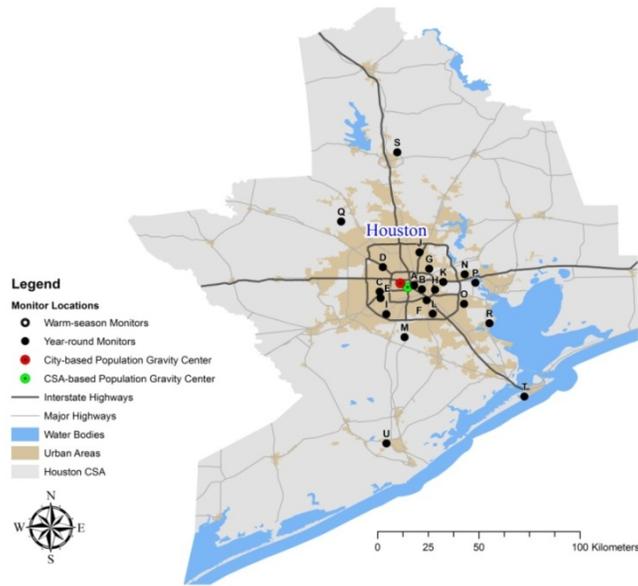


Figure 3-84 Map of the Houston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

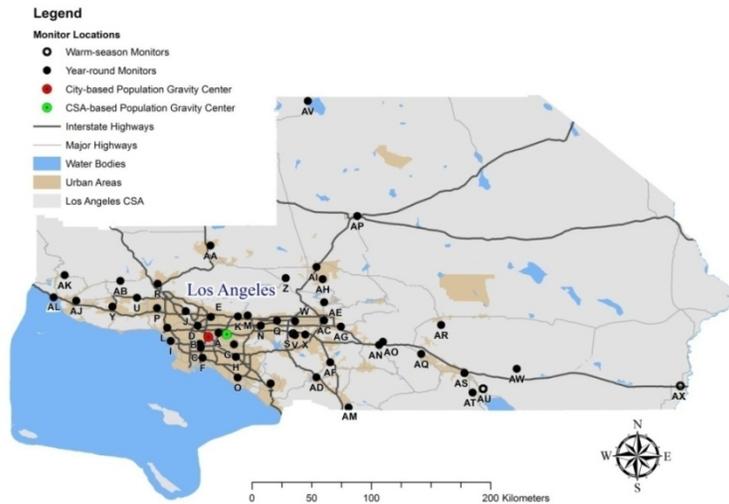


Figure 3-85 Map of the Los Angeles CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

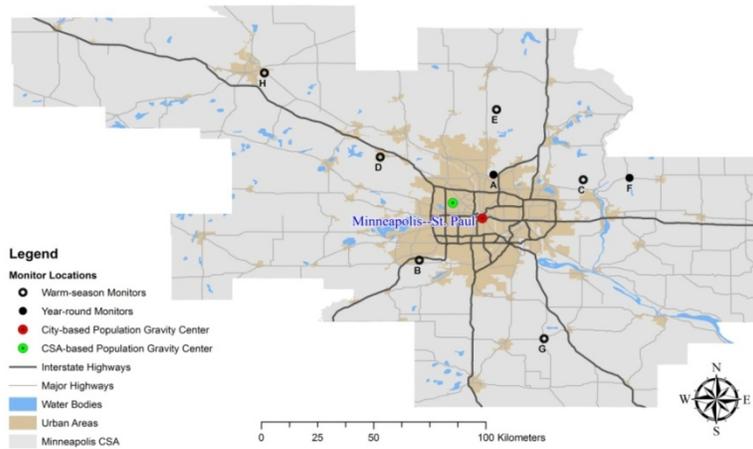


Figure 3-86 Map of the Minneapolis CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

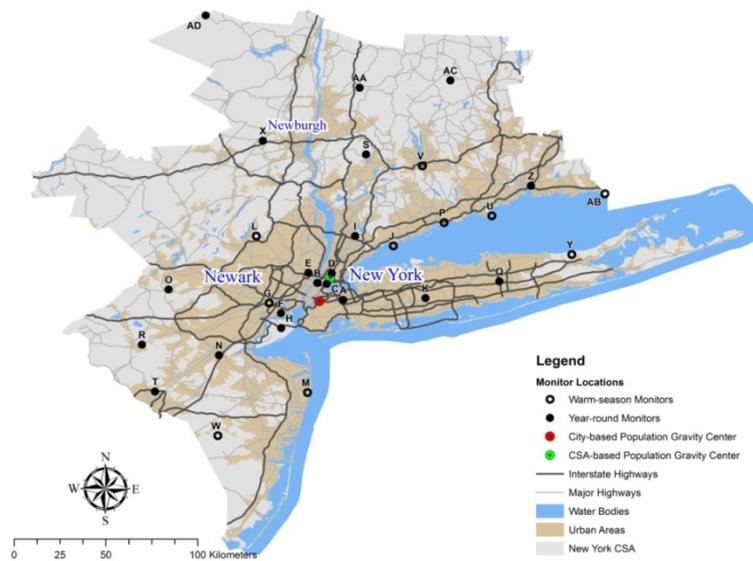


Figure 3-87 Map of the New York CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

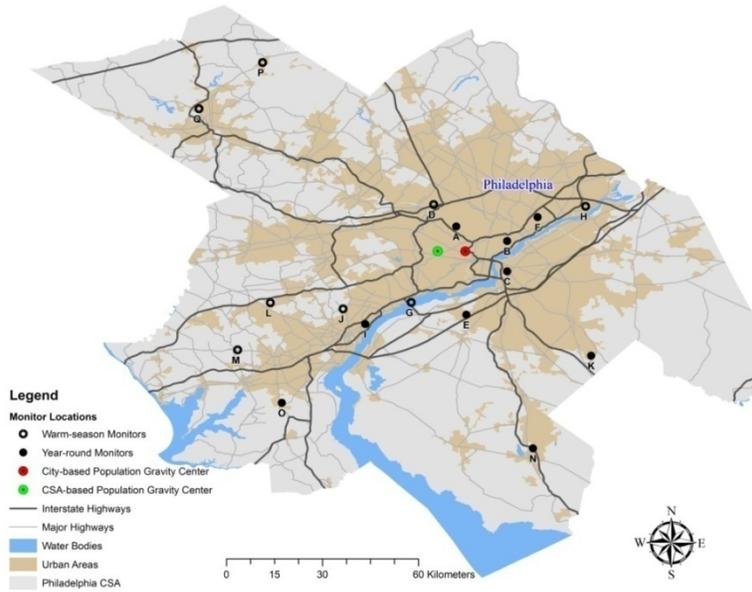


Figure 3-88 Map of the Philadelphia CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

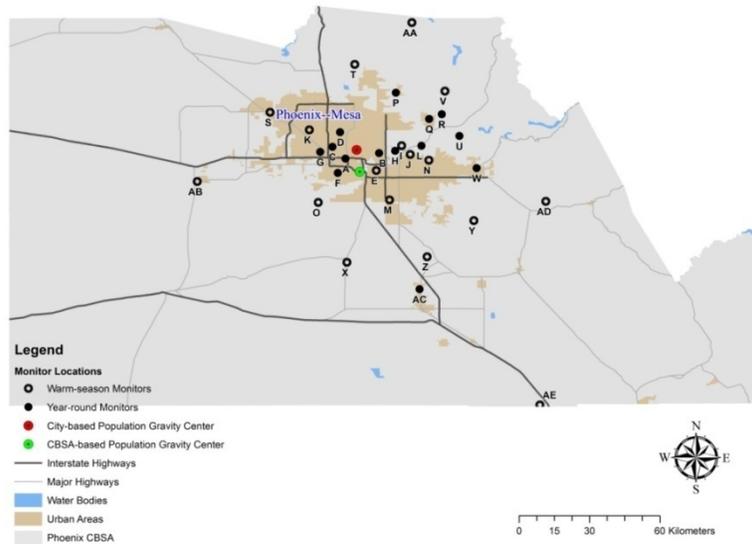


Figure 3-89 Map of the Phoenix CBSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

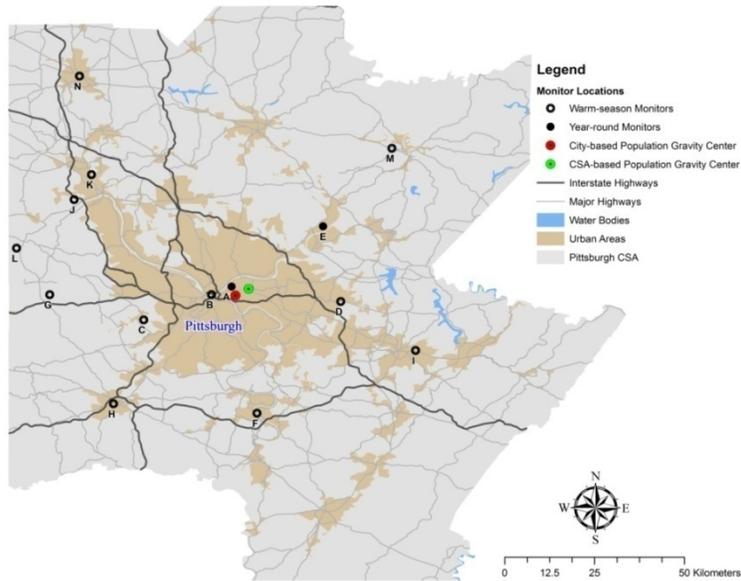


Figure 3-90 Map of the Pittsburgh CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

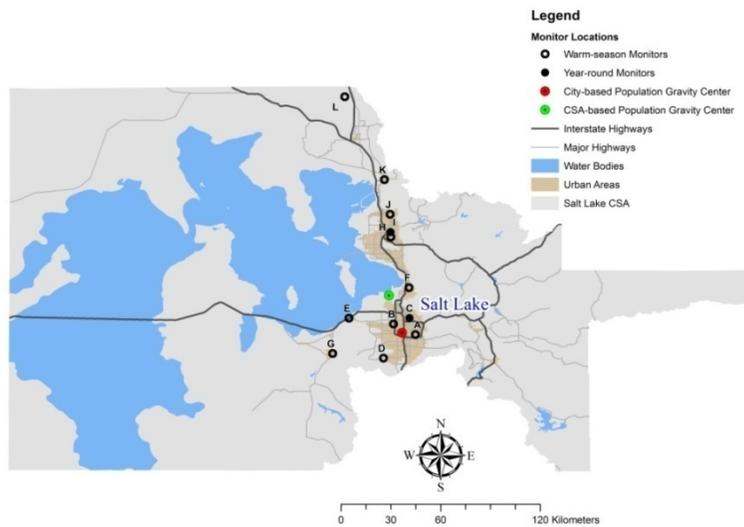


Figure 3-91 Map of the Salt Lake City CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

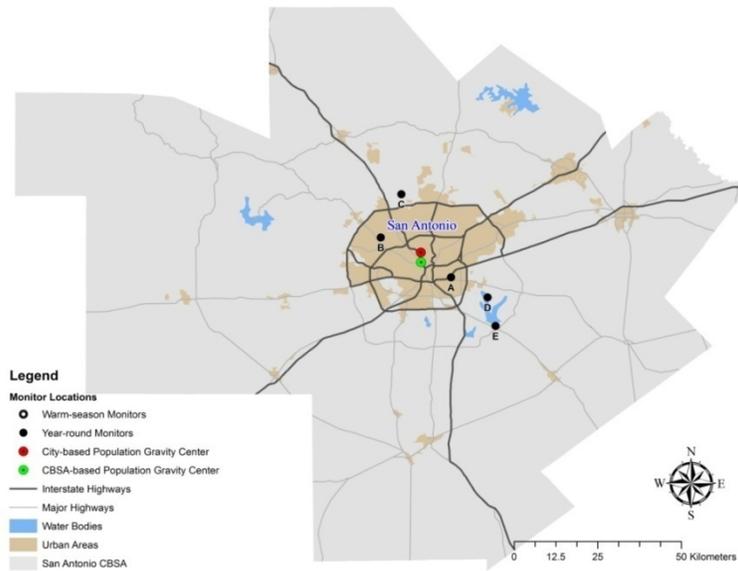


Figure 3-92 Map of the San Antonio CBSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

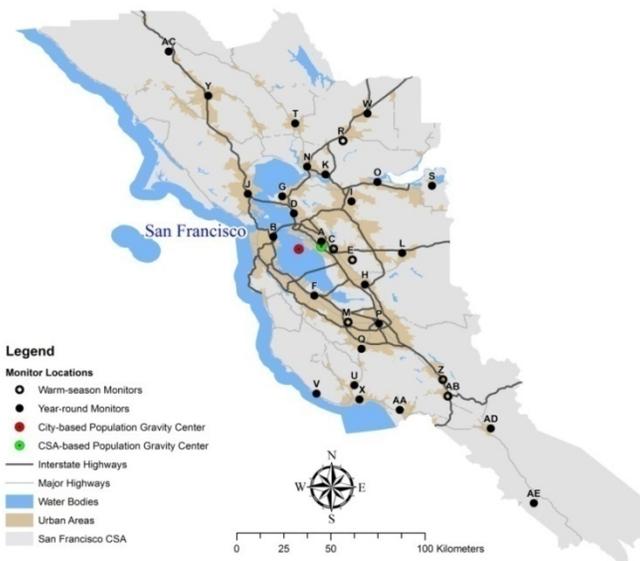


Figure 3-93 Map of the San Francisco CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

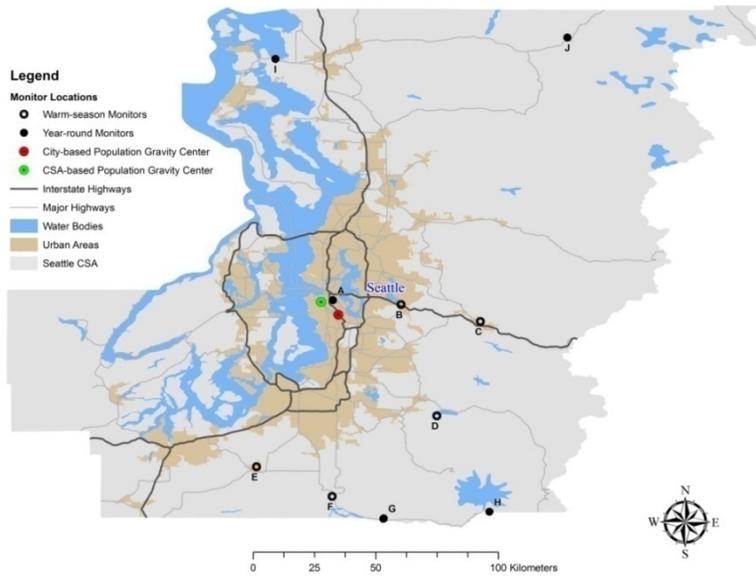


Figure 3-94 Map of the Seattle CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

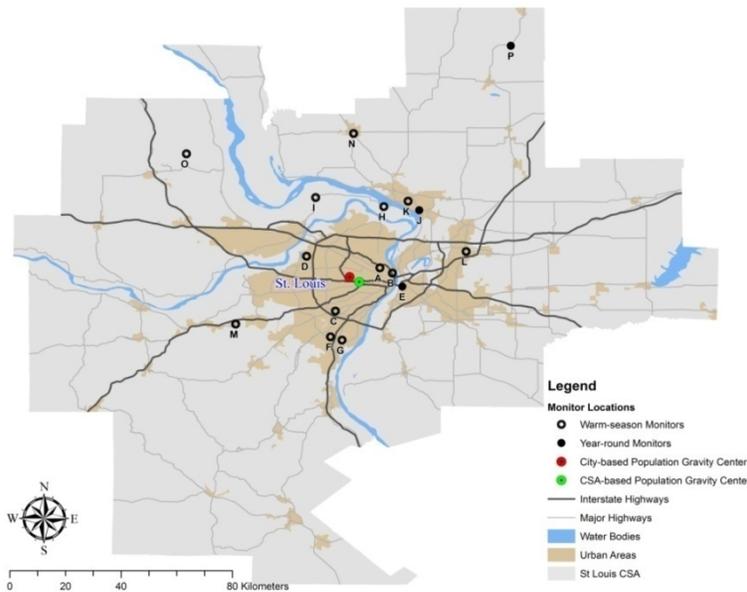


Figure 3-95 Map of the St. Louis CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.

3.9.2 Ozone Concentration Box Plots for the Urban Focus Cities

1 This section contains box plots depicting the distribution of 2007-2009 warm-season 8-h
 2 daily max O₃ data from each individual monitor in the 20 urban focus cities introduced in
 3 Section 3.6.2.1. Monitor information including the AQS site id, the years containing
 4 qualifying data between 2007 and 2009, and the number of 8-h daily max O₃
 5 observations included in the data set are listed next to the box plot. Statistics including
 6 the mean, standard deviation (SD), median and inner quartile range (IQR) are also shown
 7 for each monitor with the site letter corresponding to the sites listed in the figures above.

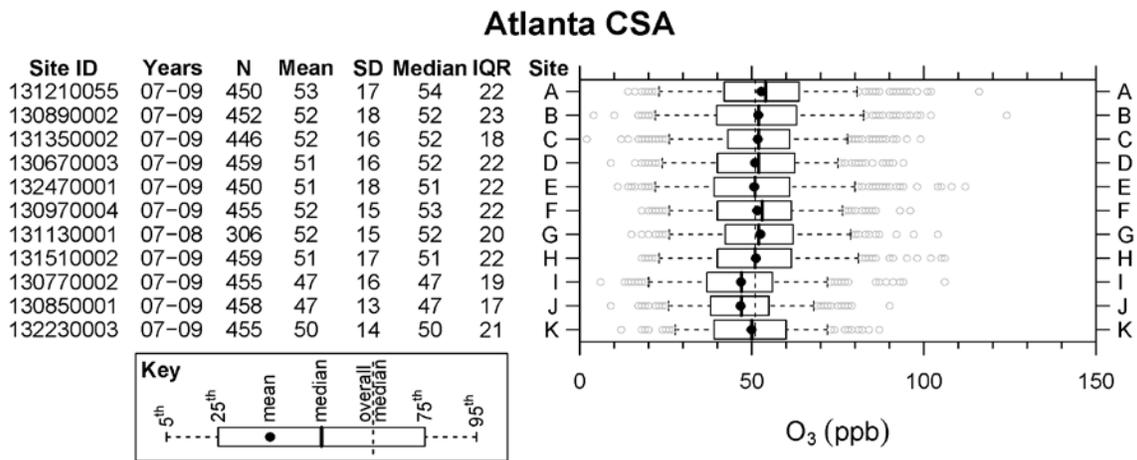


Figure 3-96 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Atlanta CSA.

Baltimore CSA

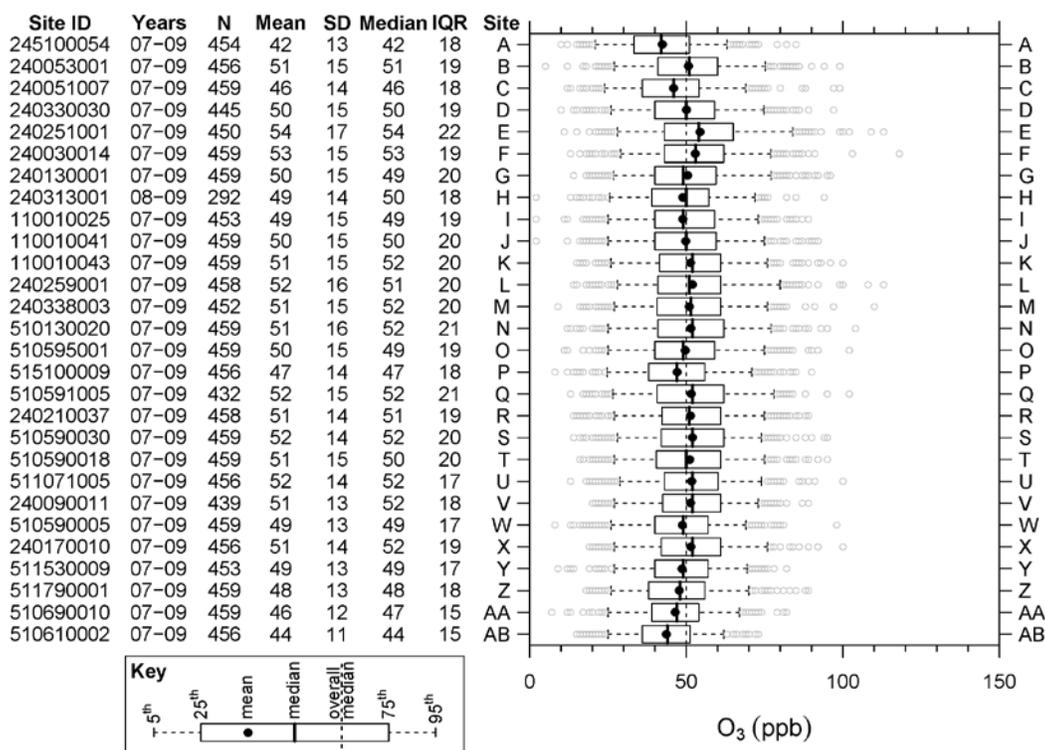


Figure 3-97 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Baltimore CSA.

Birmingham CSA

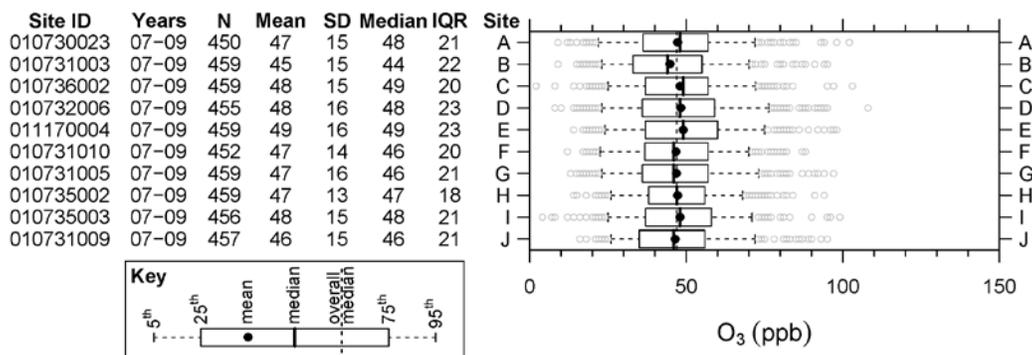


Figure 3-98 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Birmingham CSA.

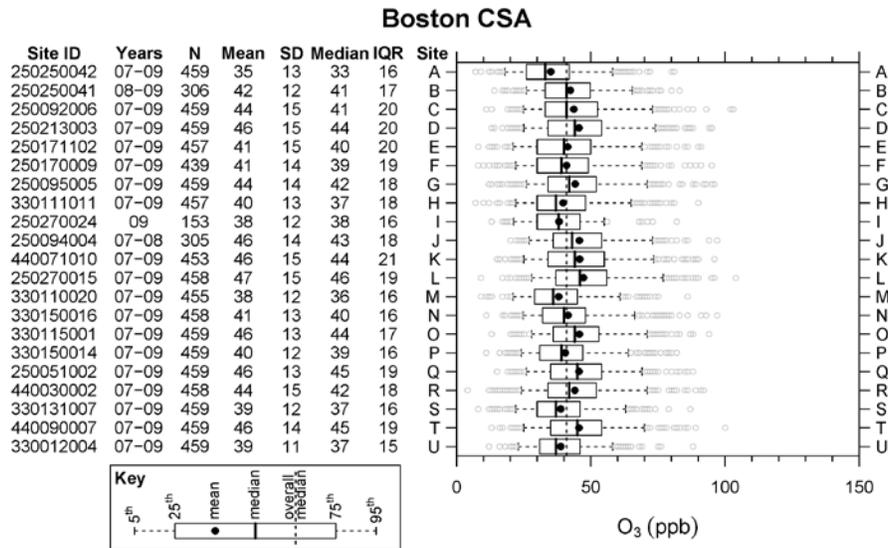


Figure 3-99 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Boston CSA.

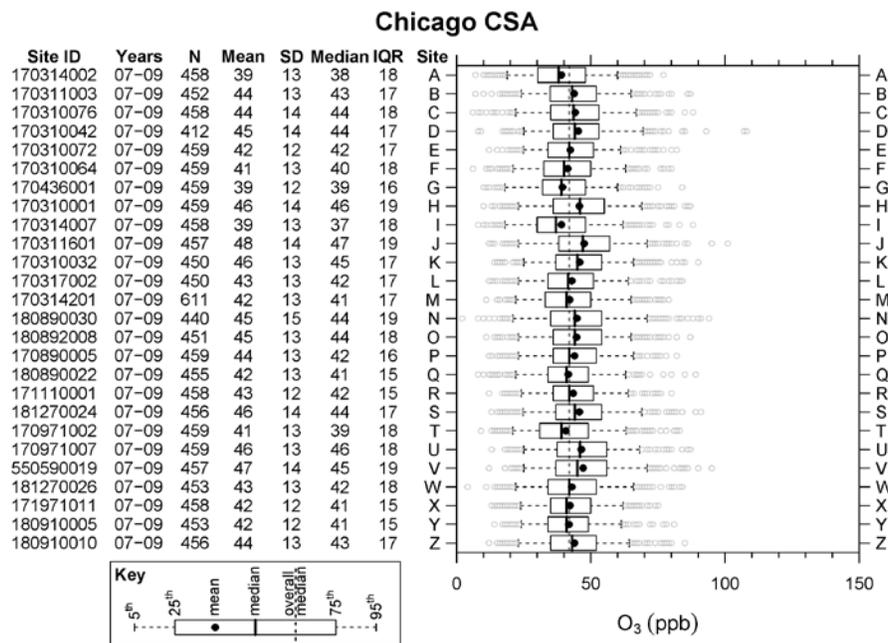


Figure 3-100 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Chicago CSA.

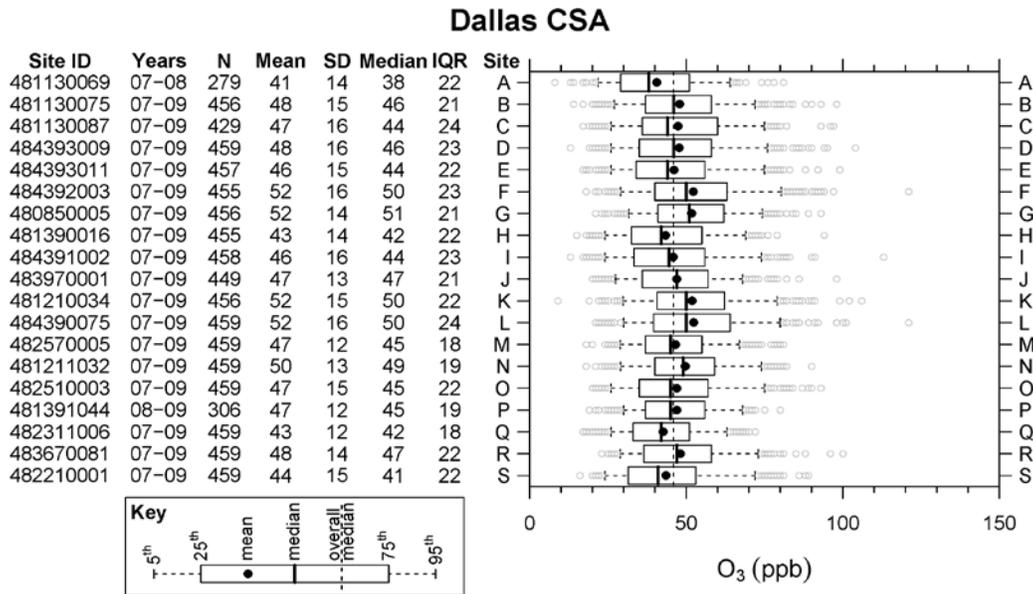


Figure 3-101 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Dallas CSA.

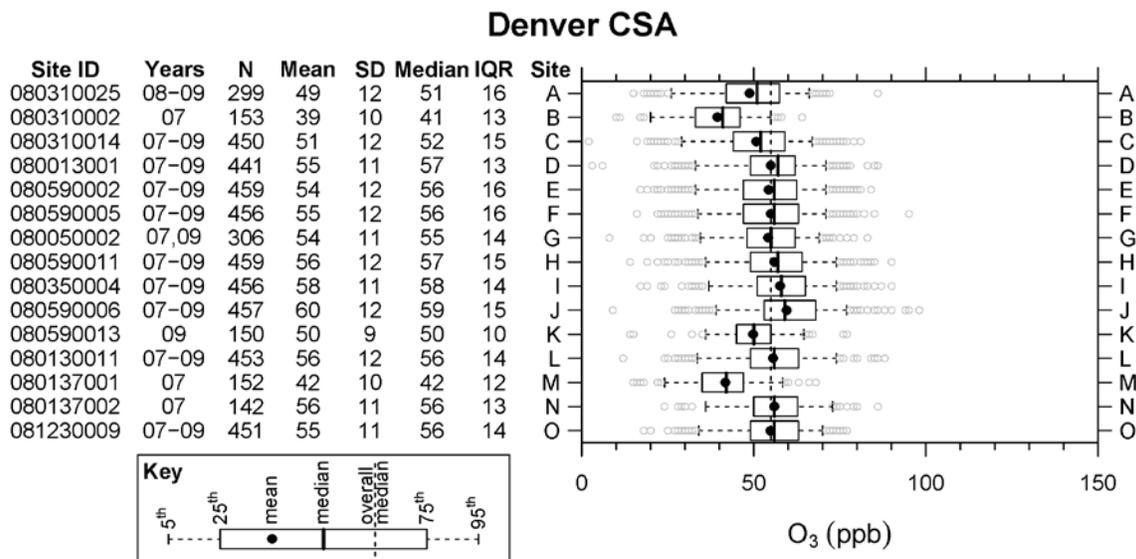


Figure 3-102 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Denver CSA.

Detroit CSA

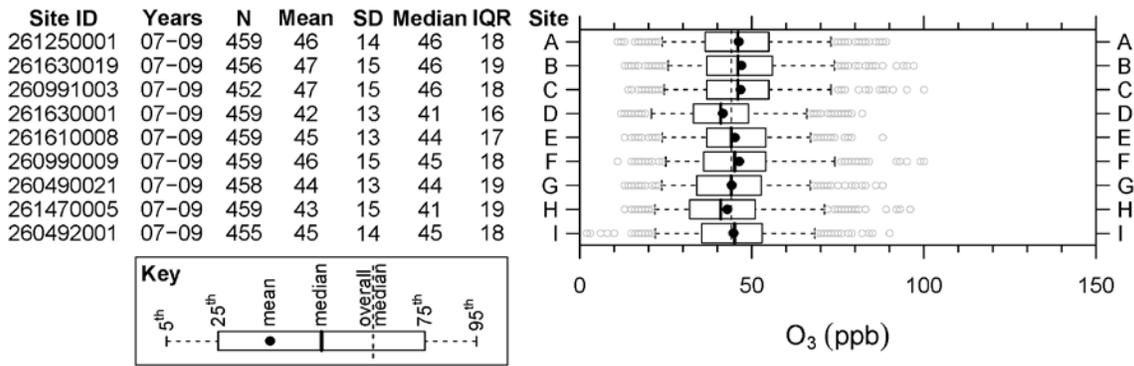


Figure 3-103 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Detroit CSA.

Houston CSA

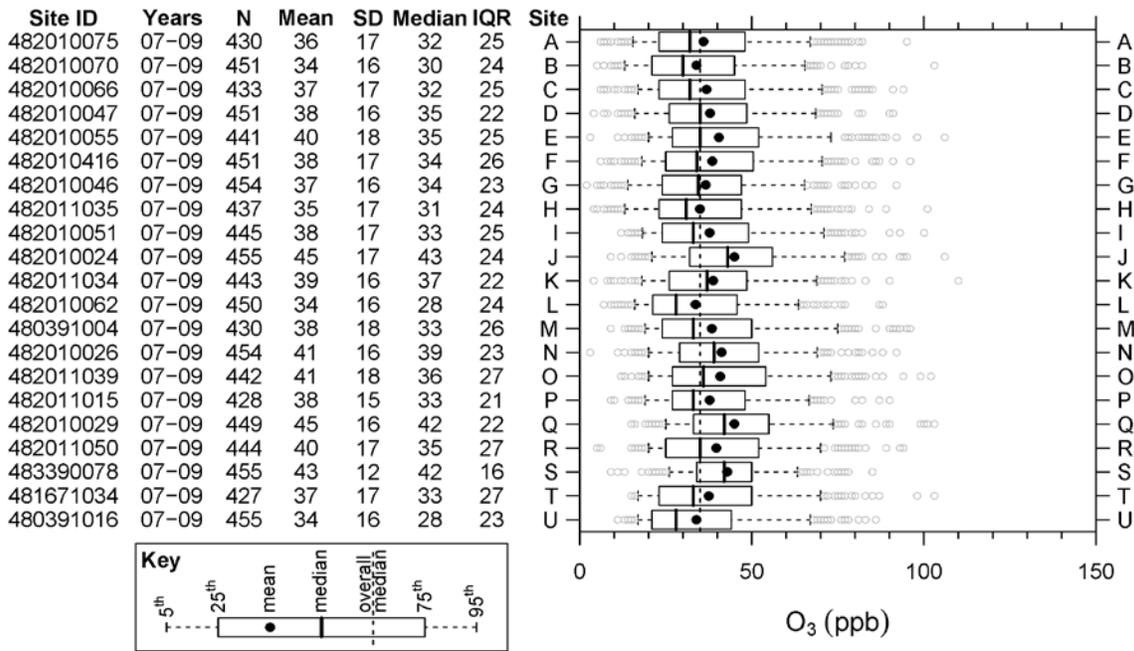


Figure 3-104 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Houston CSA.

Los Angeles CSA

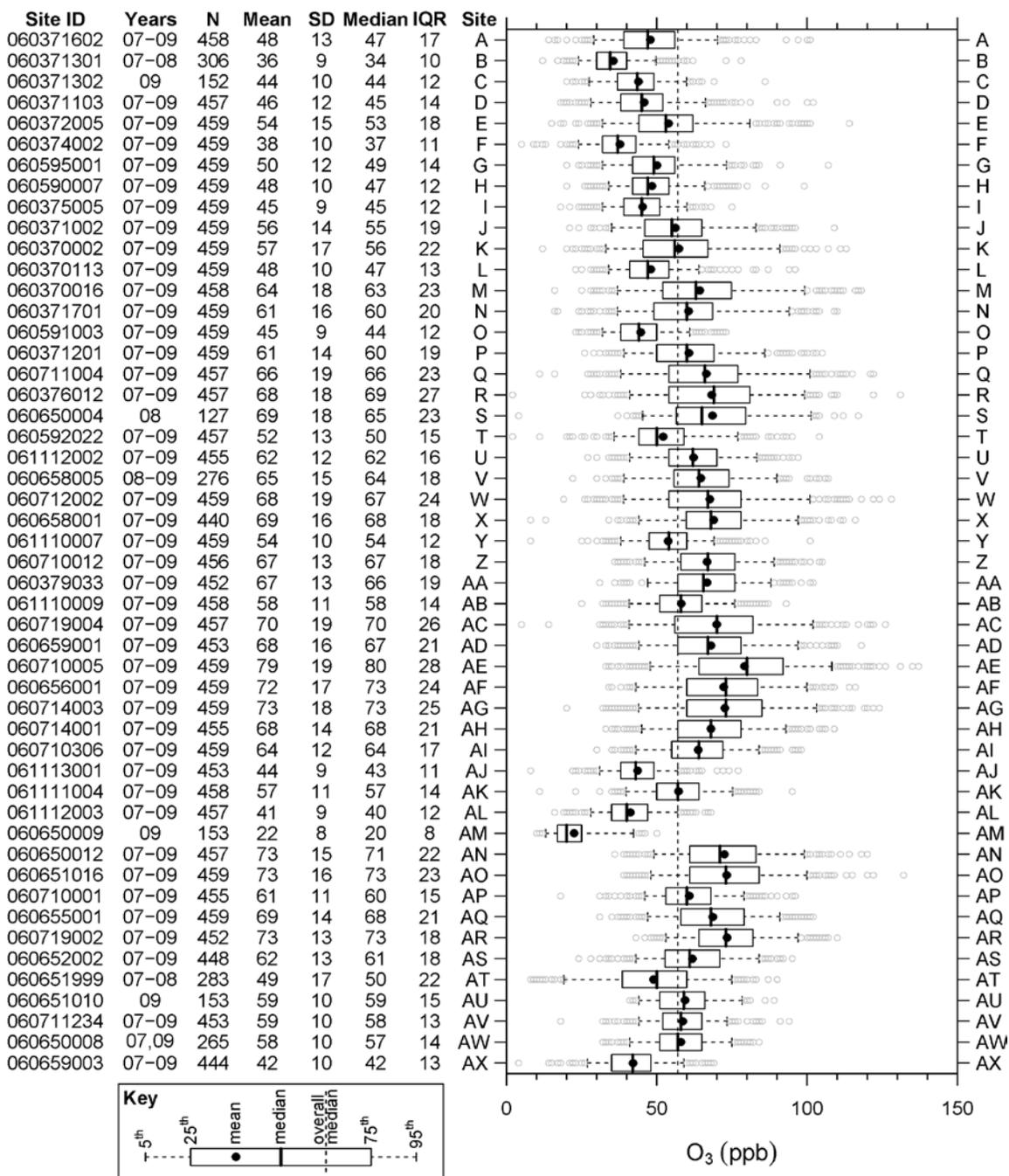


Figure 3-105 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Los Angeles CSA.

Minneapolis CSA

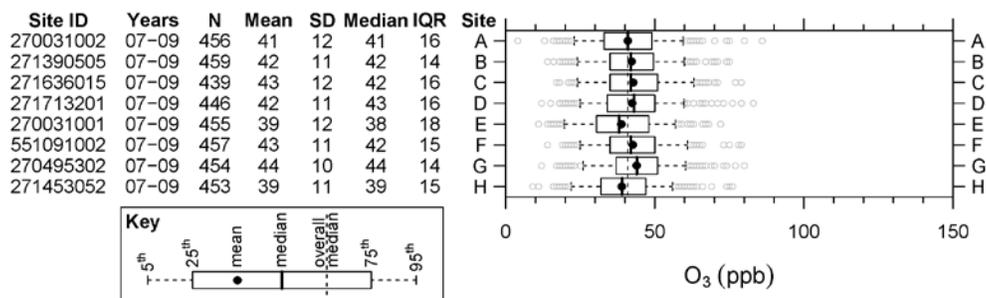


Figure 3-106 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Minneapolis CSA.

New York CSA

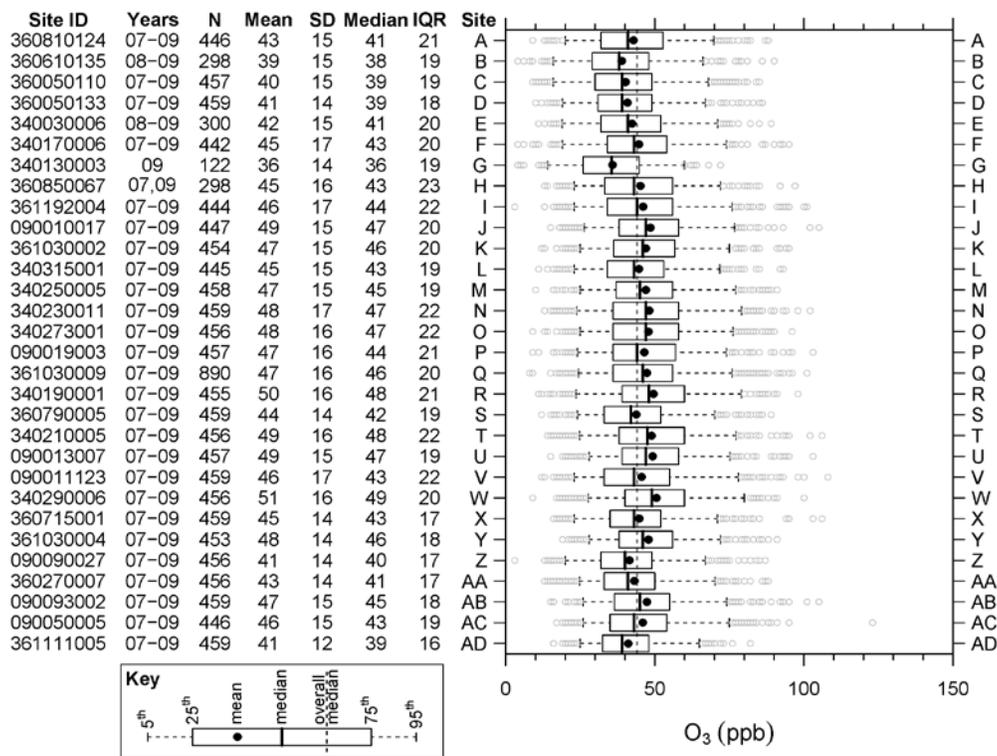


Figure 3-107 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the New York CSA.

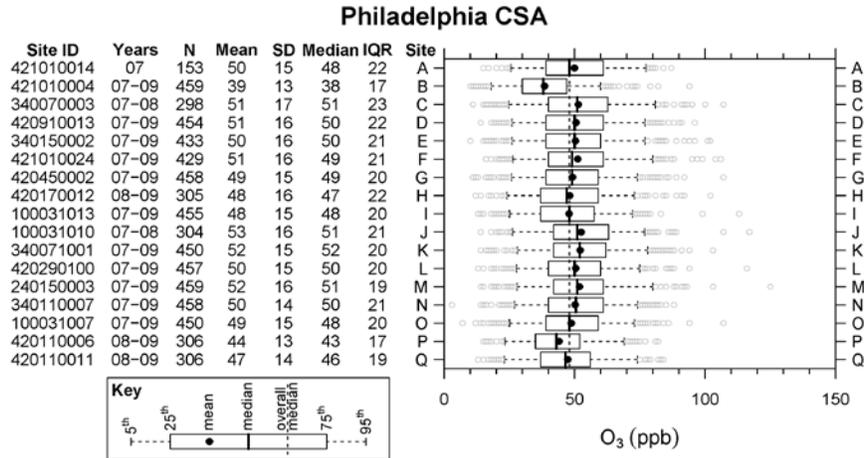


Figure 3-108 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Philadelphia CSA.

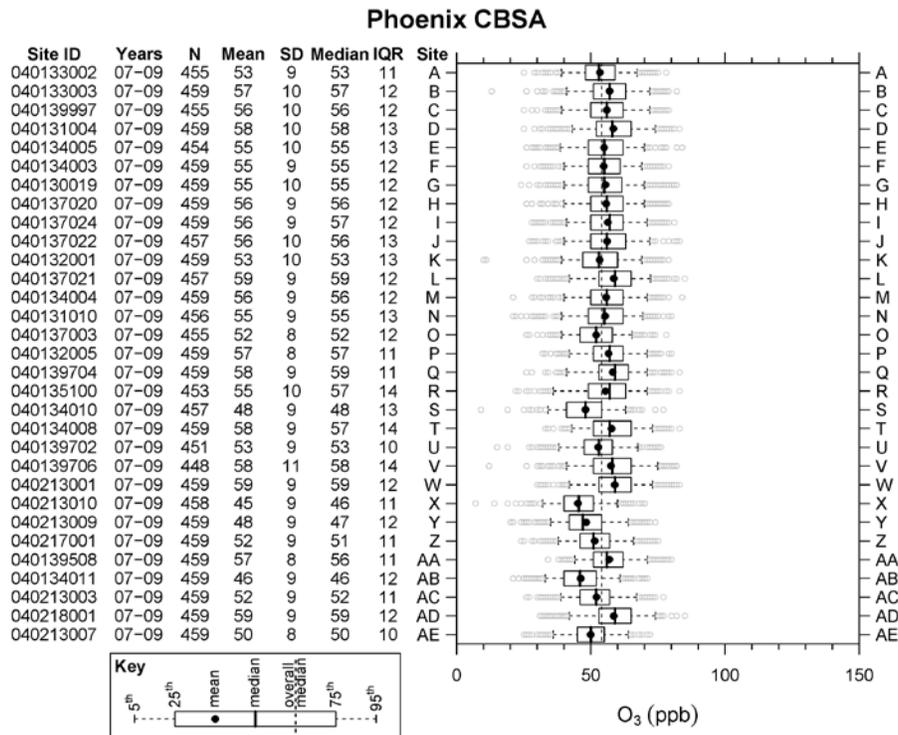


Figure 3-109 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Phoenix CBSA.

Pittsburgh CSA

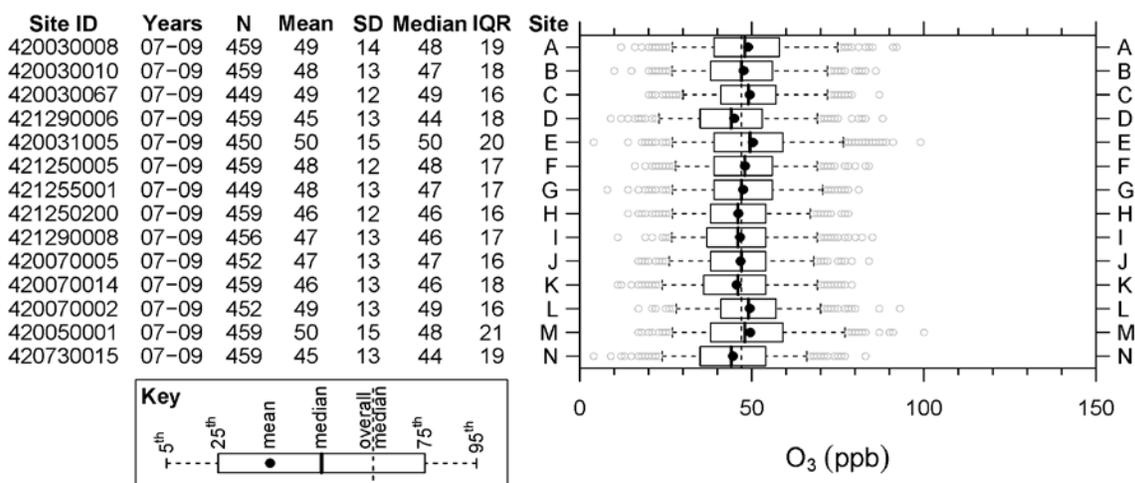


Figure 3-110 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Pittsburgh CSA.

Salt Lake City CSA

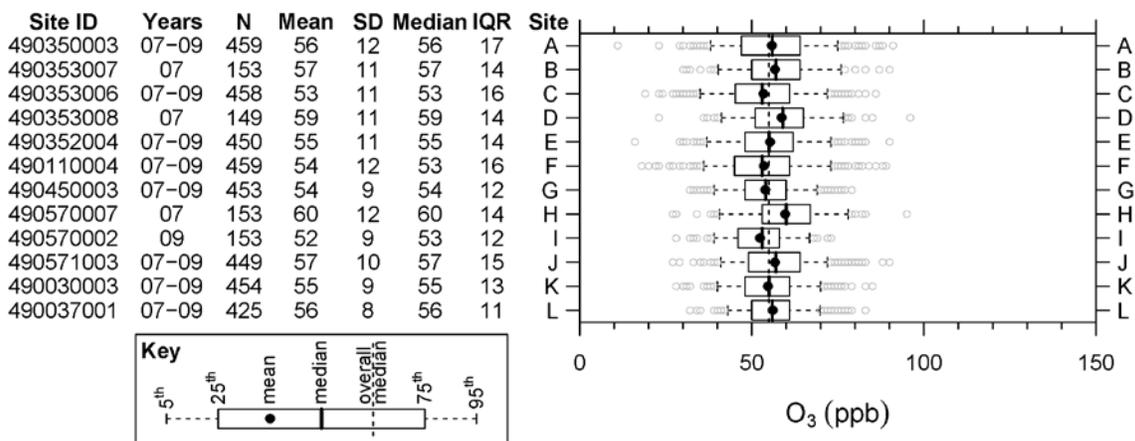


Figure 3-111 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Salt Lake City CSA.

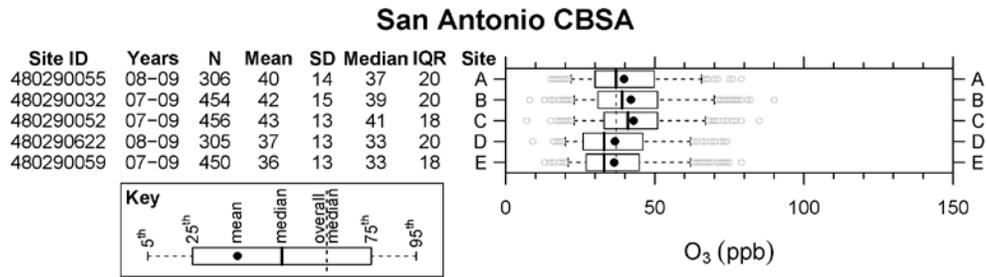


Figure 3-112 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the San Antonio CBSA.

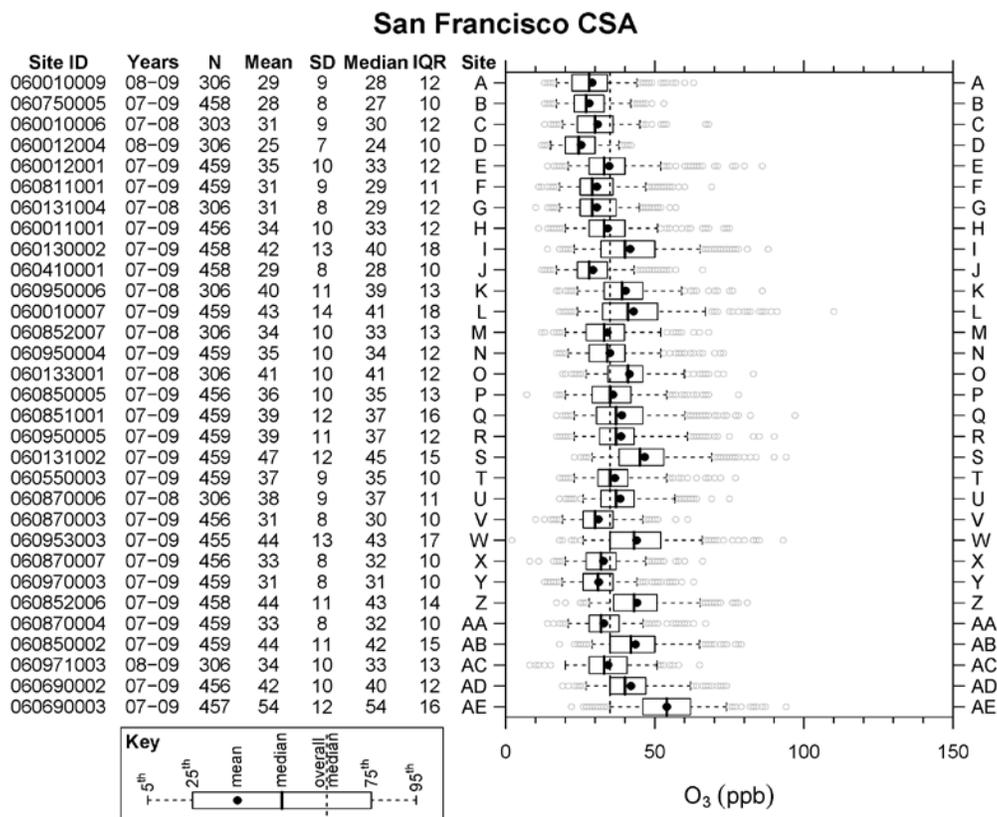


Figure 3-113 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the San Francisco CSA.

Seattle CSA

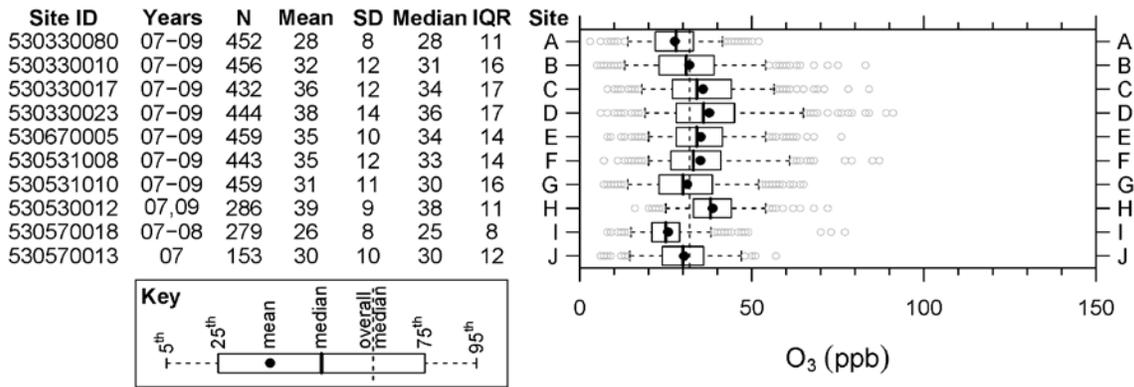


Figure 3-114 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Seattle CSA.

St. Louis CSA

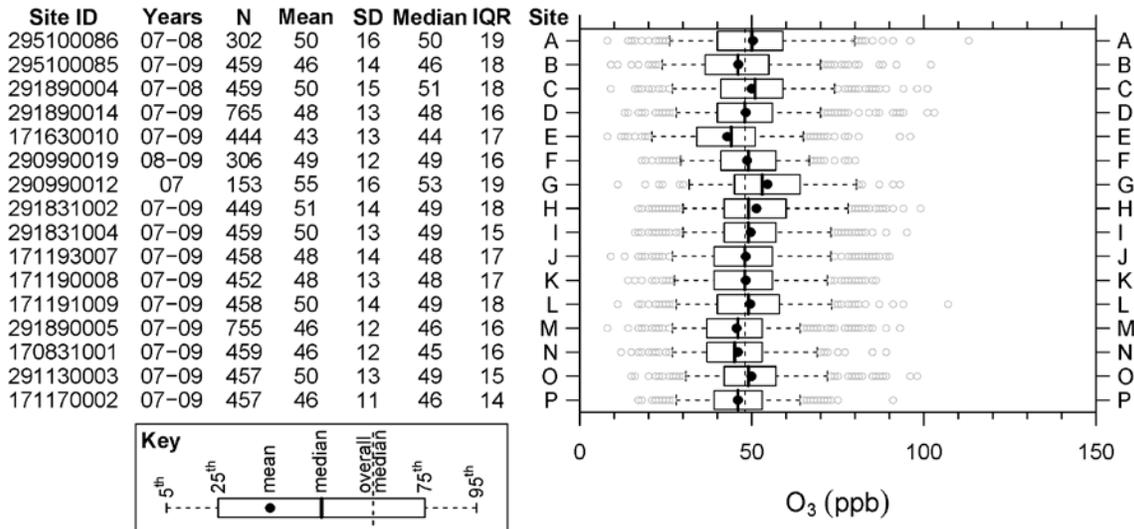
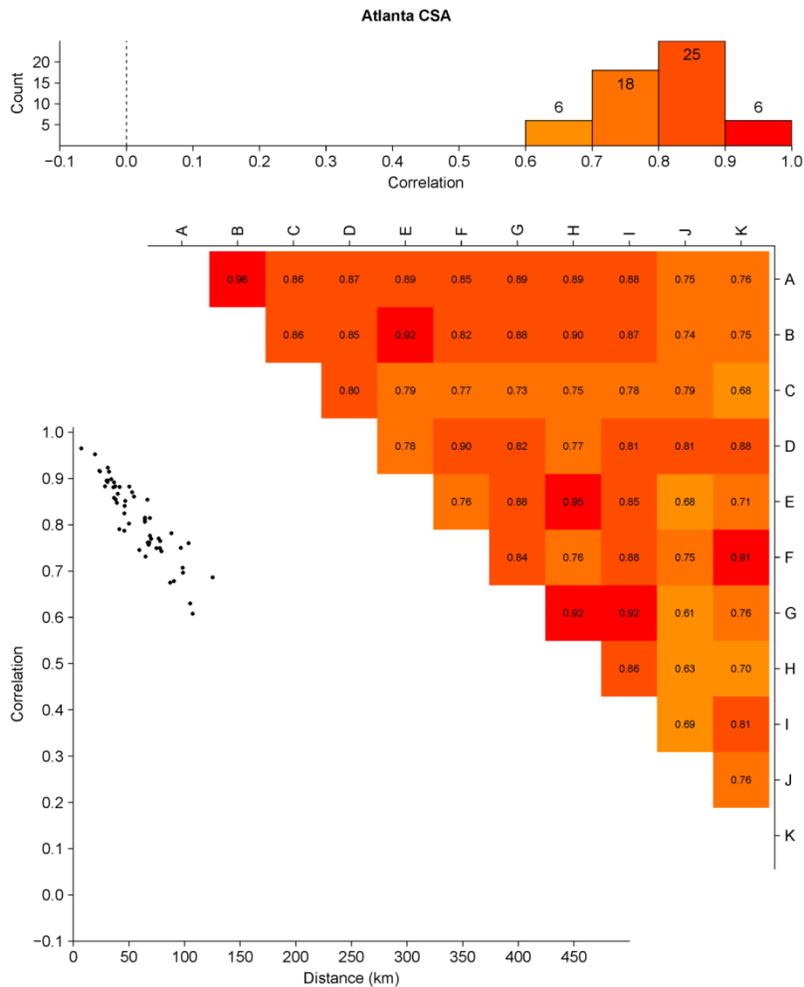


Figure 3-115 Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the St. Louis CSA.

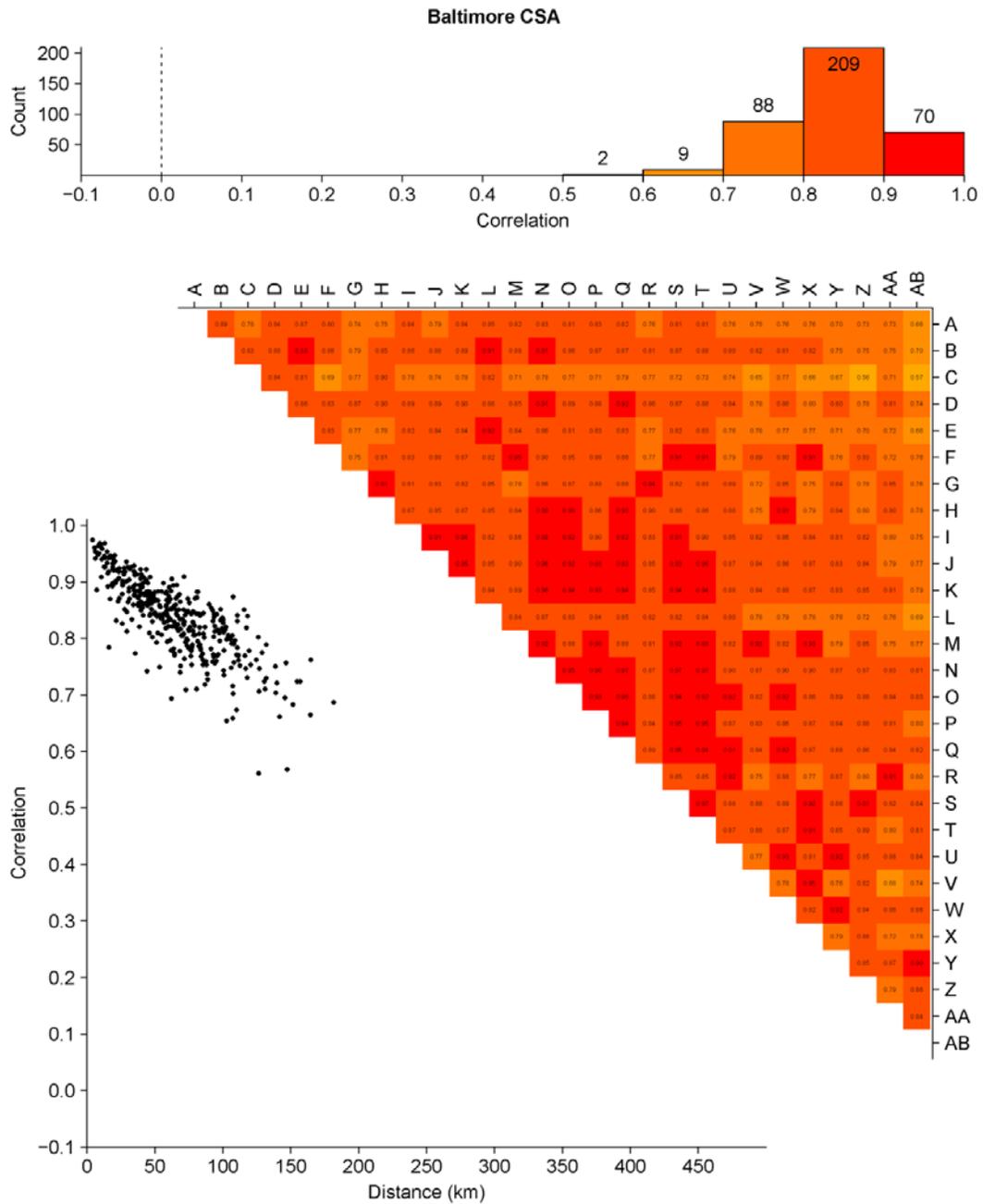
3.9.3 Ozone Concentration Relationships for the Urban Focus Cities

1 This section contains histograms and contour matrices of the Pearson correlation
 2 coefficient (R) and the coefficient of divergence (COD) between 8-h daily max O₃
 3 concentrations from each monitor pair within the 20 urban focus cities discussed in
 4 Section 3.6.2.1. These figures also contain scatter plots of R and COD as a function of
 5 straight-line distance between monitor pairs.



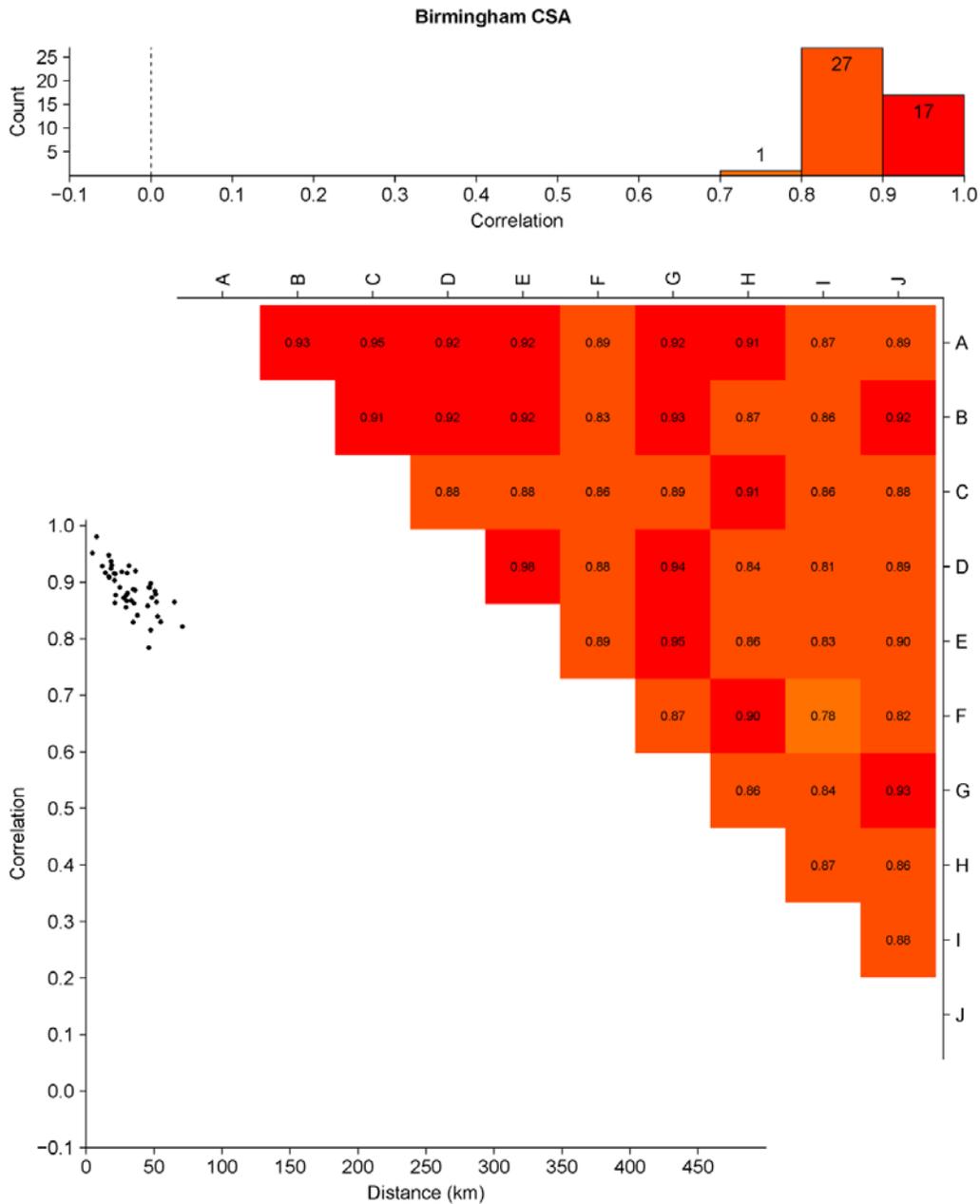
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-116 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



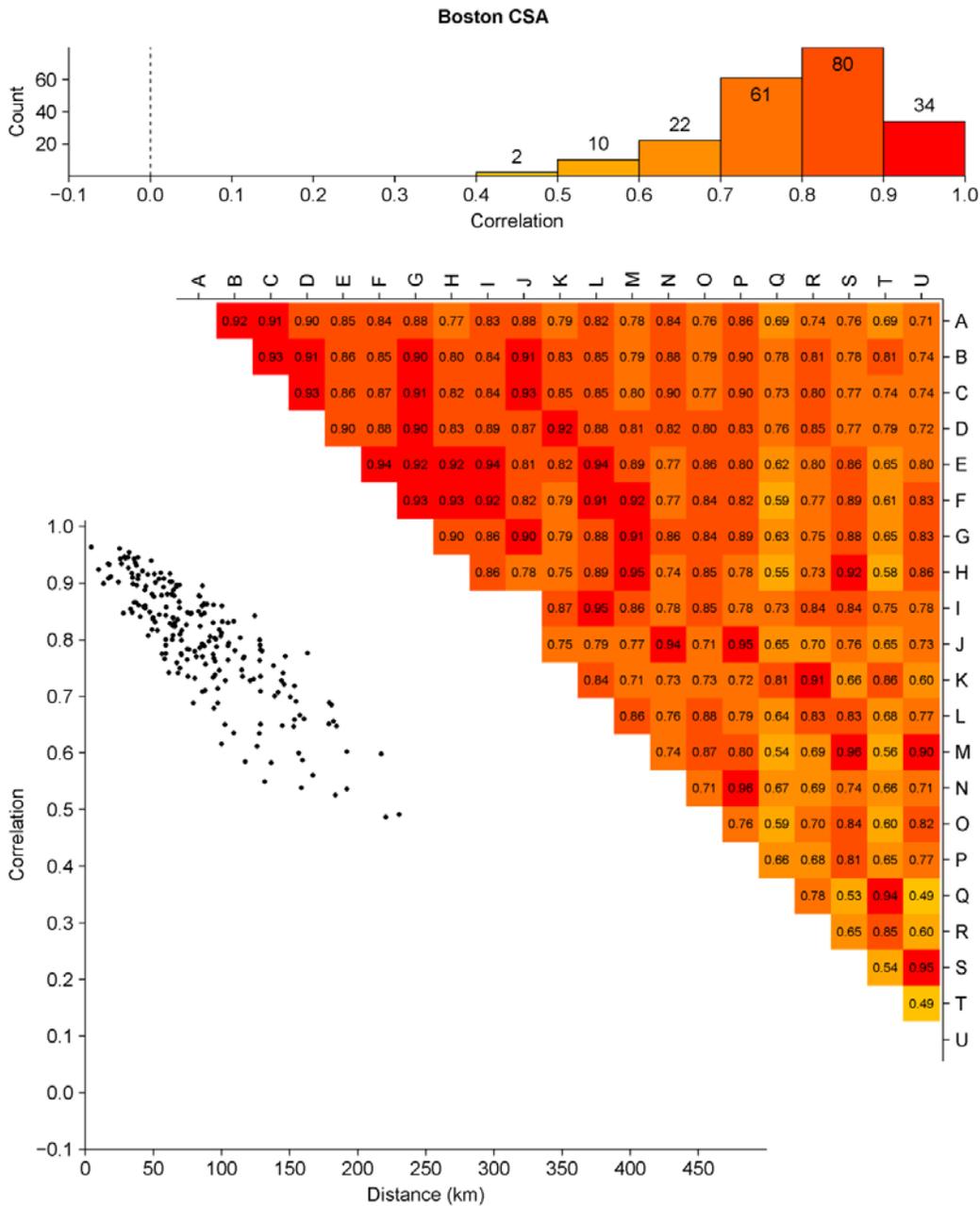
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-117 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Baltimore CSA.



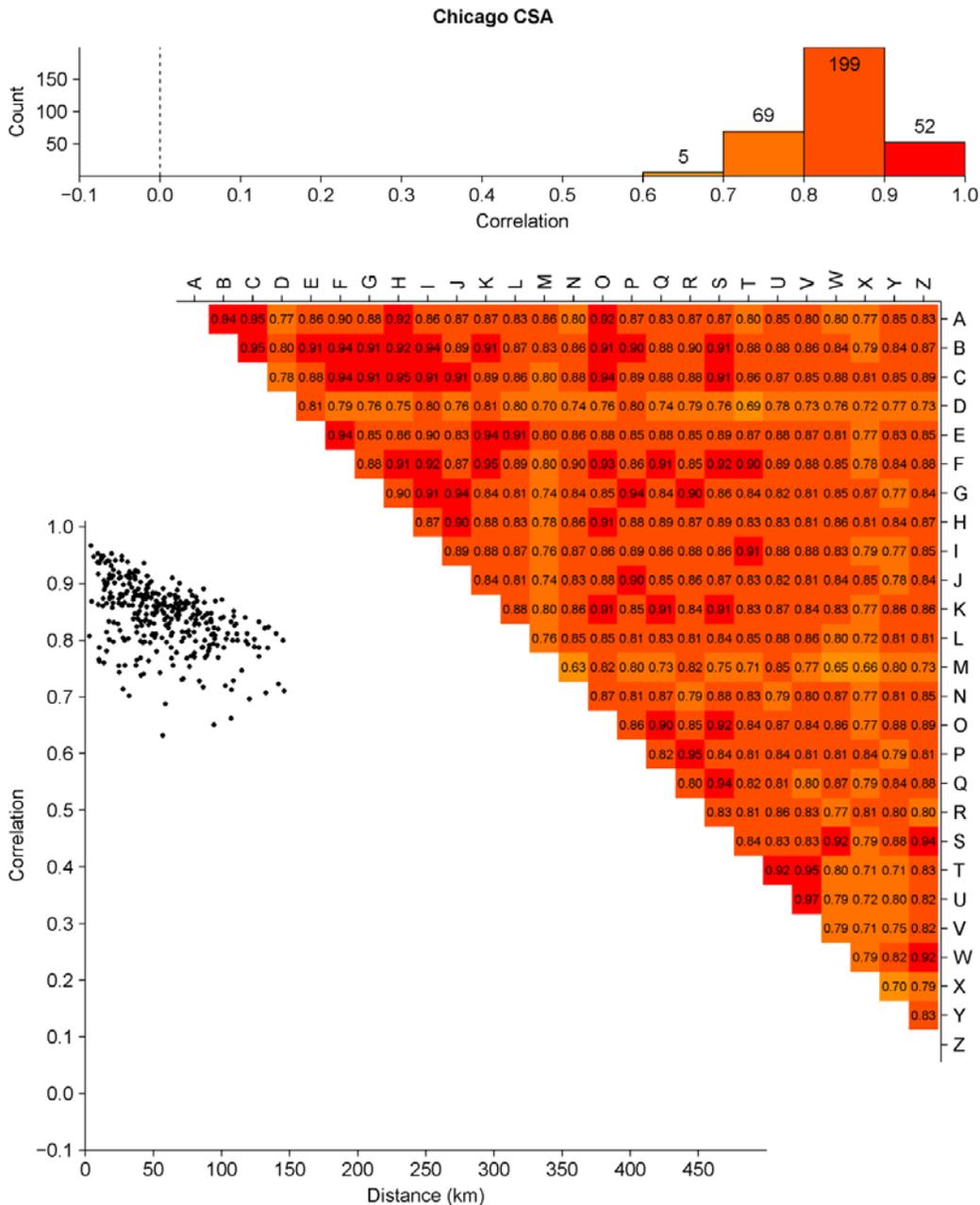
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-118 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Birmingham CSA.



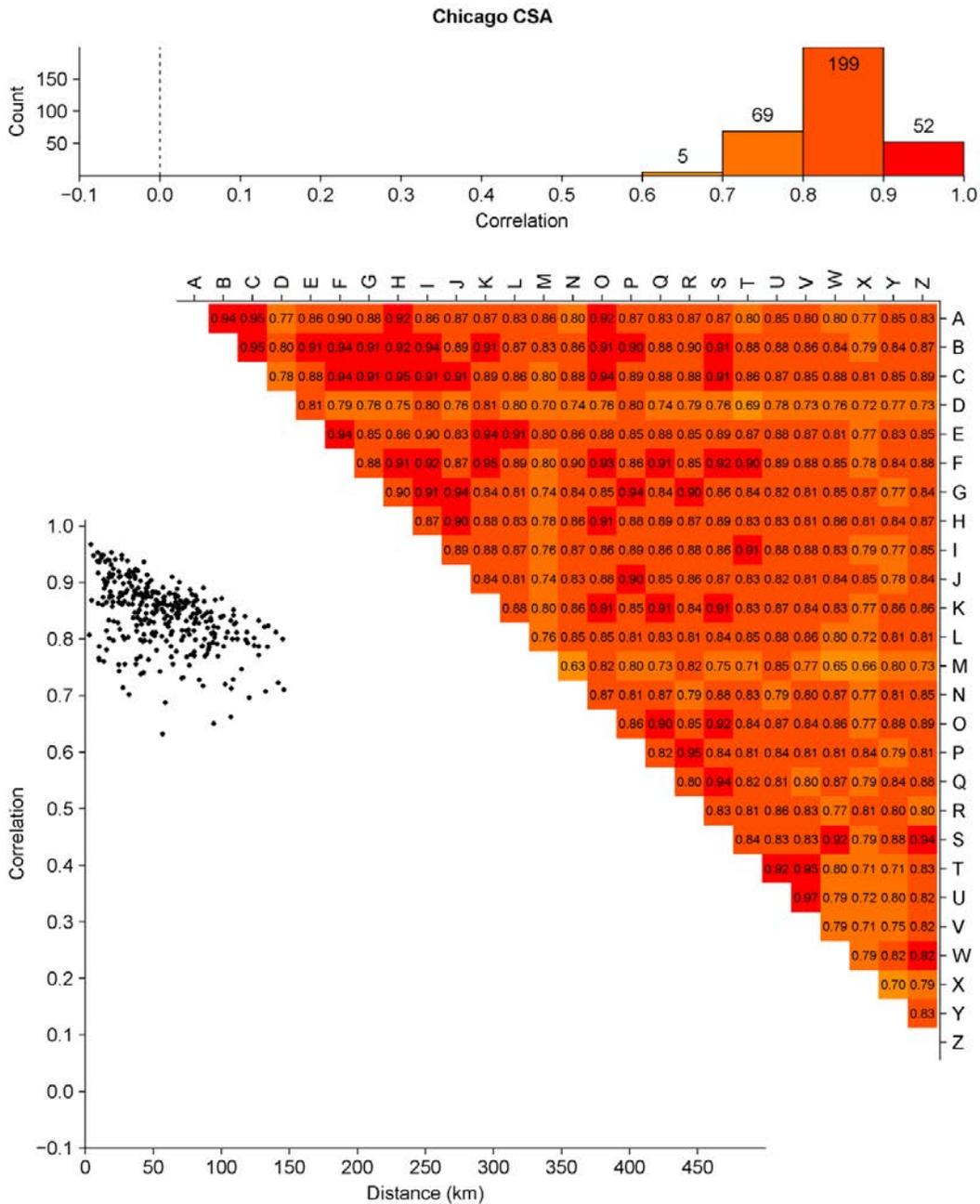
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-119 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.



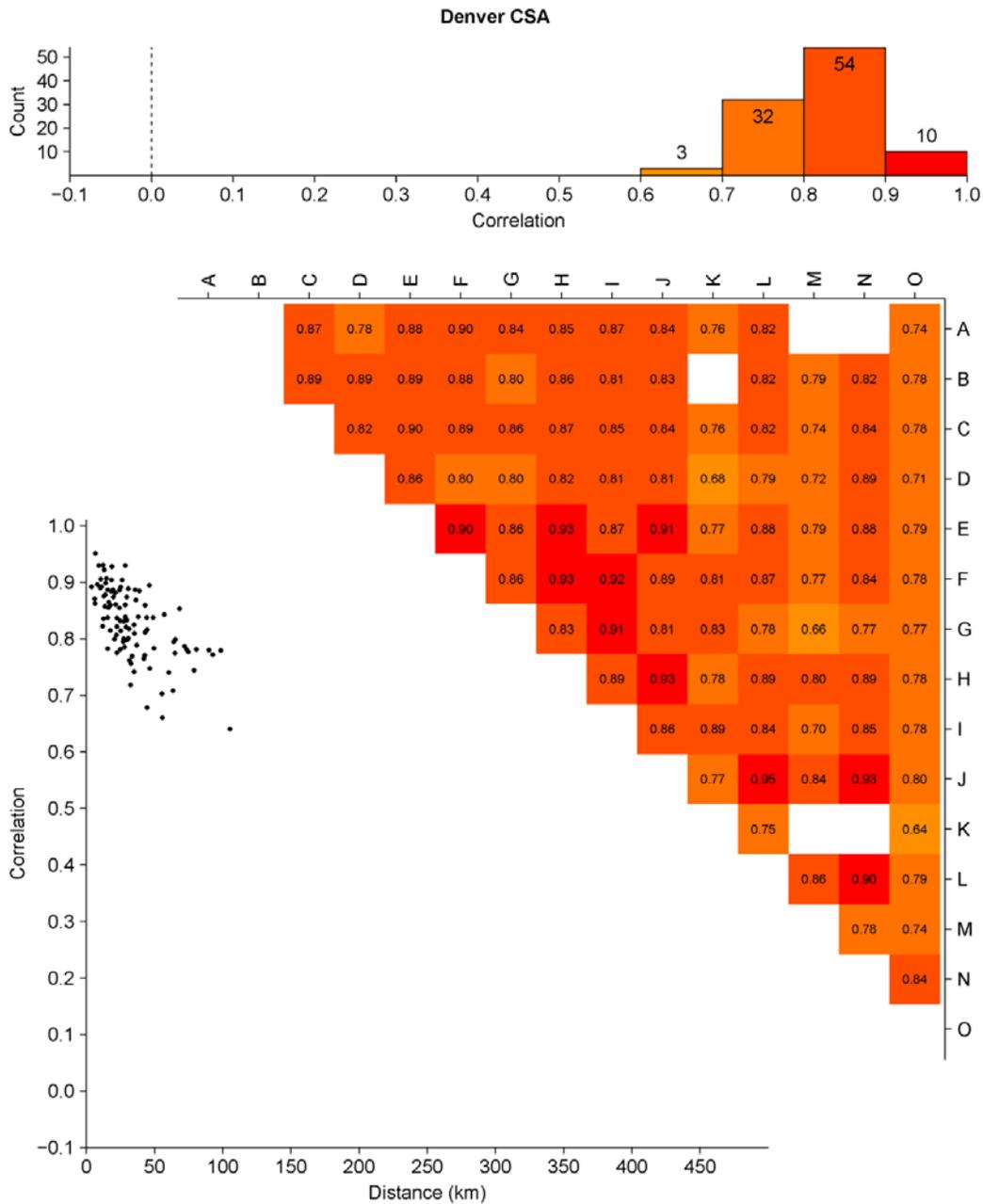
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-120 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Chicago CSA.



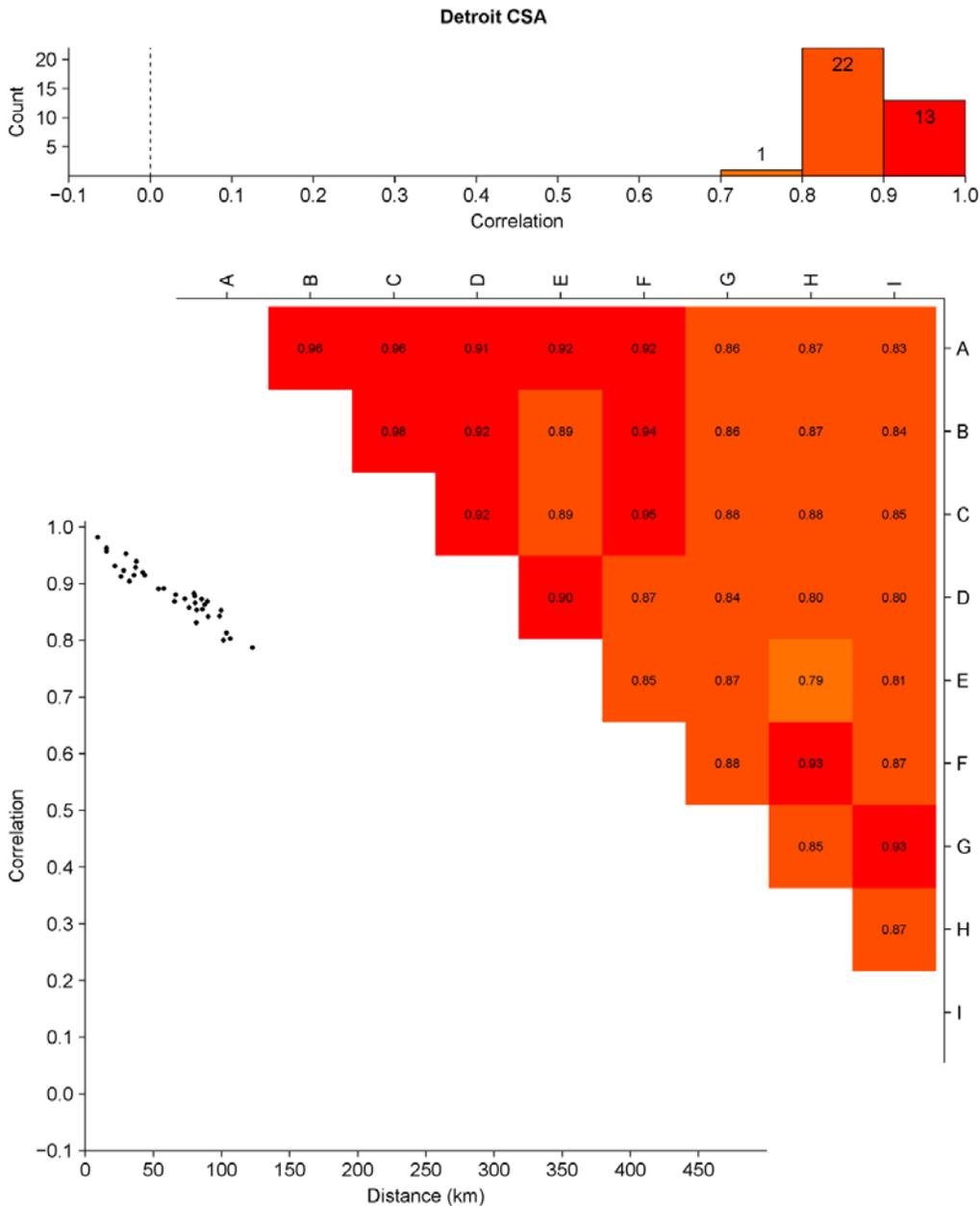
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-121 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Dallas CSA.



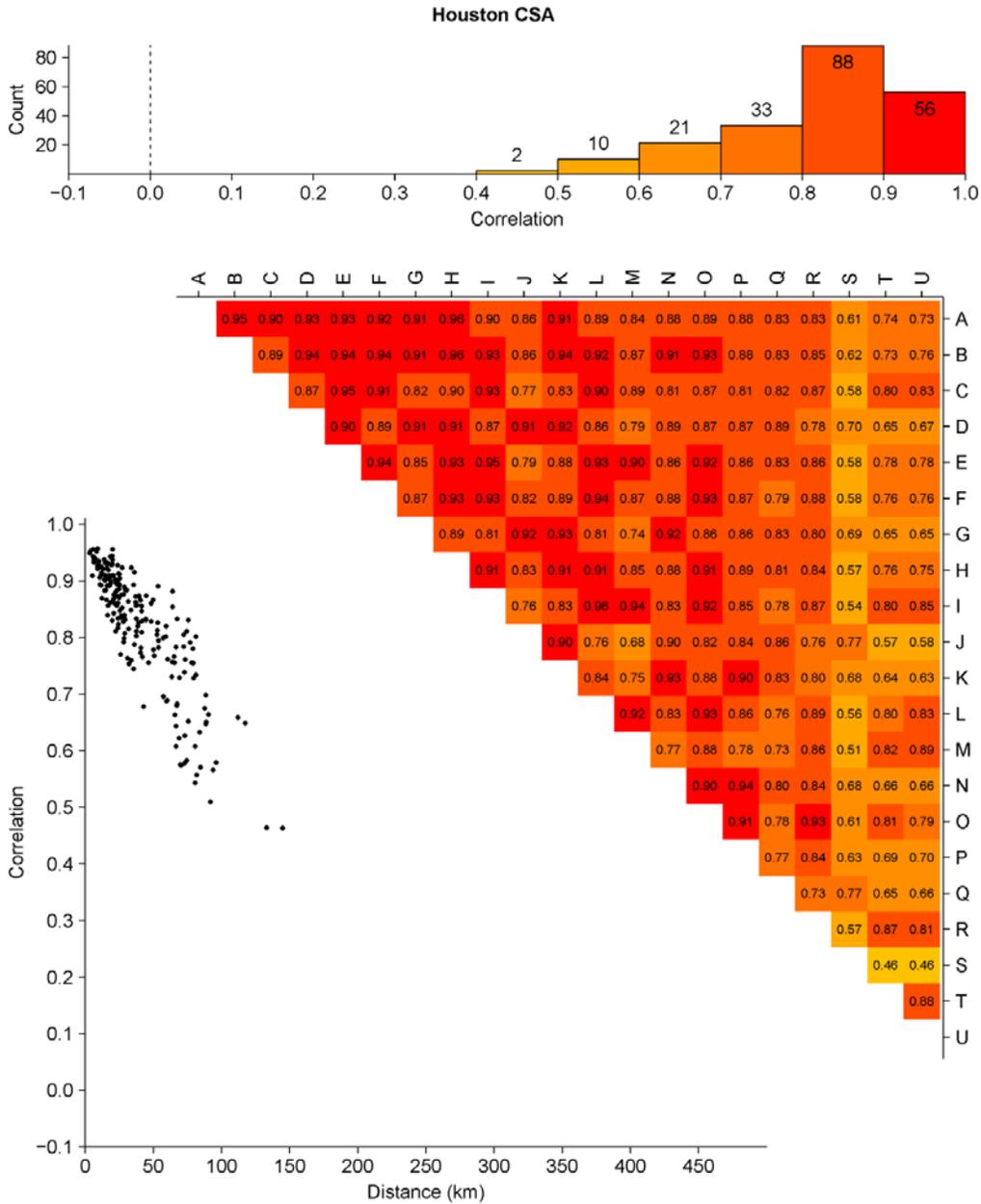
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-122 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Denver CSA.



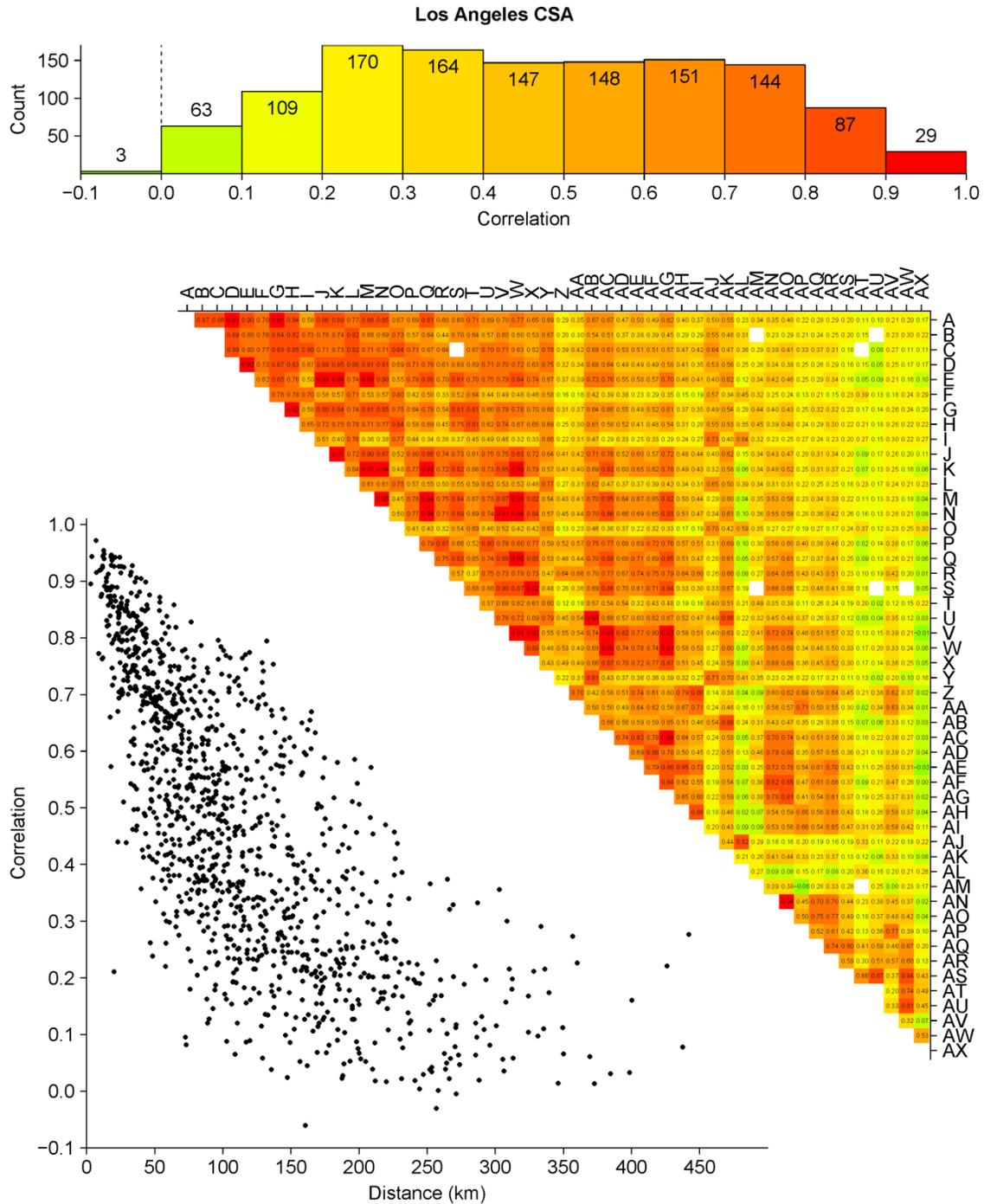
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-123 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Detroit CSA.



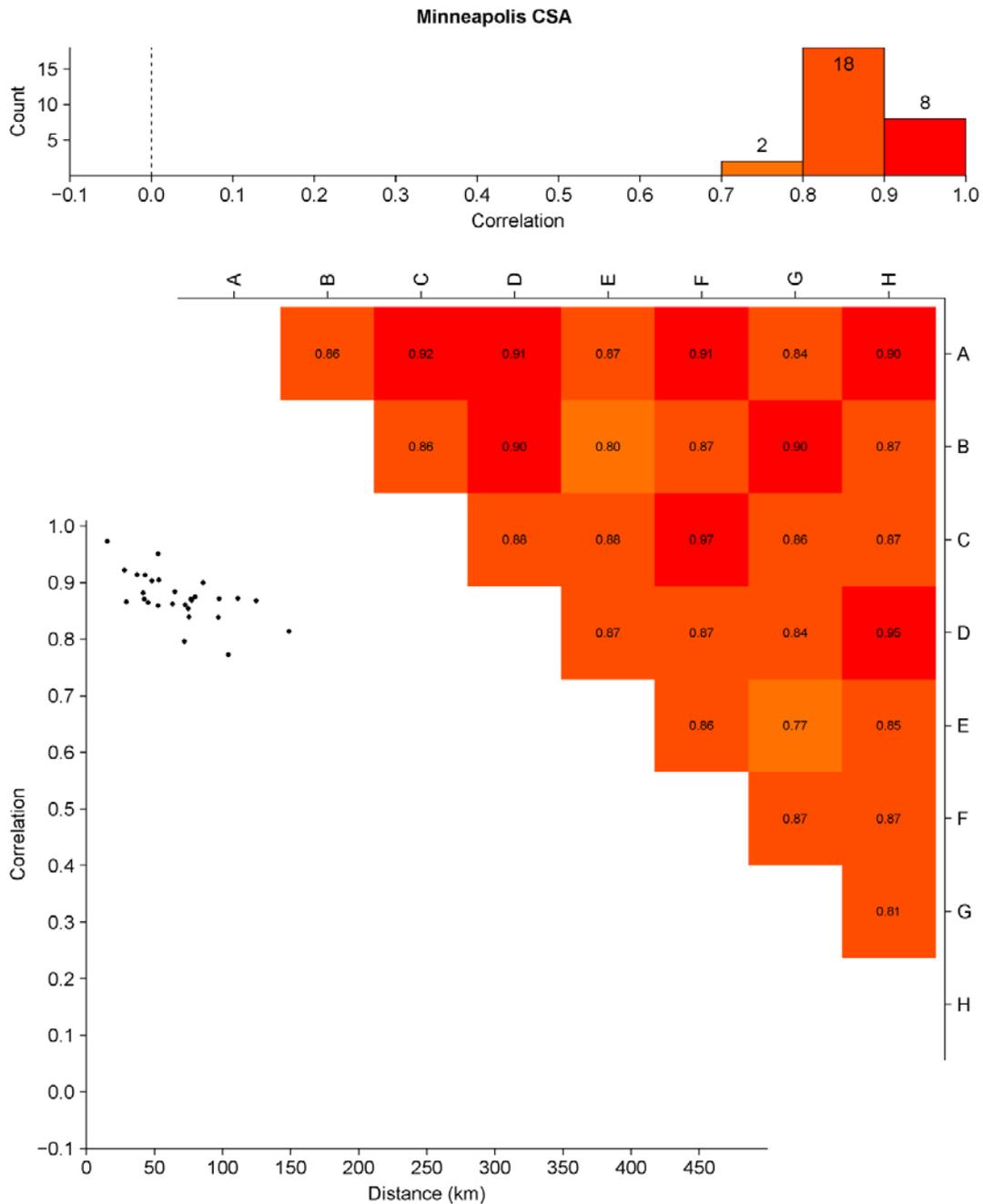
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-124 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Houston CSA.



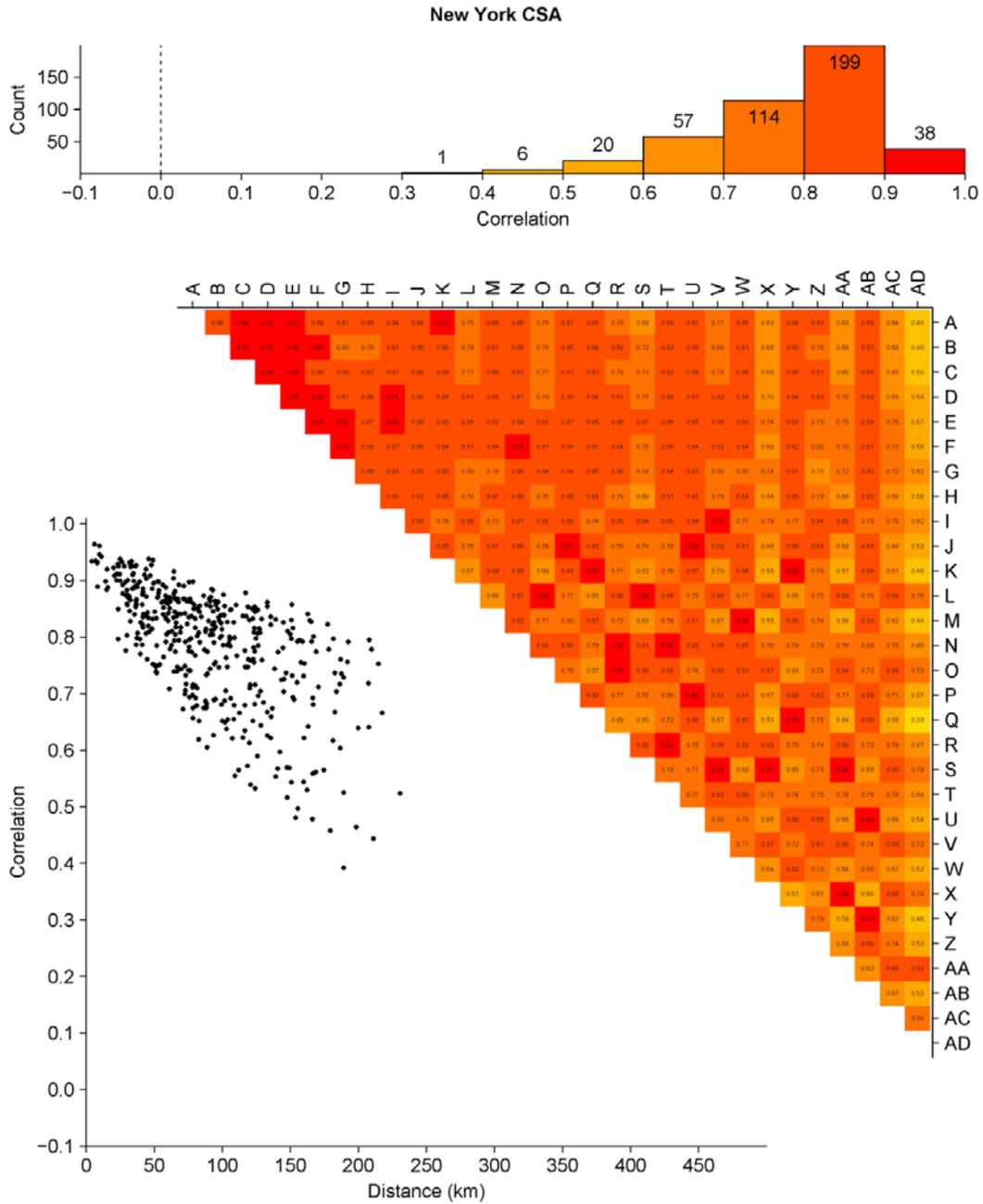
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-125 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA.



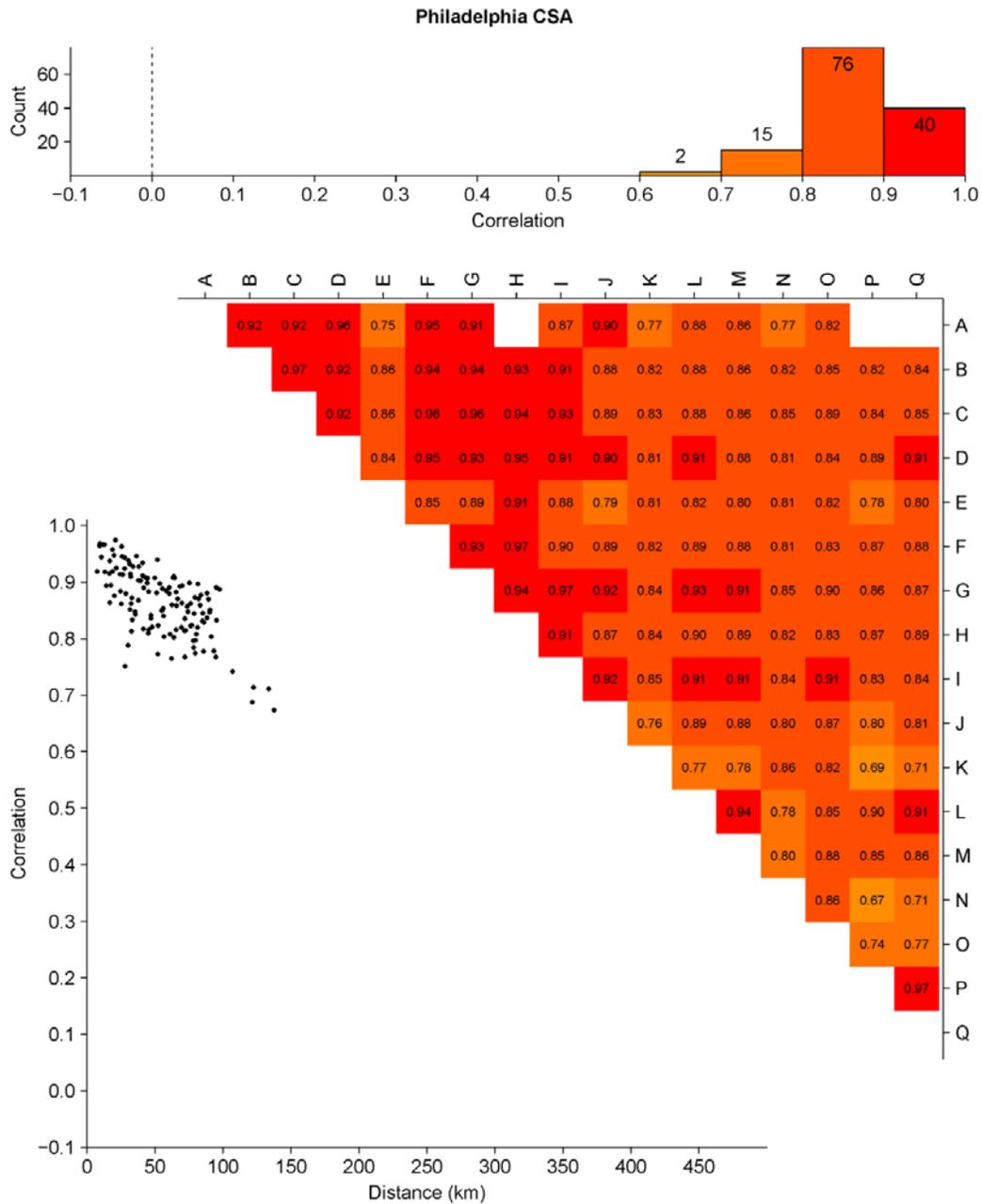
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-126 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Minneapolis CSA.



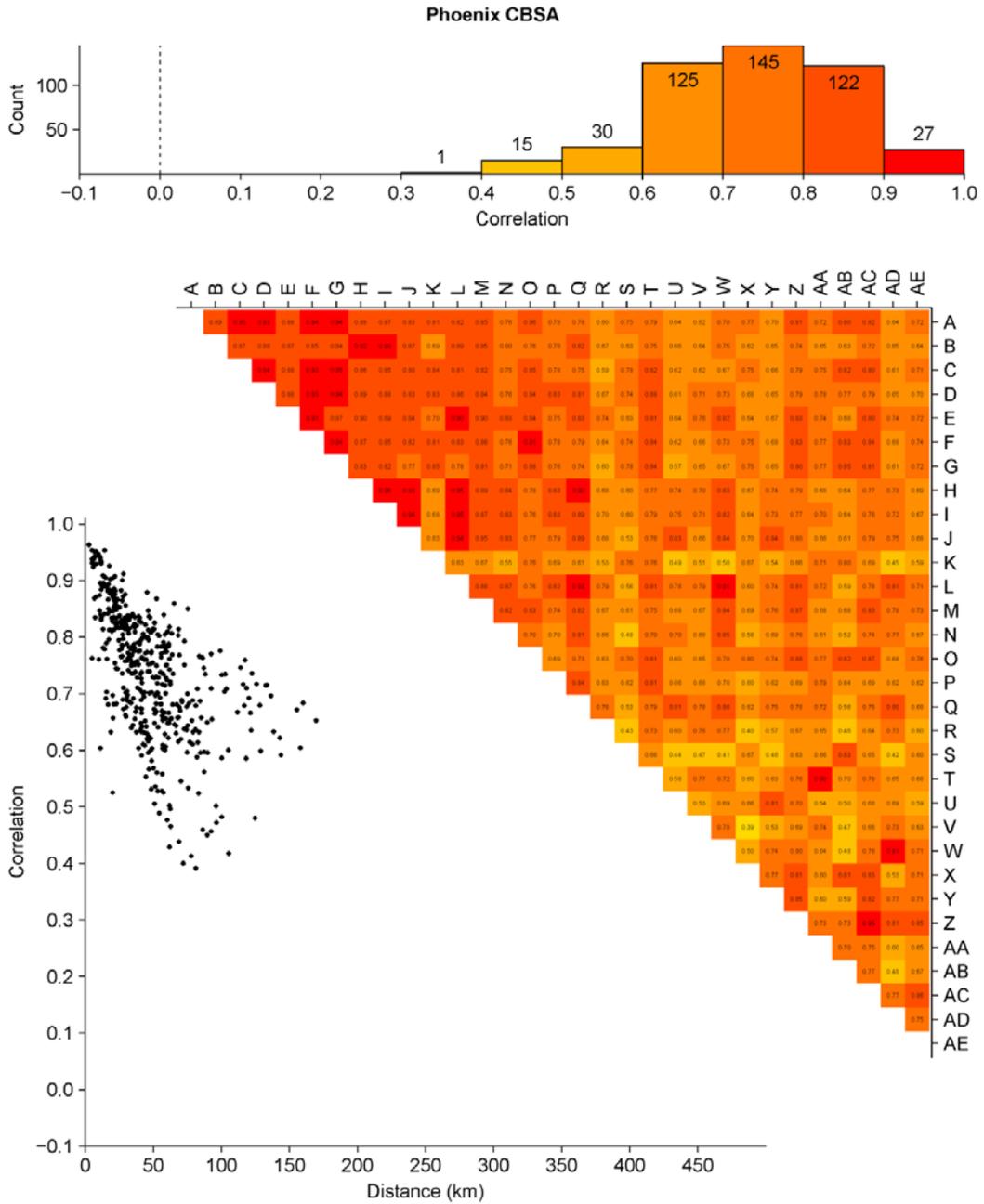
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-127 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the New York CSA.



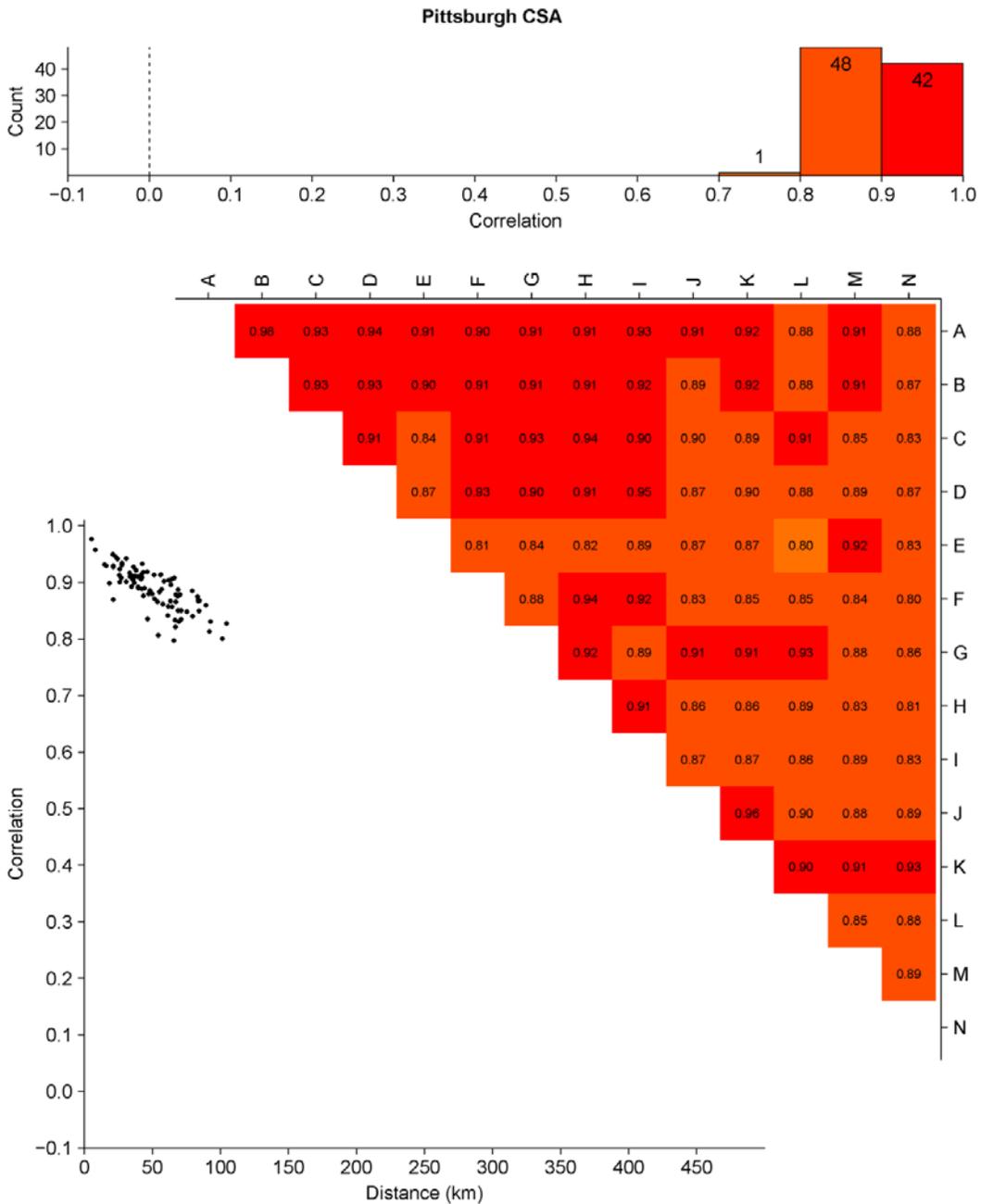
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-128 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Philadelphia CSA.



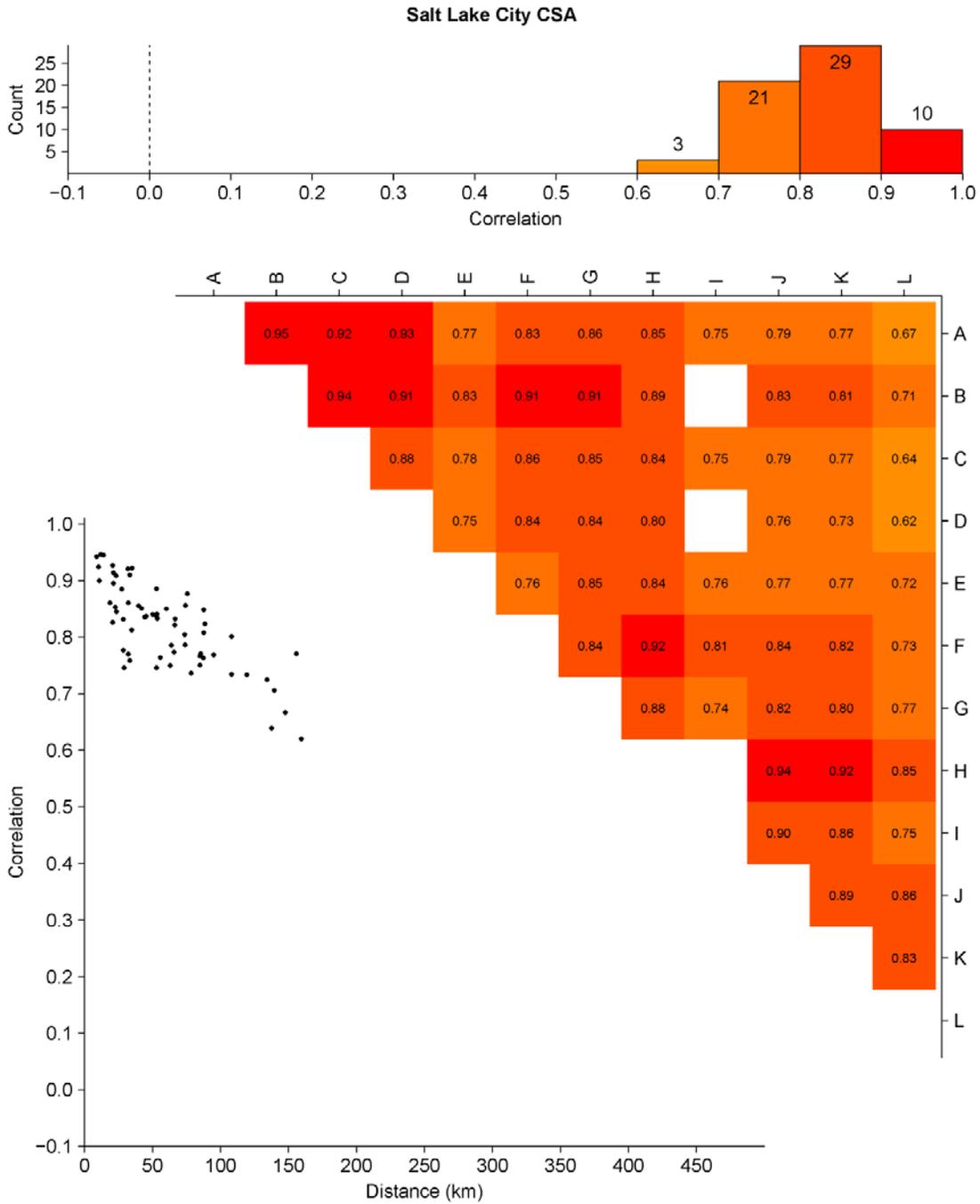
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-129 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Phoenix CBSA.



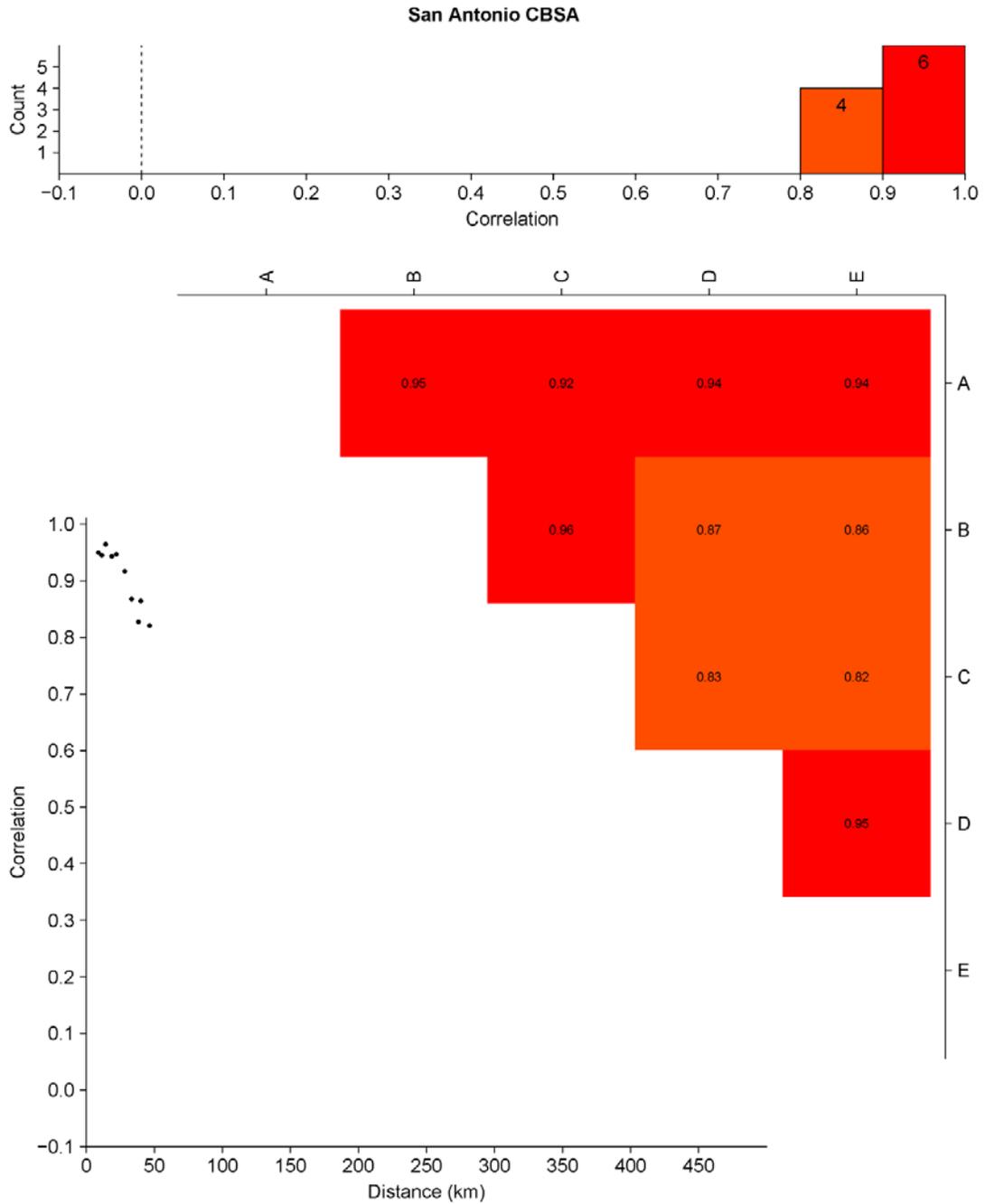
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-130 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Pittsburgh CSA.



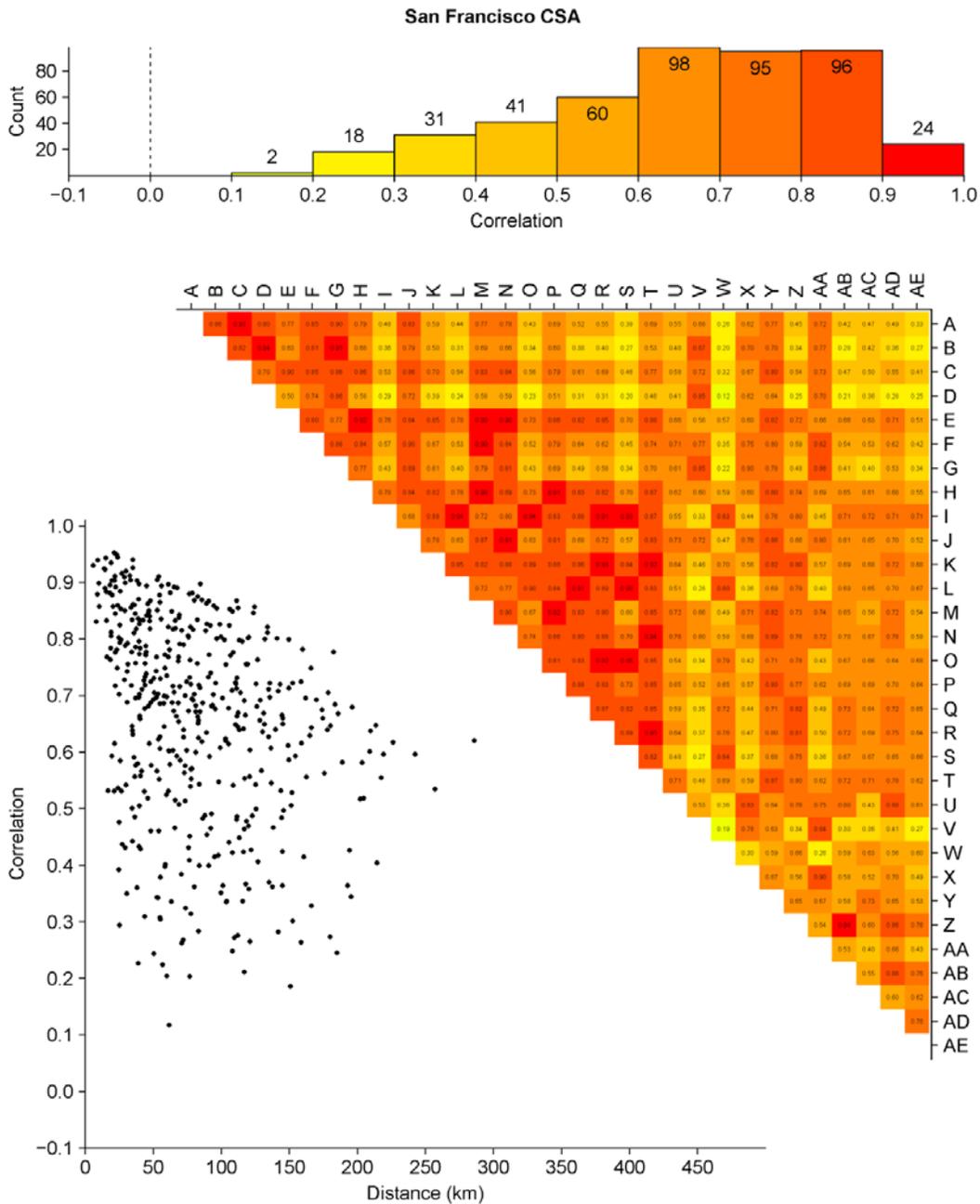
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-131 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Salt Lake City CSA.



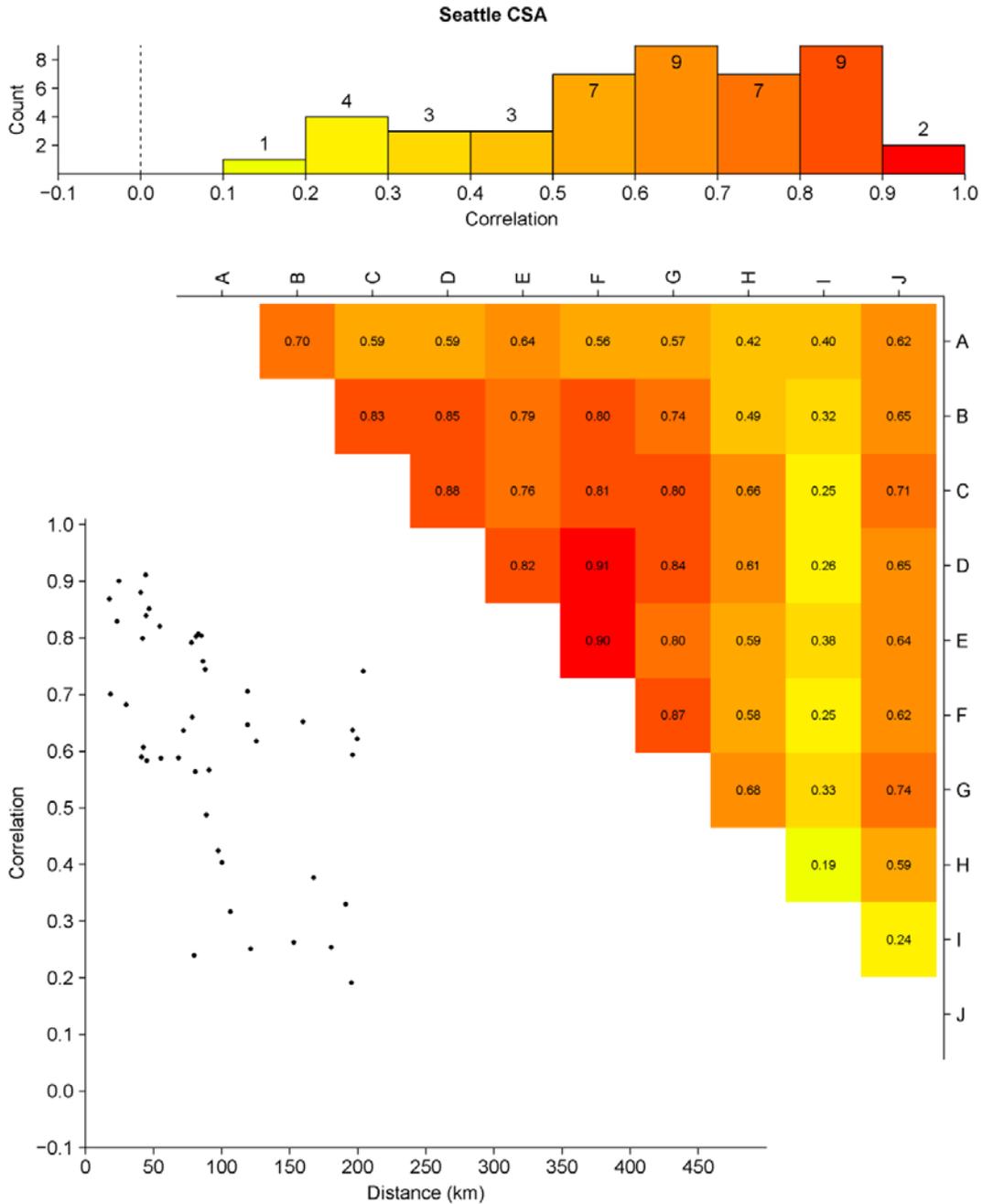
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-132 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Antonio CBSA.



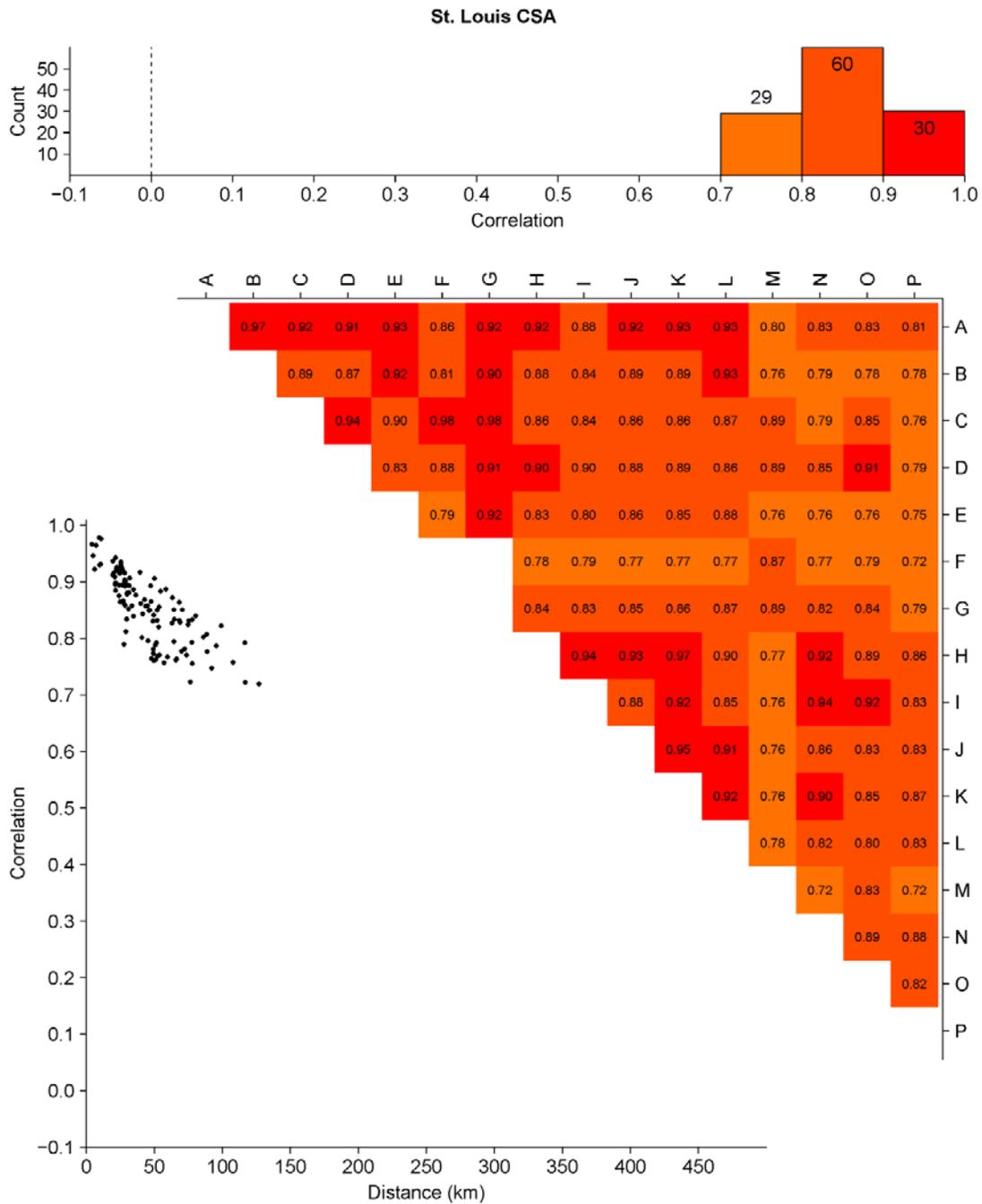
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-133 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Francisco CSA.



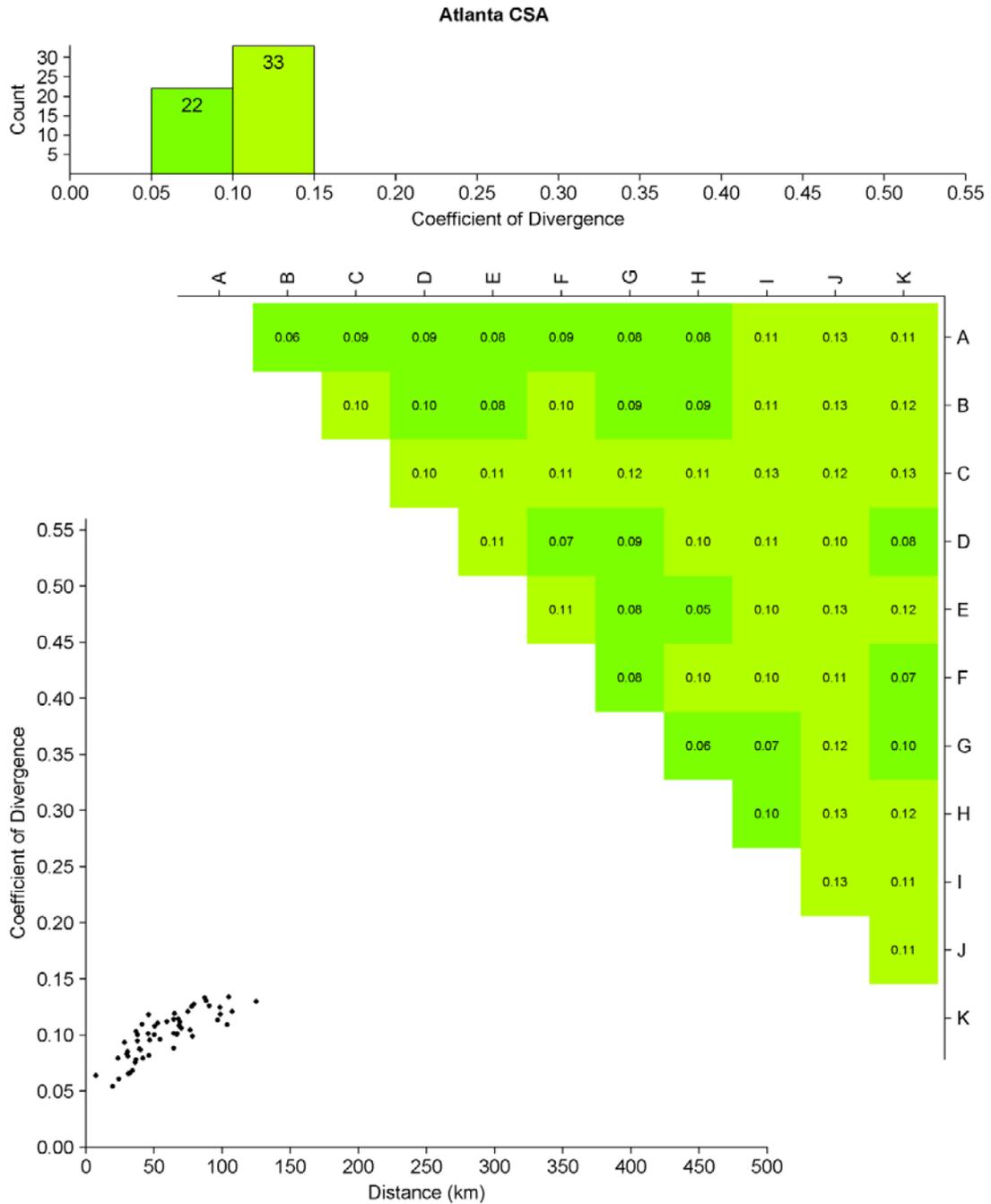
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-134 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Seattle CSA.



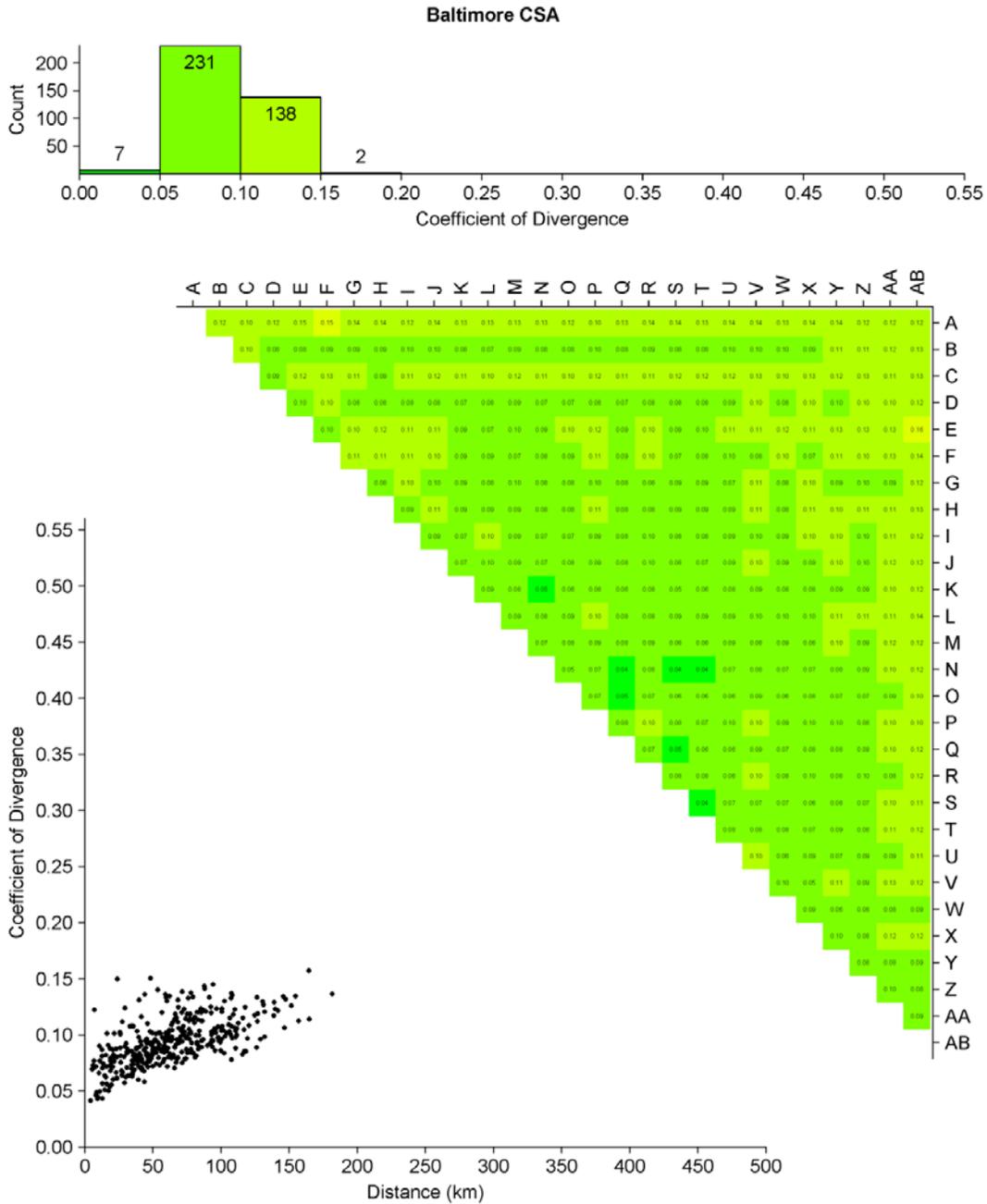
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-135 Pair-wise monitor correlation coefficients (R) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the St. Louis CSA.



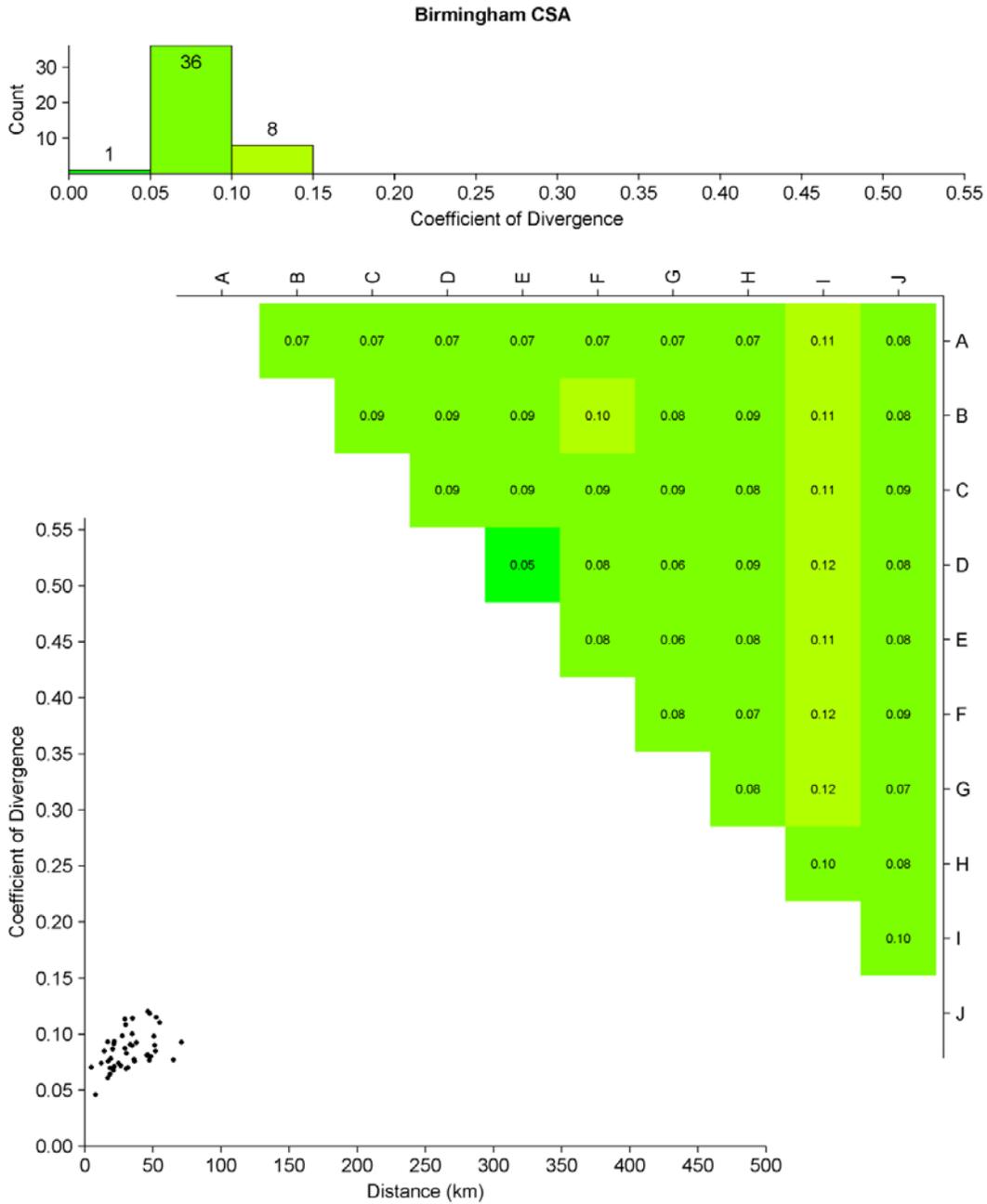
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-136 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA.



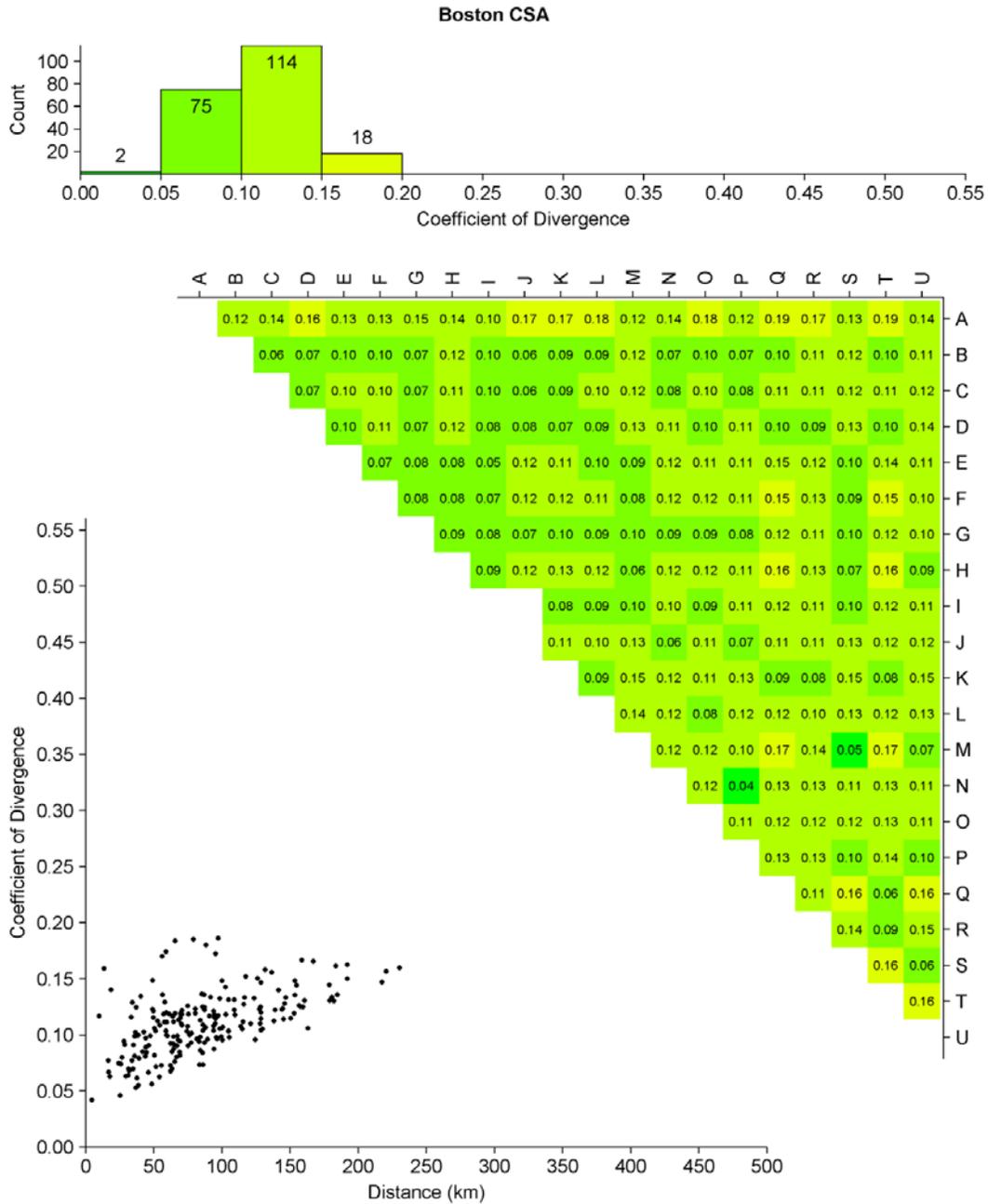
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-137 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Baltimore CSA.



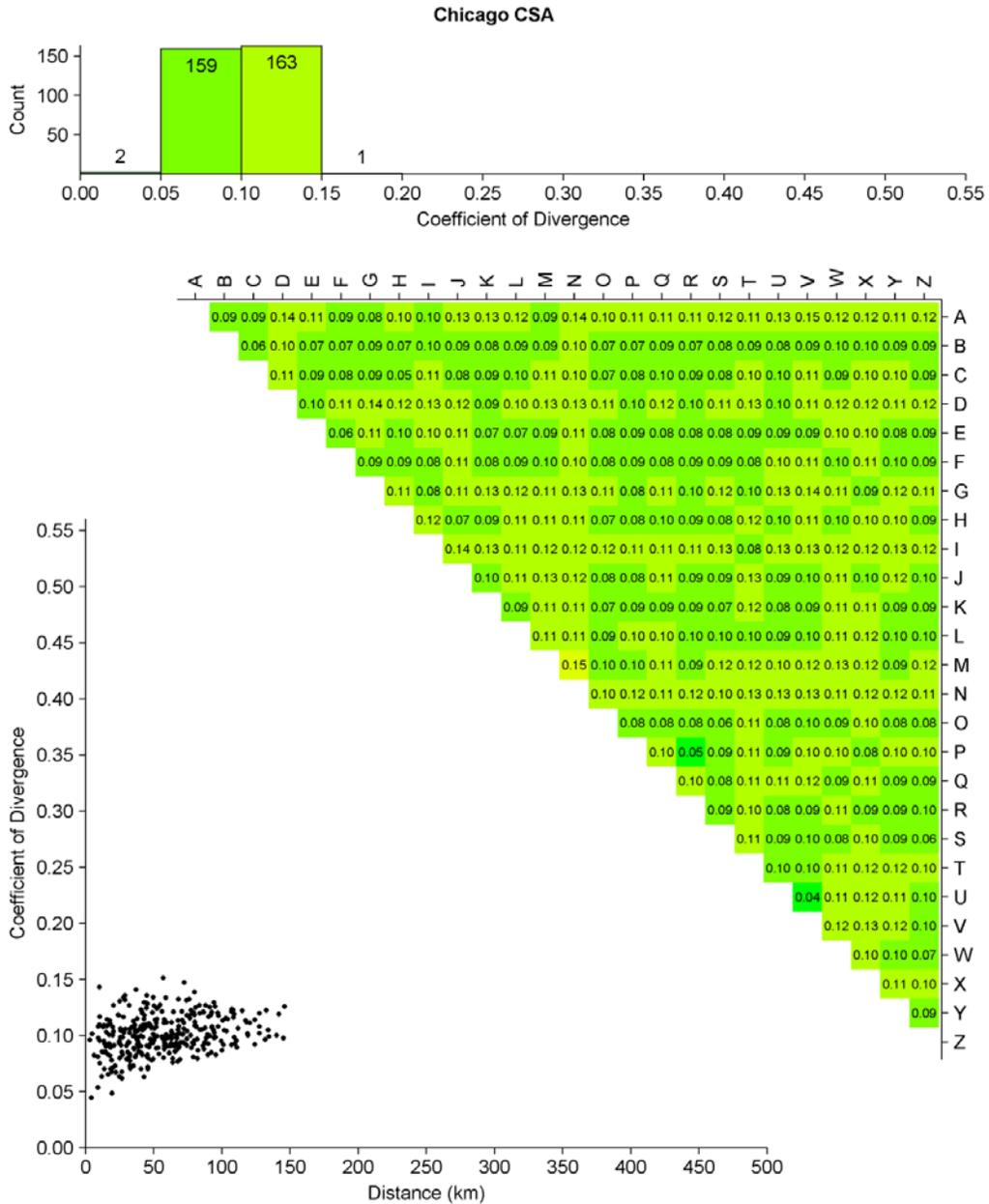
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-138 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Birmingham CSA.



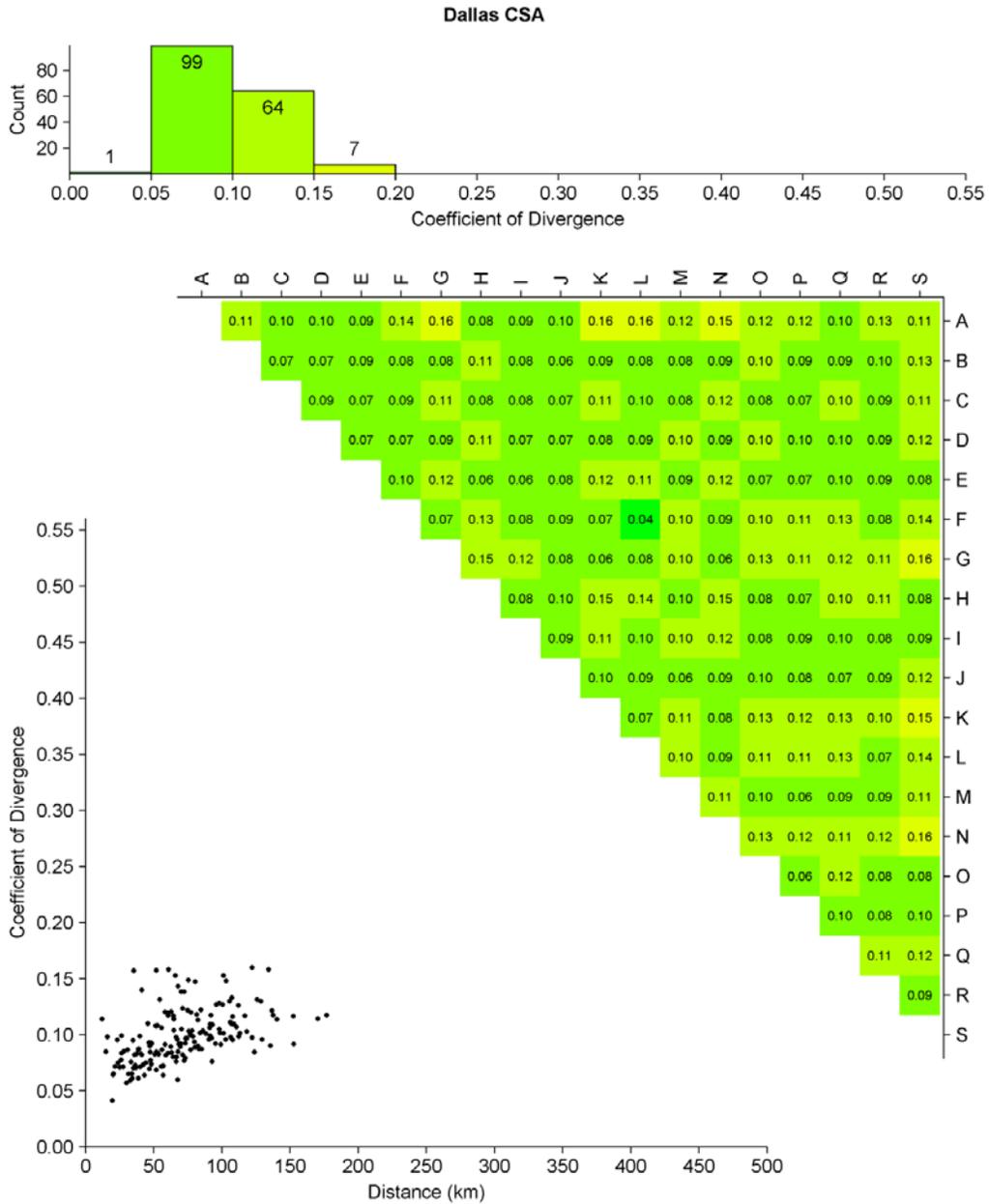
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-139 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA.



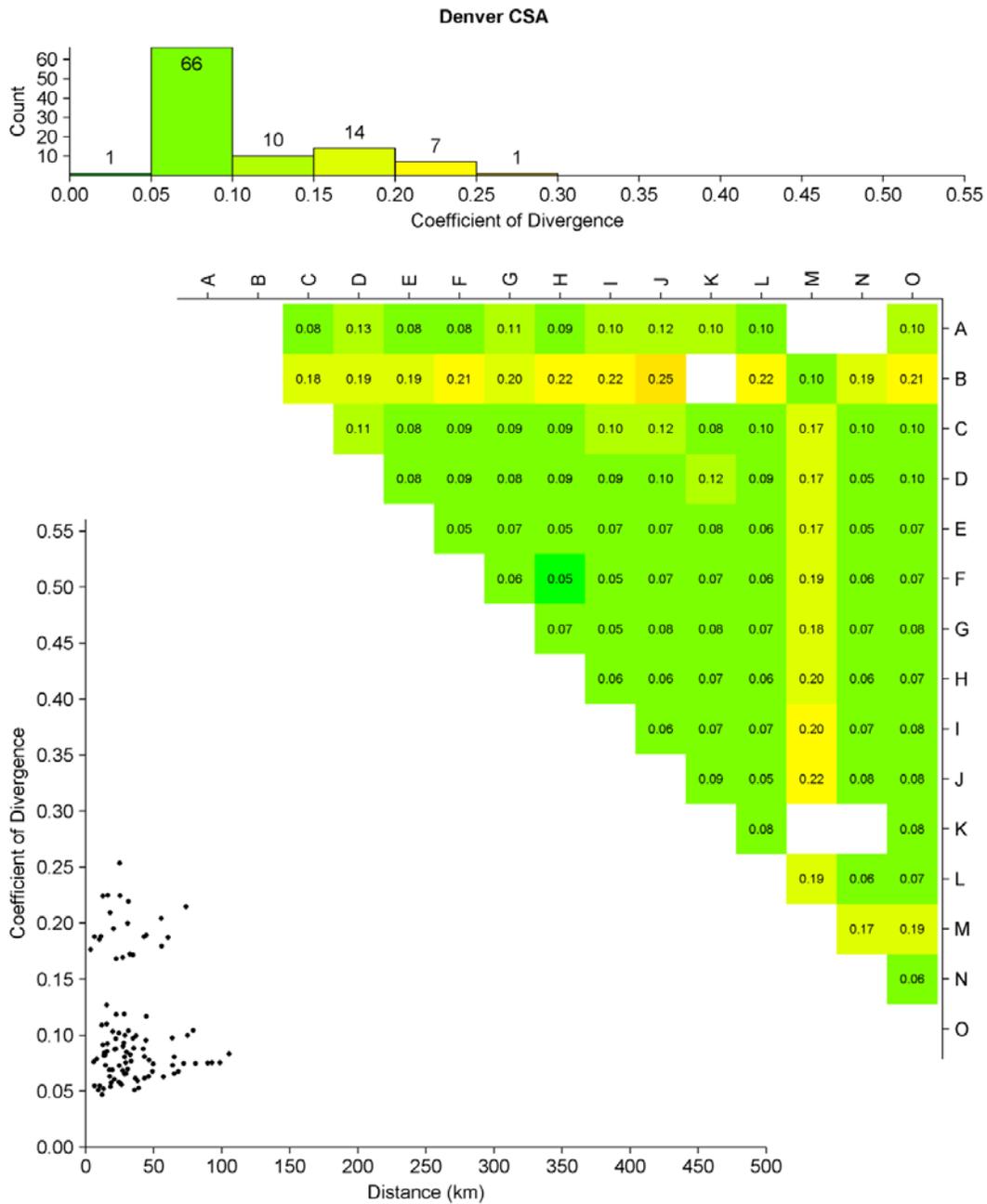
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-140 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Chicago CSA.



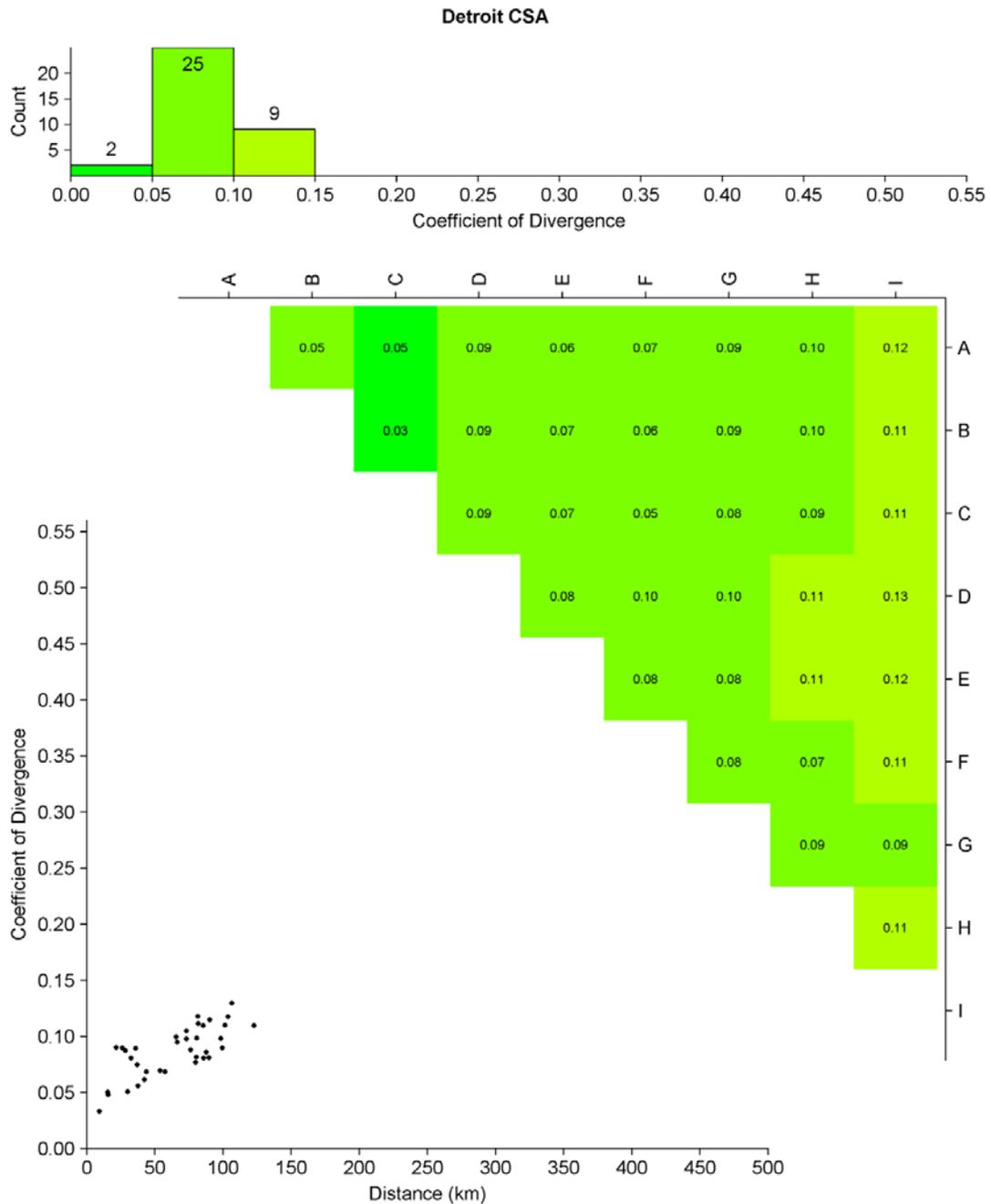
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-141 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Dallas CSA.



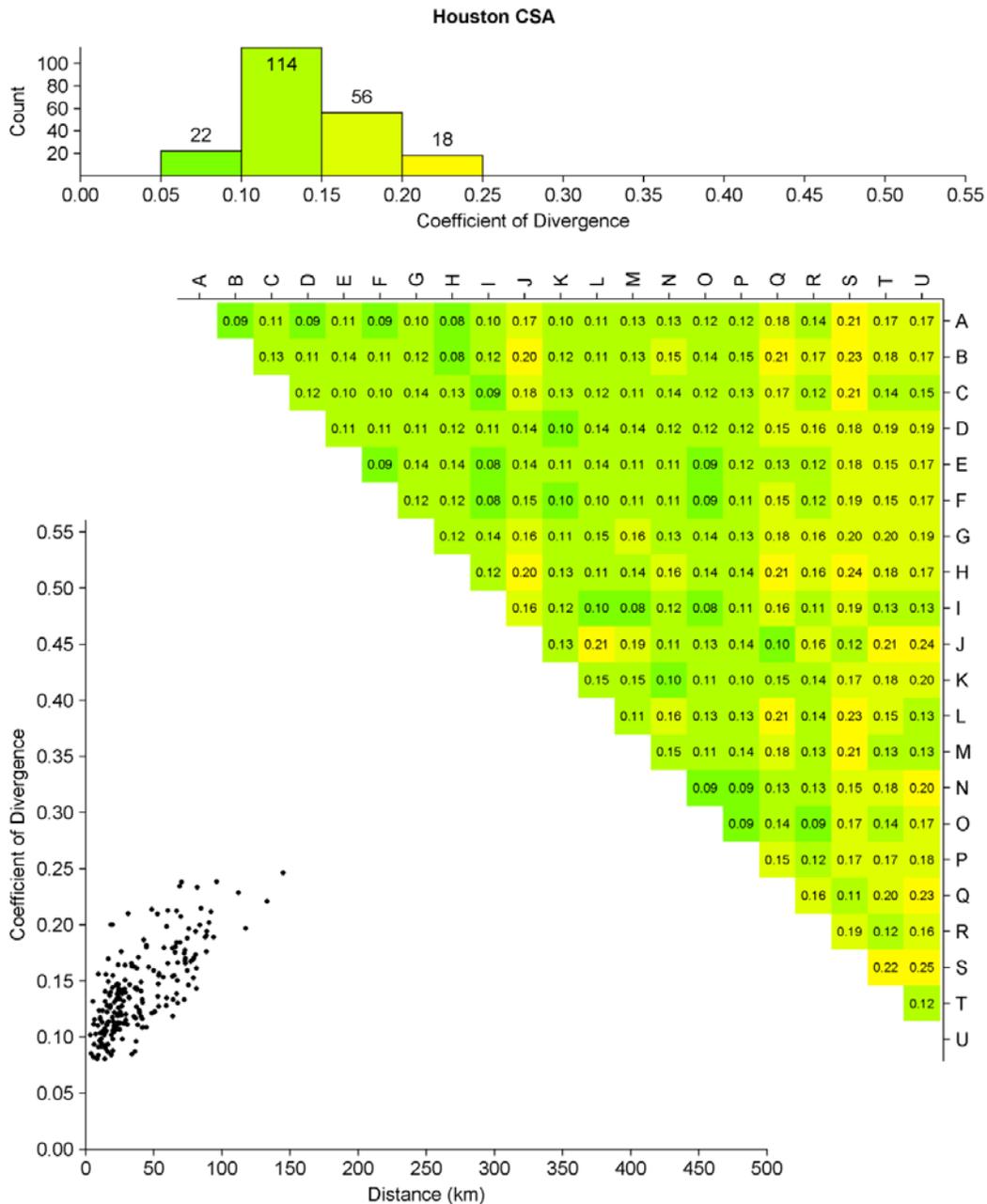
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-142 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Denver CSA.



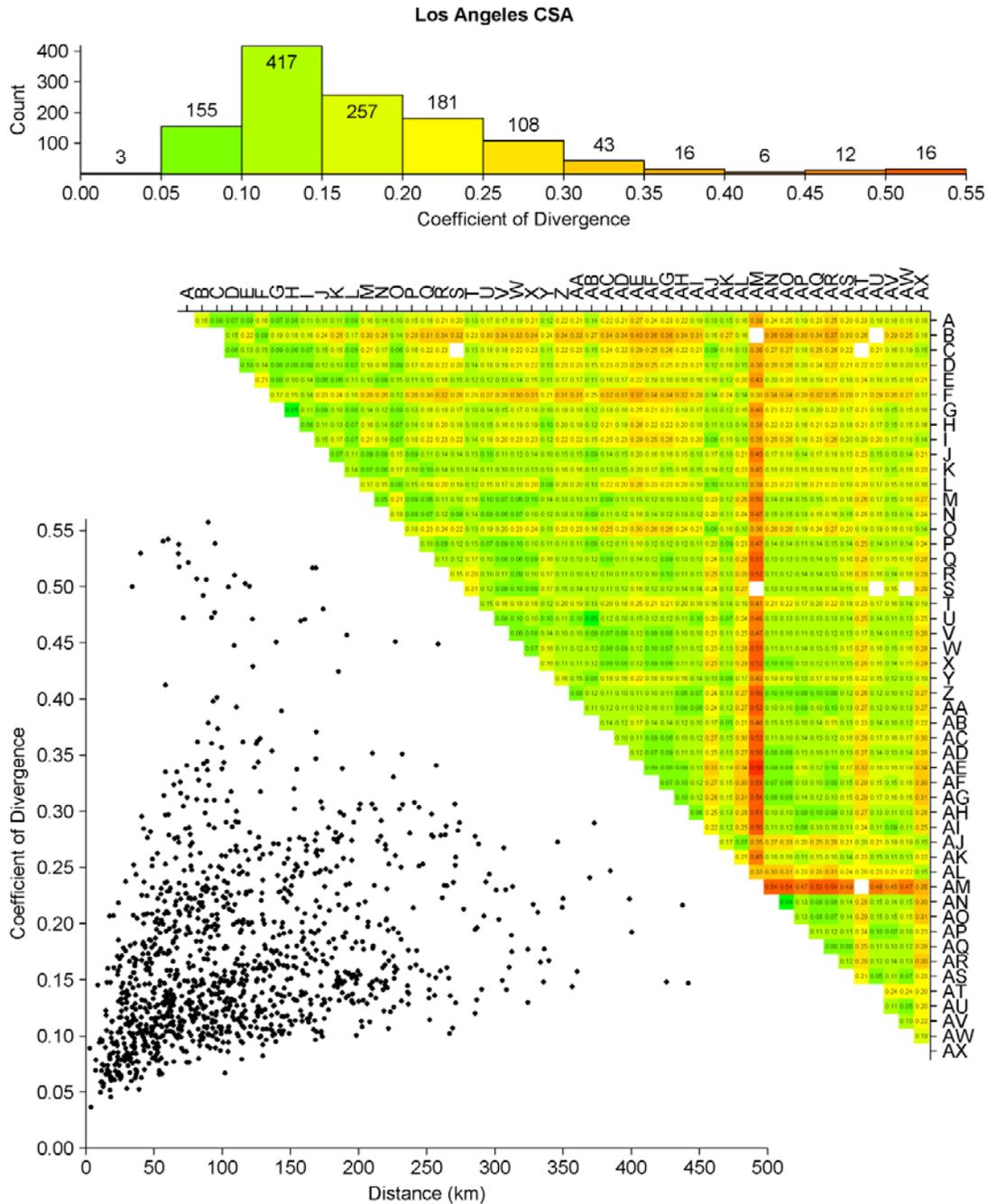
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-143 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Detroit CSA.



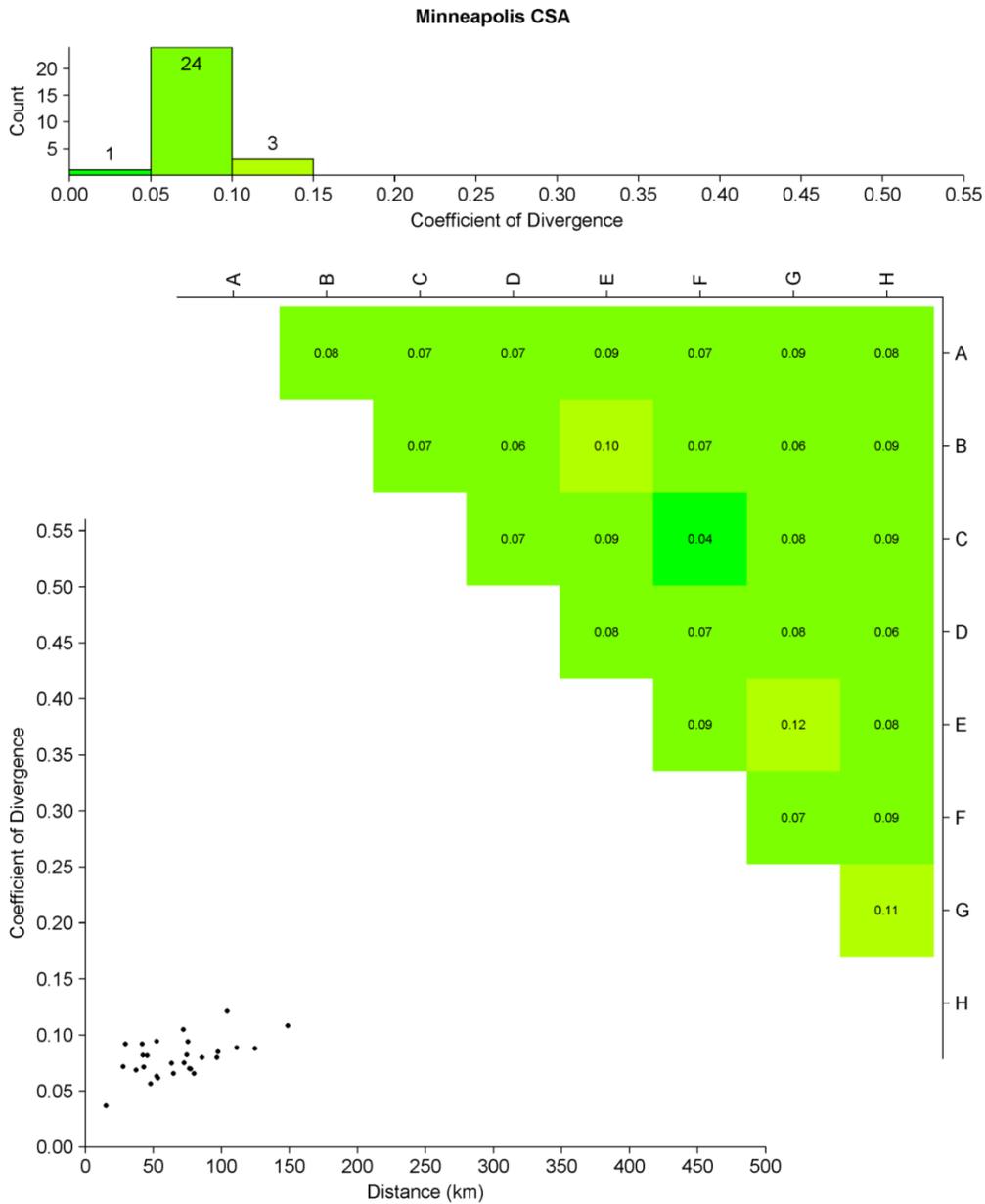
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-144 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Houston CSA.



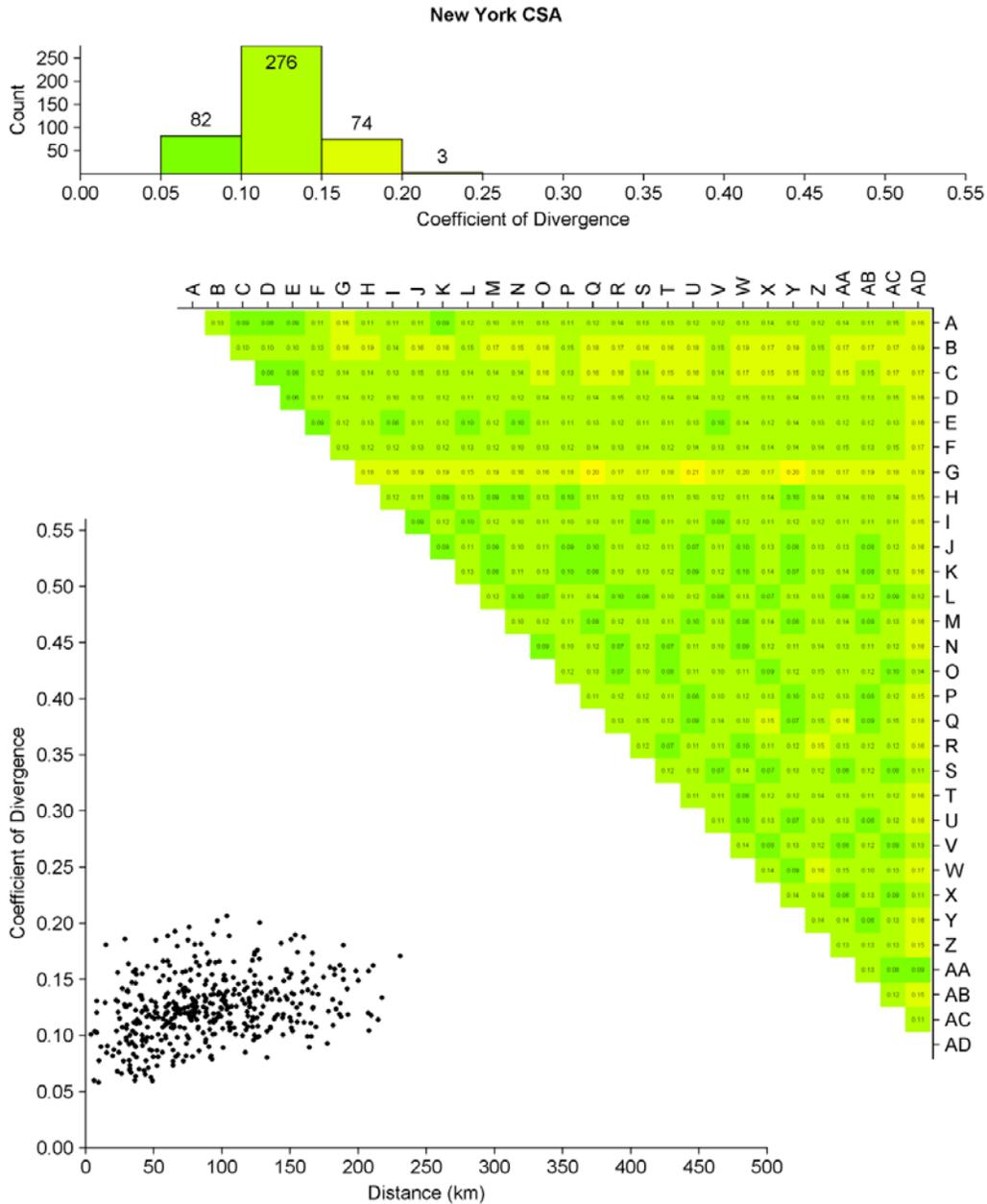
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-145 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA.



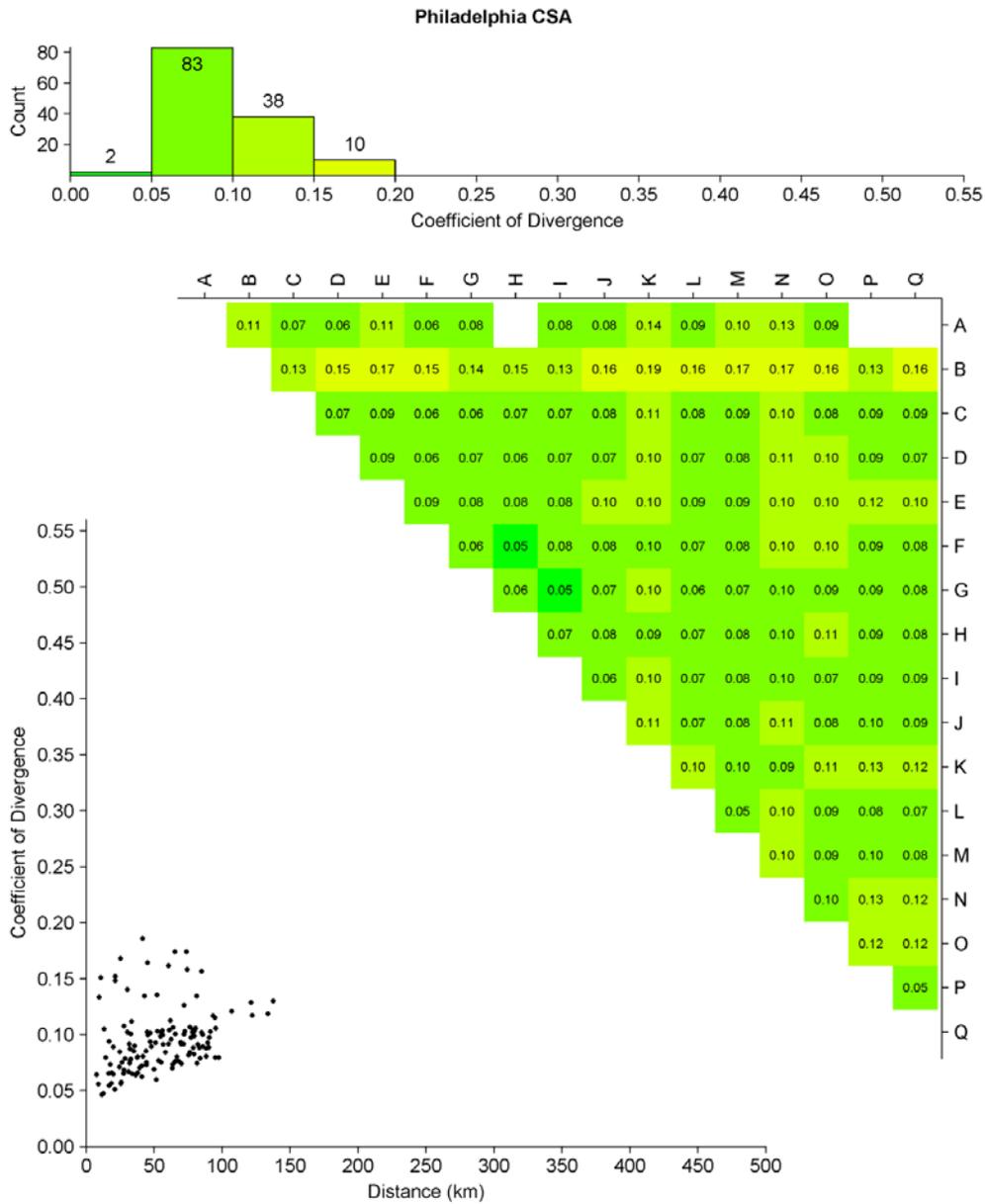
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-146 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Minneapolis CSA.



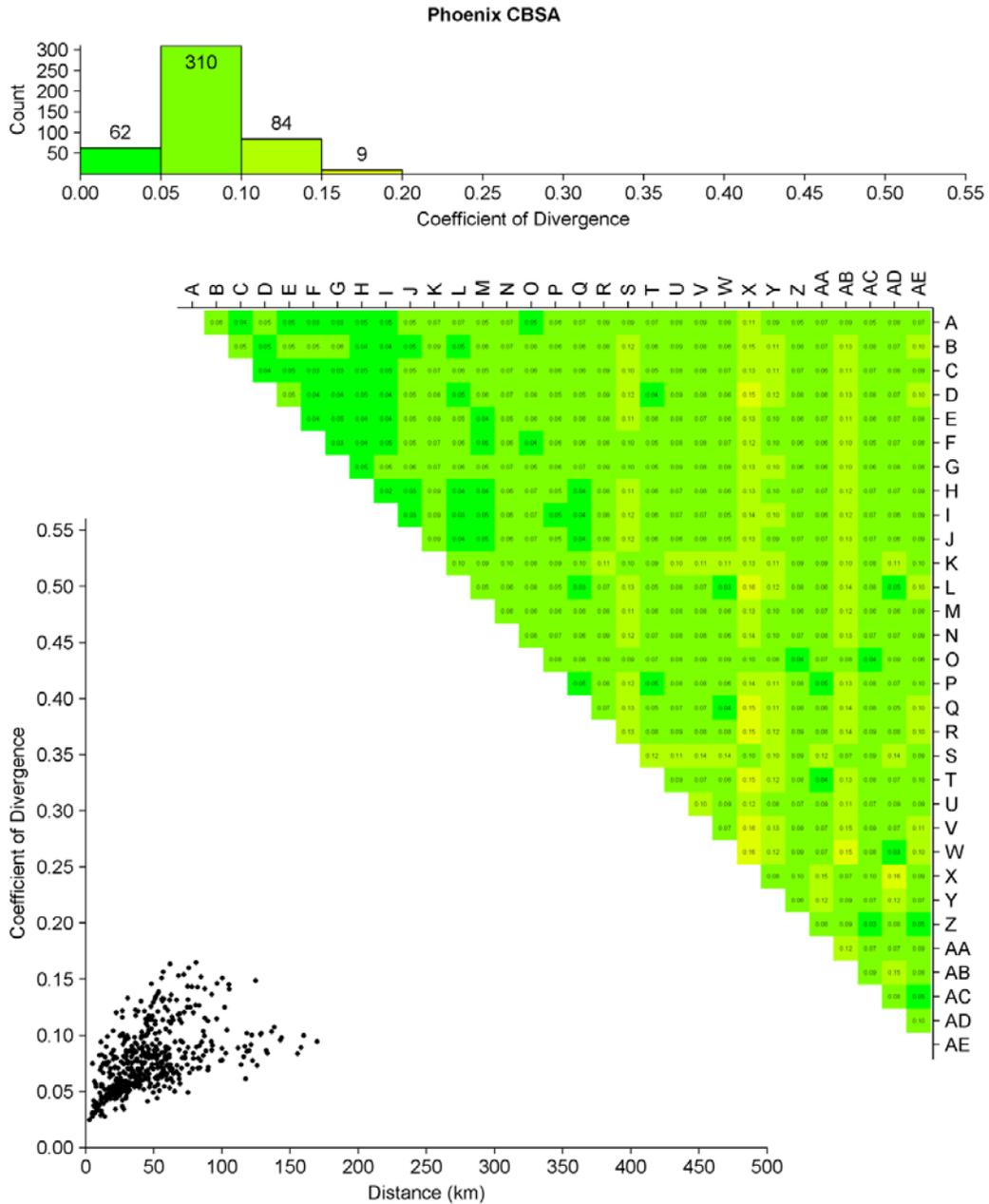
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-147 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the New York CSA.



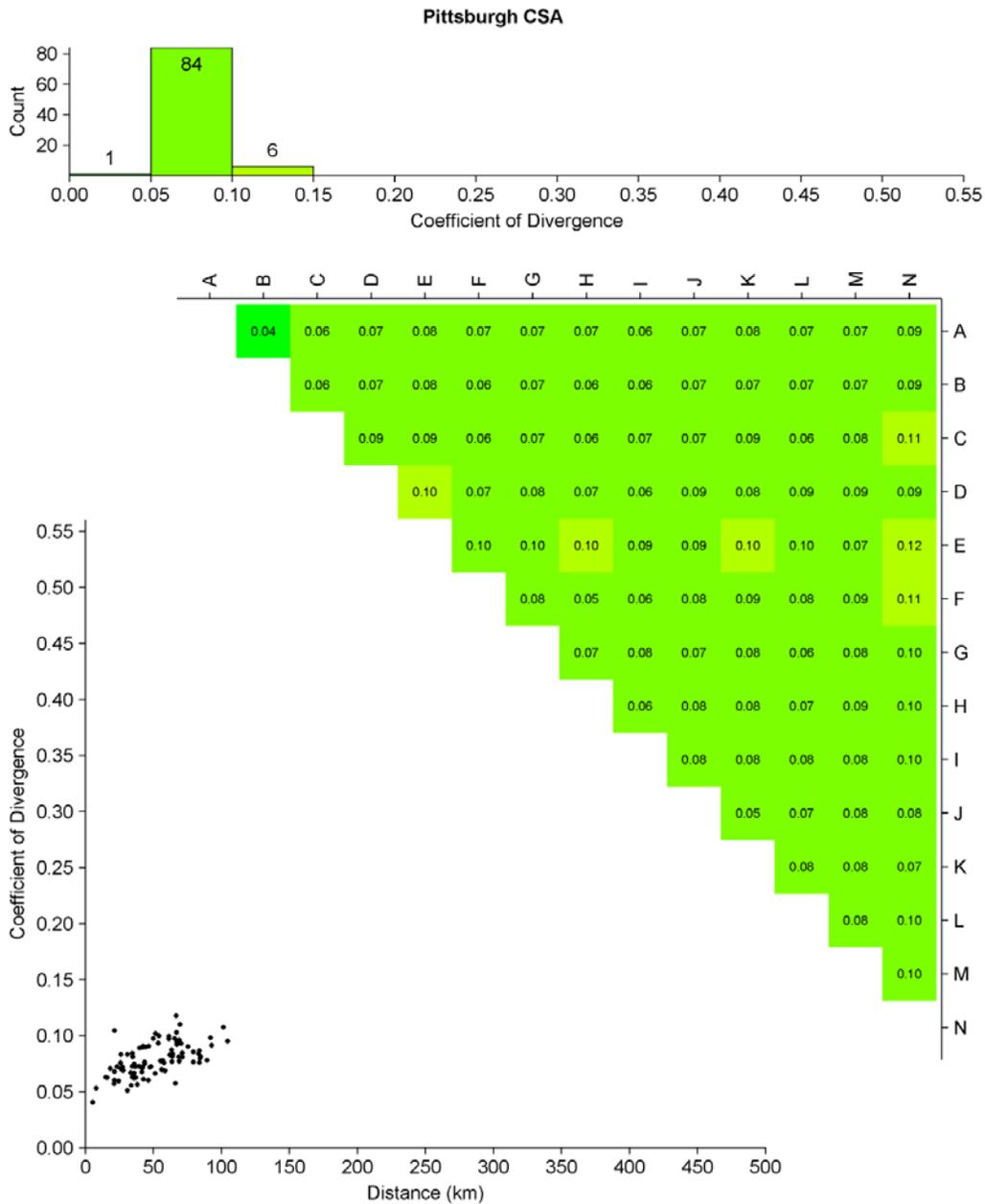
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-148 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Philadelphia CSA.



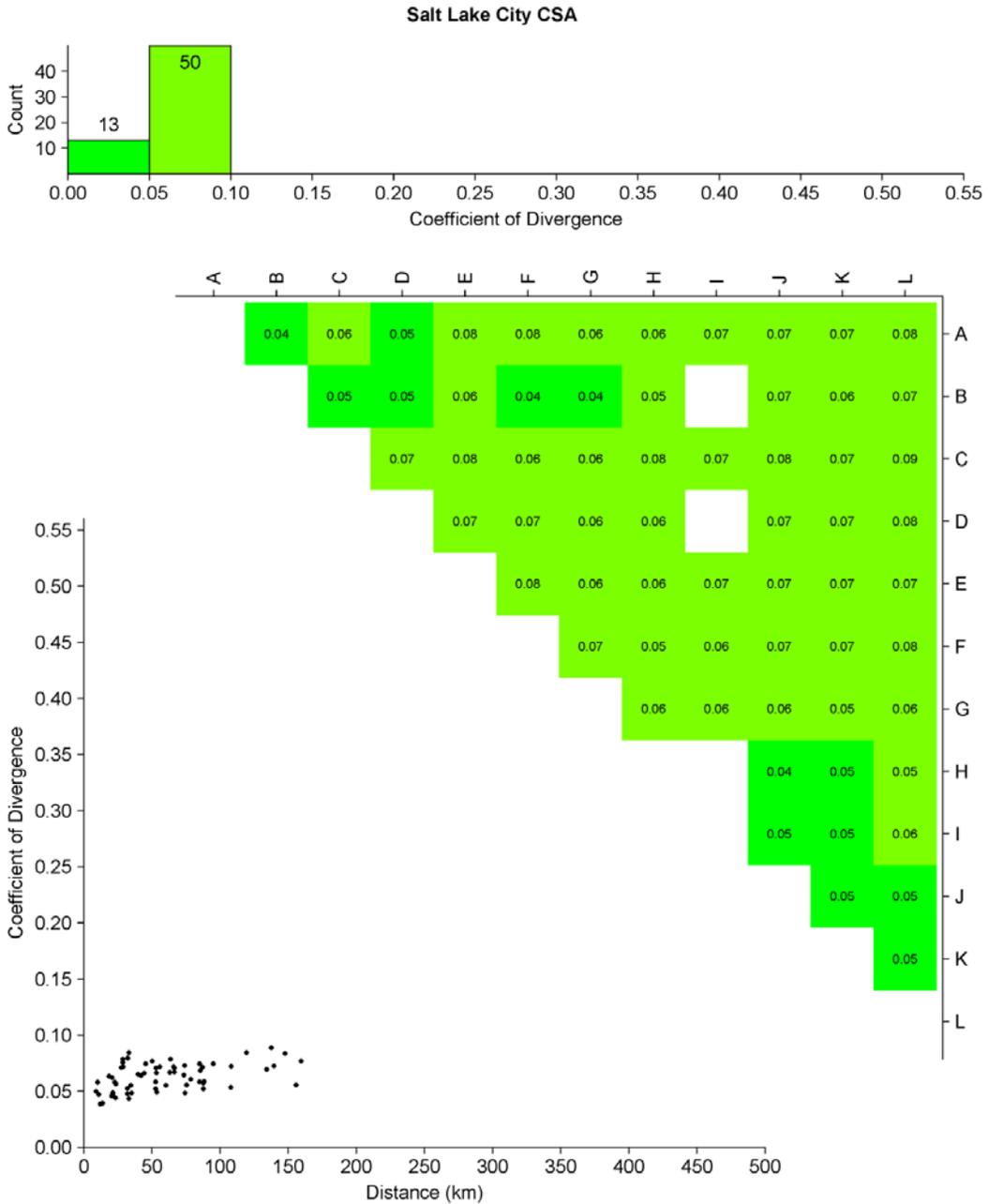
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-149 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Phoenix CBSA.



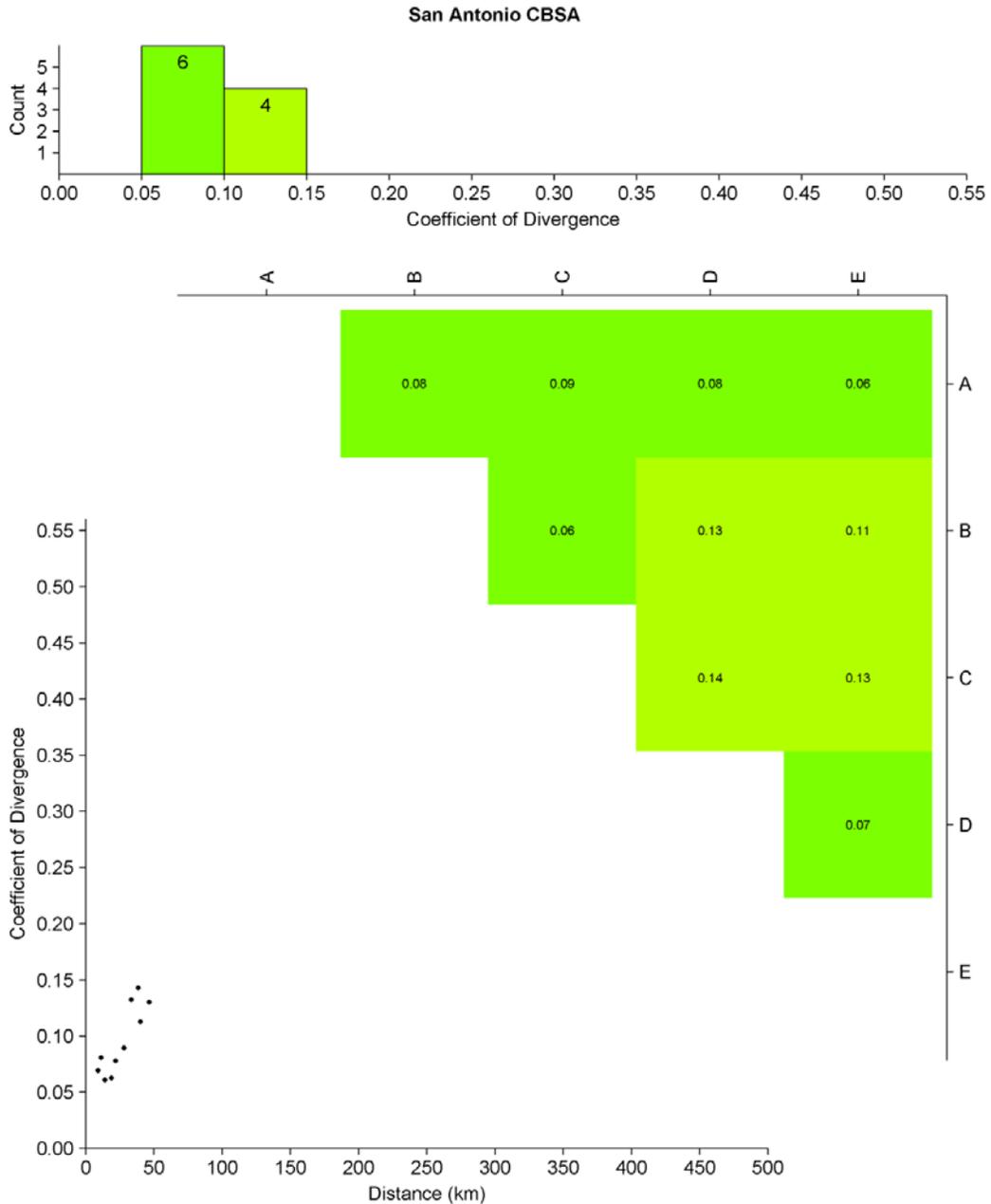
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-150 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Pittsburgh CSA.



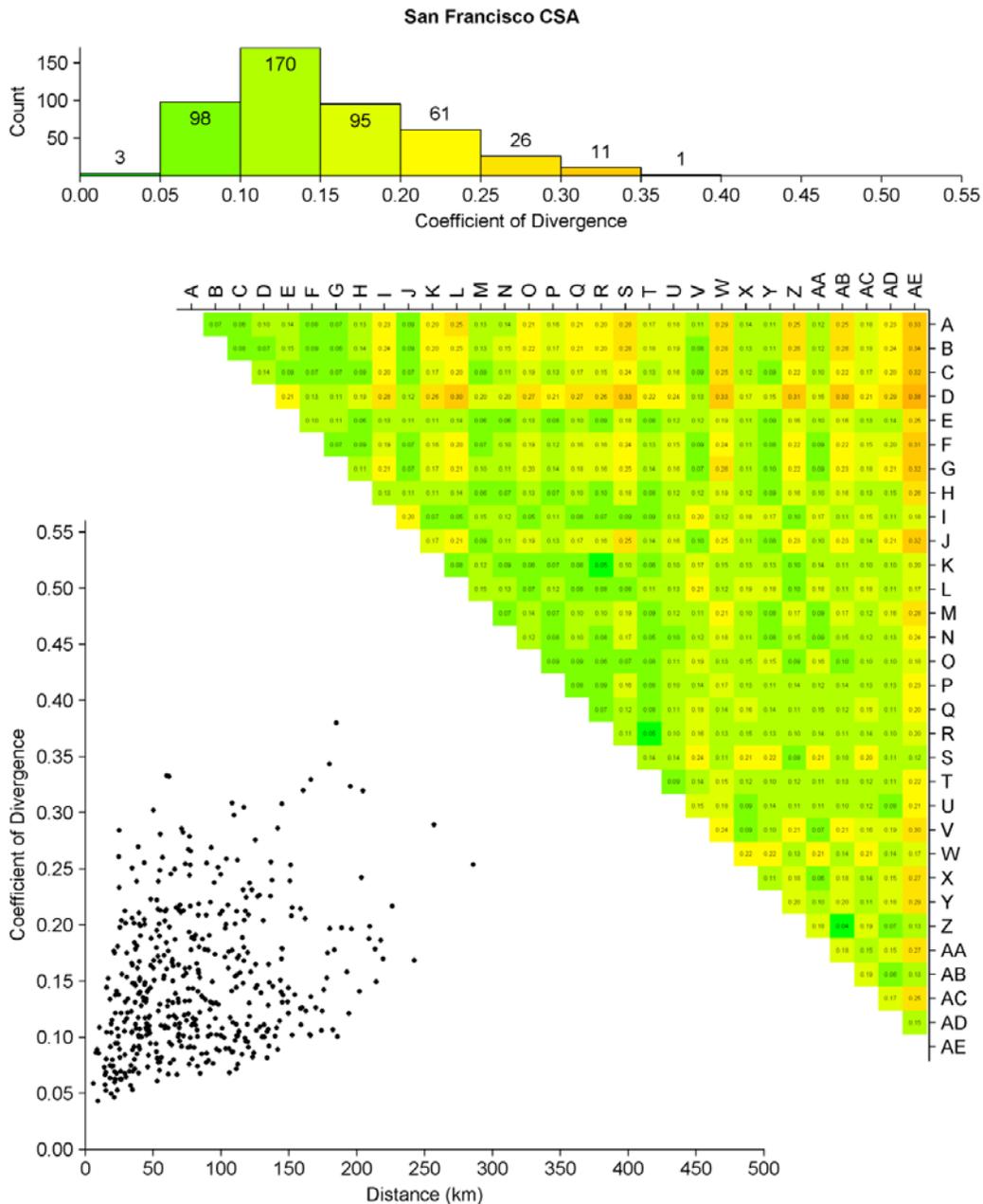
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-151 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Salt Lake City CSA.



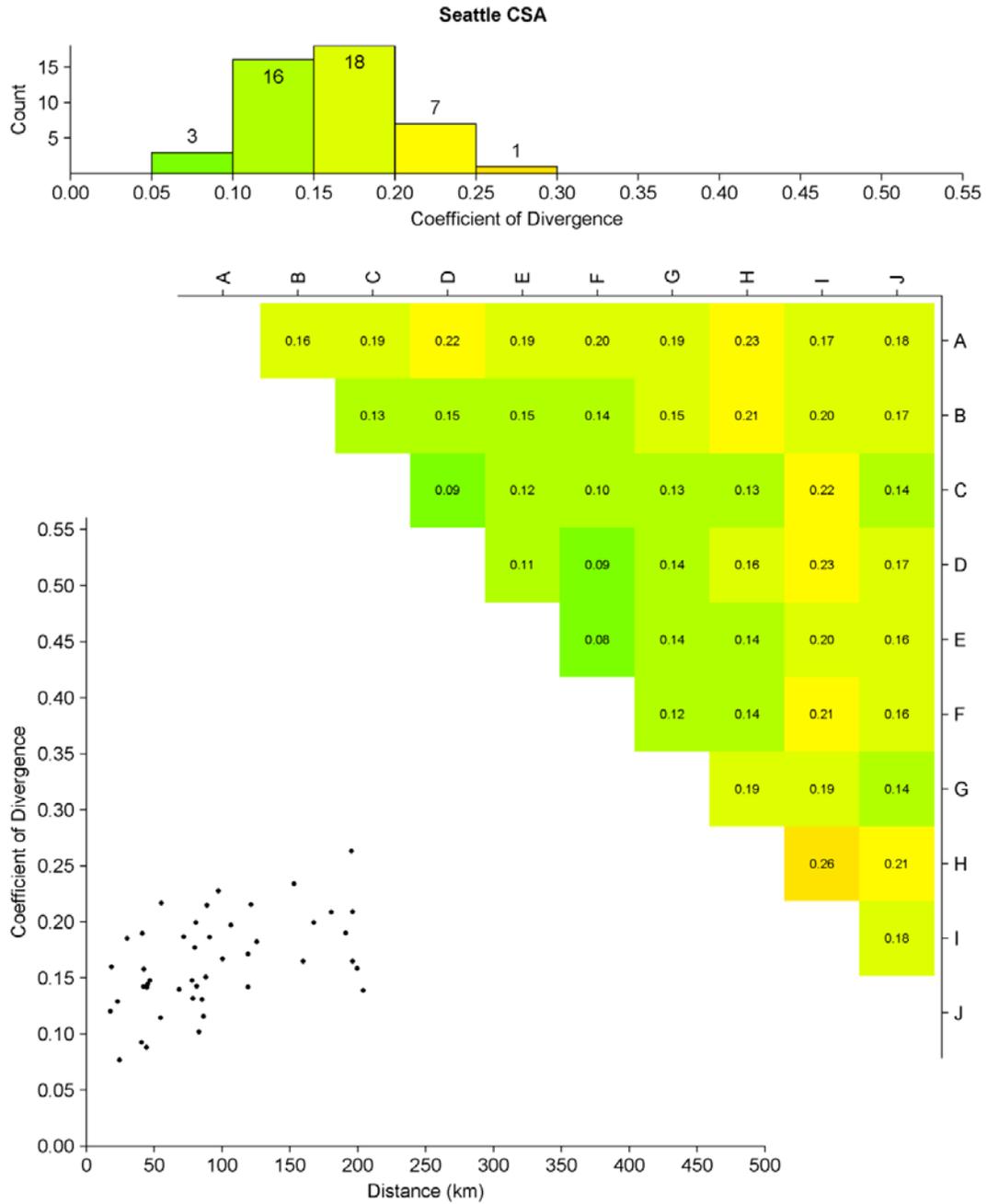
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-152 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Antonio CBSA.



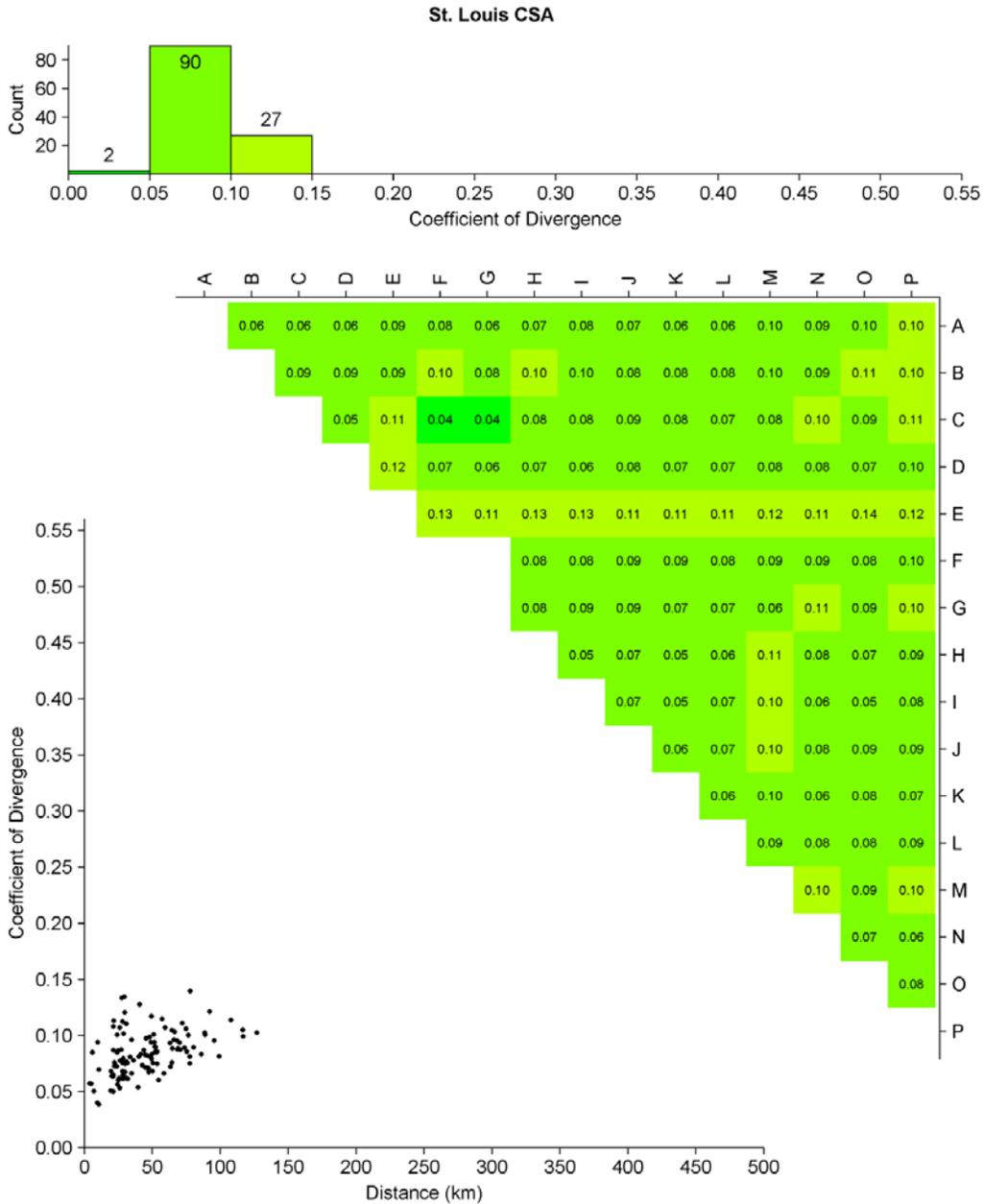
Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-153 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Francisco CSA.



Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-154 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Seattle CSA.

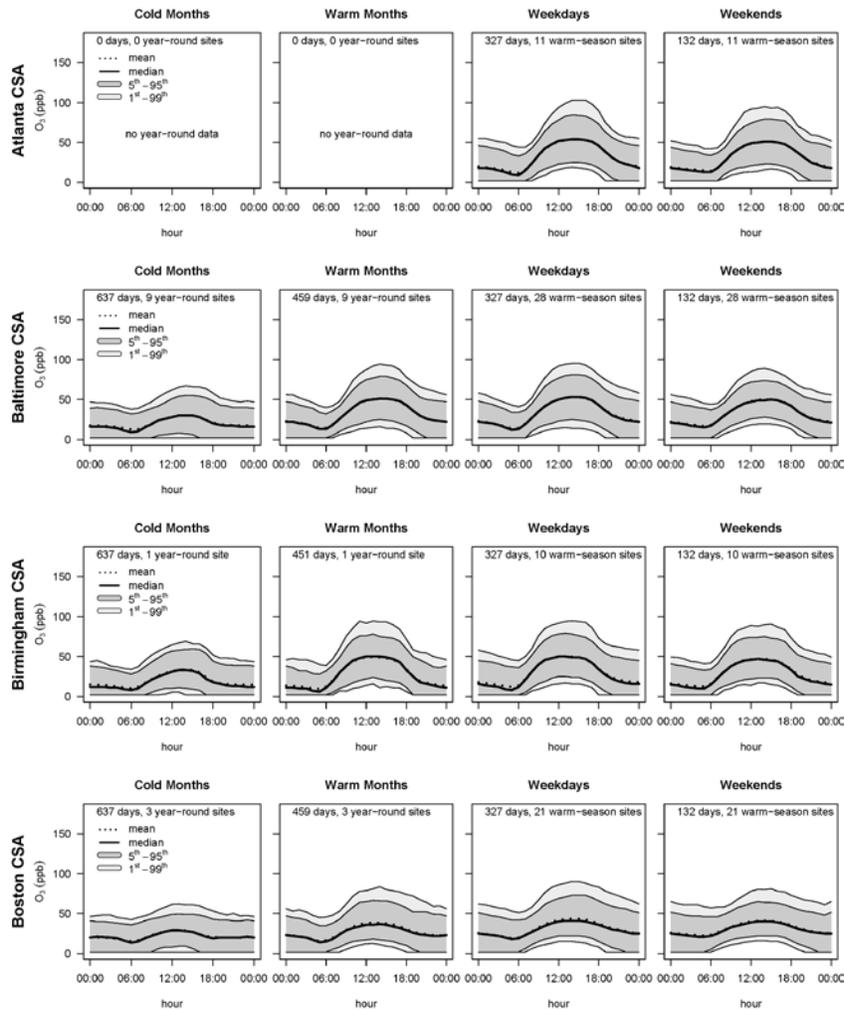


Note: The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of R.

Figure 3-155 Pair-wise monitor coefficient of divergence (COD) expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the St. Louis CSA.

3.9.4 Hourly Variations in Ozone for the Urban Focus Cities

1 This section contains diel plots of 1-h avg O₃ data to supplement the discussion on hourly
2 variations in O₃ concentrations from Section 3.6.3.2 using data from the 20 urban focus
3 cities first introduced in Section 3.6.2.1. Comparisons are made between cold months
4 (October-April) and warm months (May-September), using the year-round data set, and
5 between weekdays (Mon-Fri) and weekends (Sat-Sun) using the warm-season data set.



Note: No year-round monitors were available for the cold month/warm month comparison in the Atlanta CSA.

Figure 3-156 Diel patterns in 1-h avg ozone for select CSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

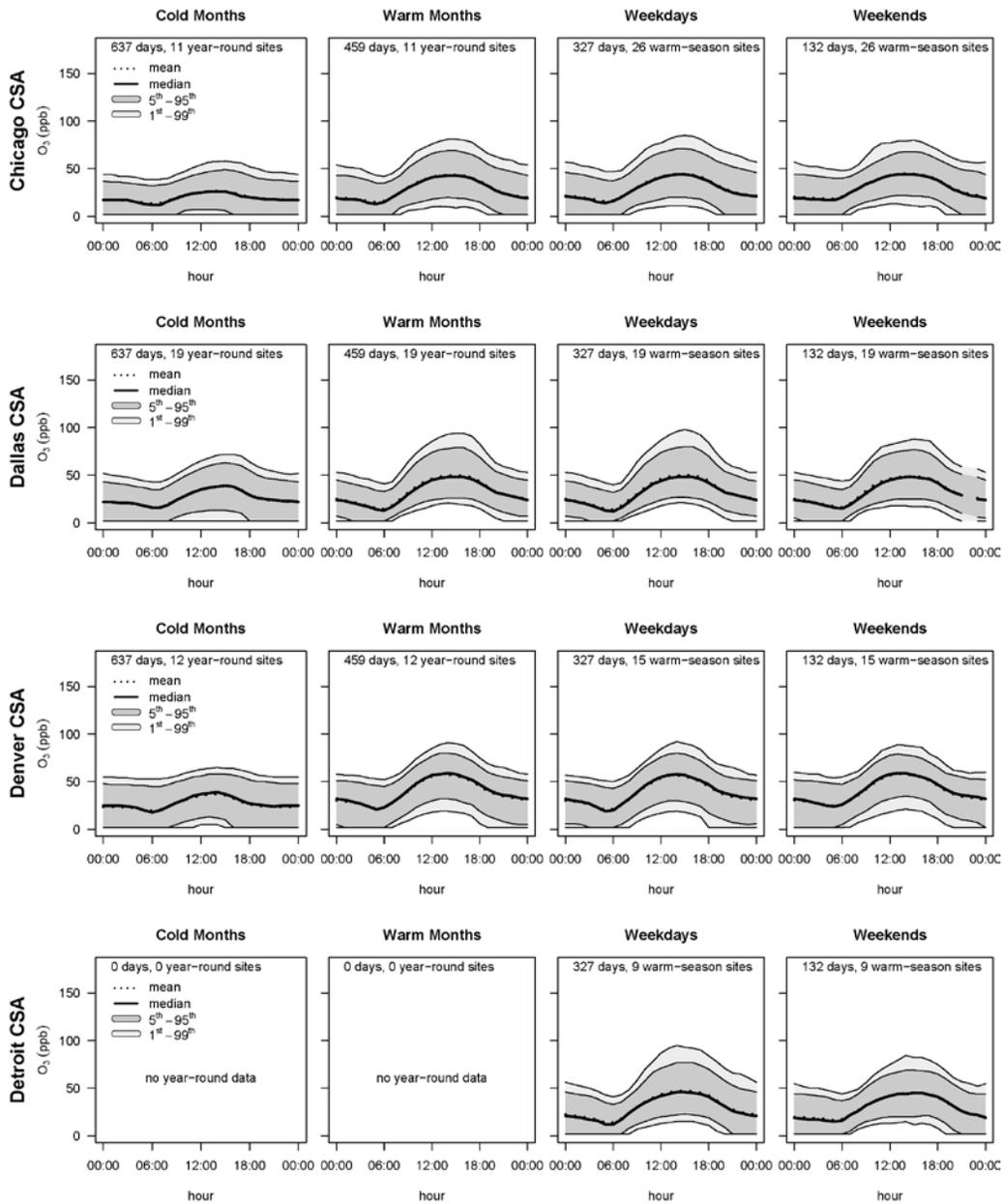
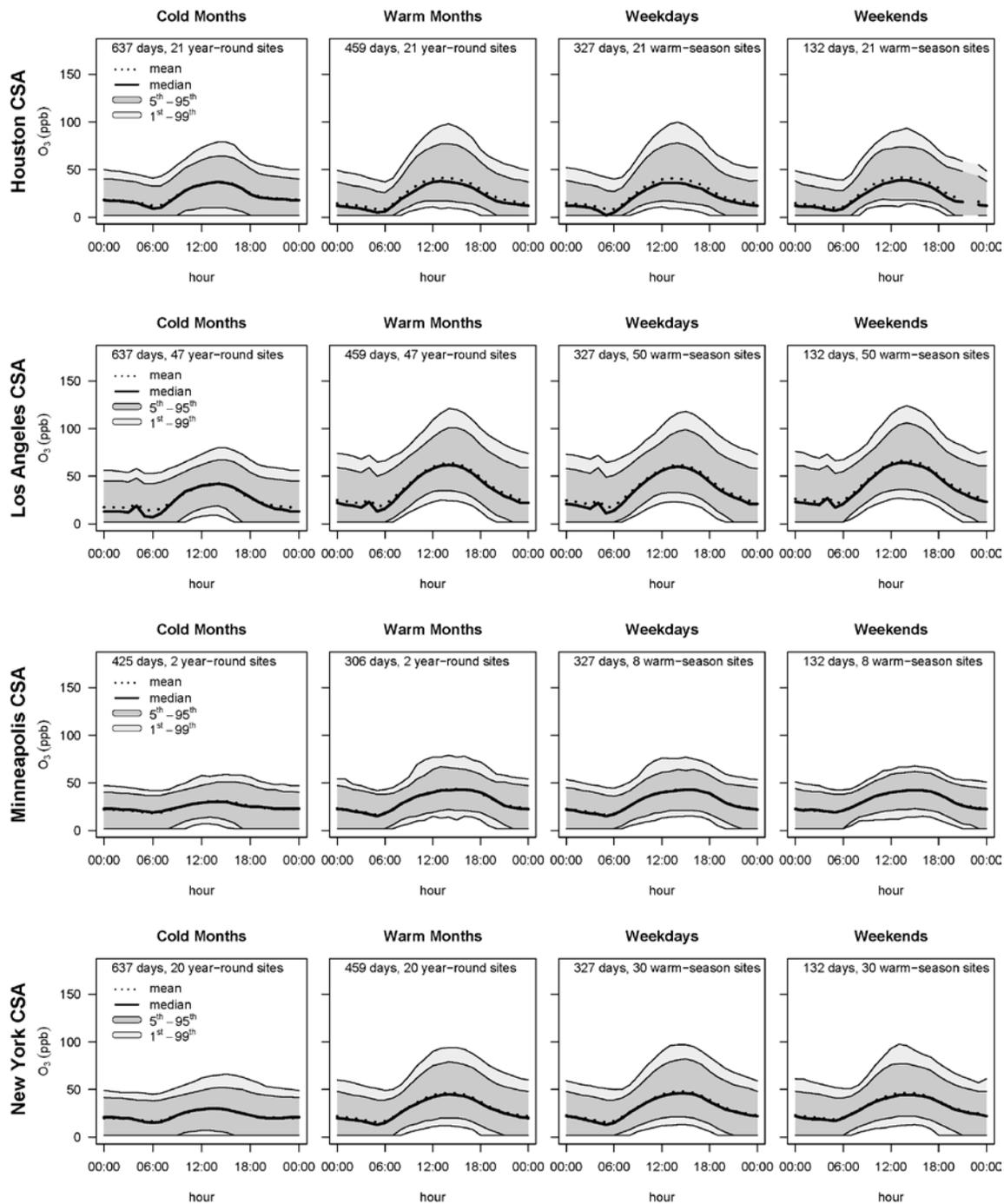


Figure 3-157 Diel patterns in 1-h avg ozone for select CSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).



Note: No year-round monitors were available for the cold month/warm month comparison in the Detroit CSA.

Figure 3-158 Diel patterns in 1-h avg ozone for select CSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

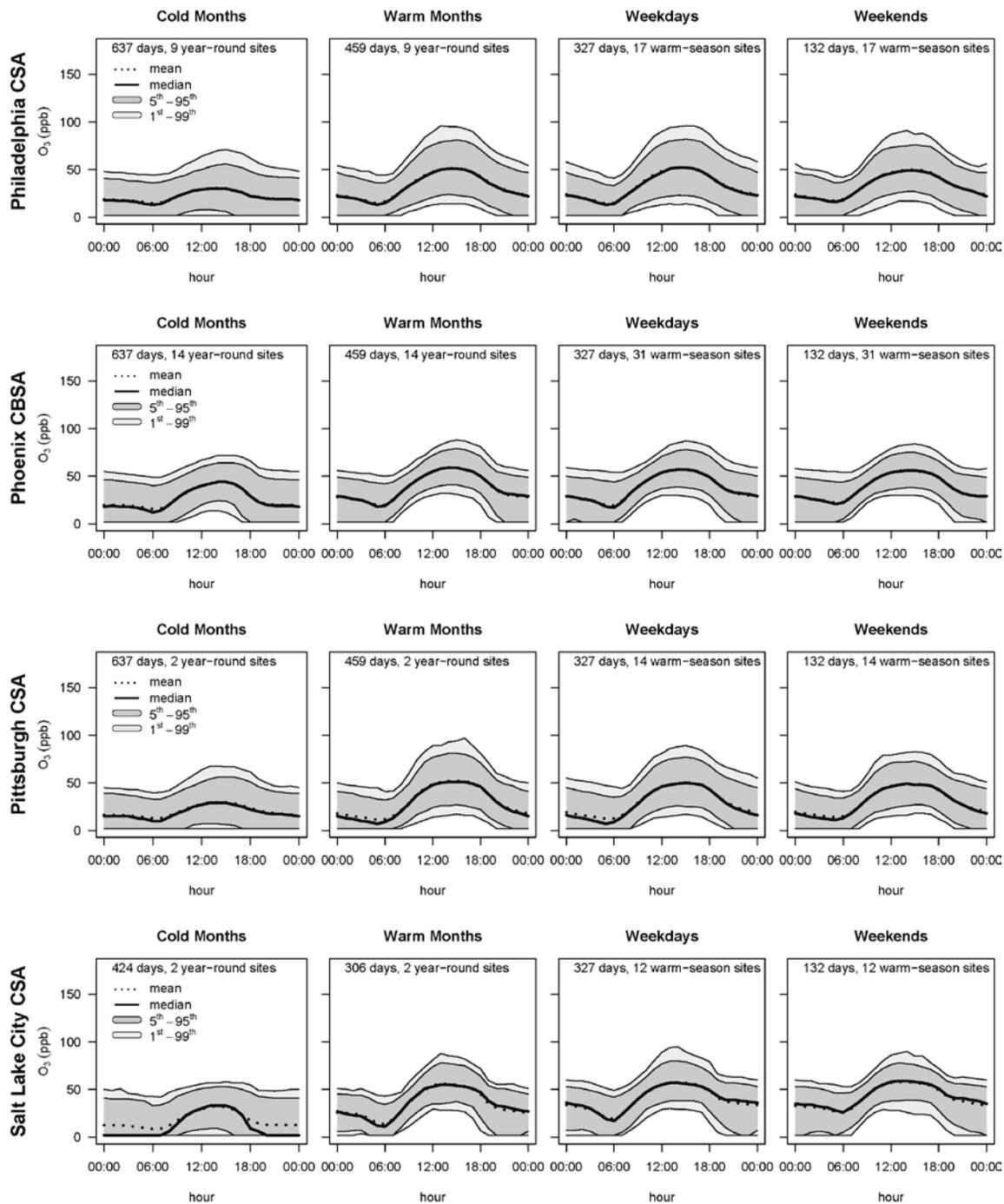


Figure 3-159 Diel patterns in 1-h avg ozone for select CSAs/CBSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

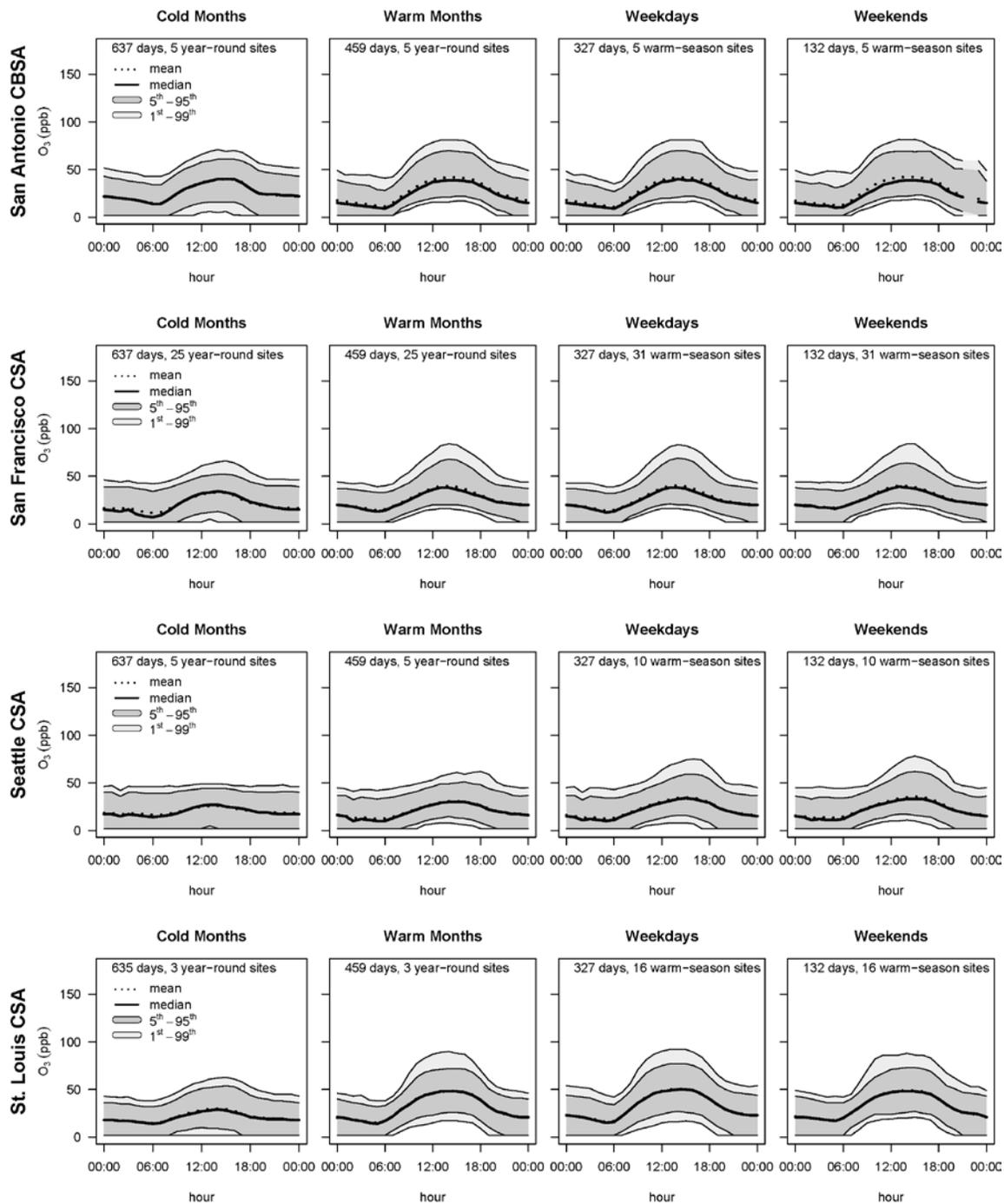


Figure 3-160 Diel patterns in 1-h avg ozone for select CSAs/CBSAs between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

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4 EXPOSURE TO AMBIENT OZONE

4.1 Introduction

1 The 2006 O₃ AQCD evaluated O₃ concentrations and exposures in multiple
2 microenvironments, discussed methods for estimating personal and population exposure
3 via monitoring and modeling, analyzed relationships between personal exposure and
4 ambient concentrations, and discussed the implications of using ambient O₃
5 concentrations as an estimate of exposure in epidemiologic studies. This chapter presents
6 new information regarding exposure to ambient O₃ which builds upon the body of
7 evidence presented in the 2006 O₃ AQCD. A brief summary of findings from the 2006 O₃
8 AQCD is presented at the beginning of each section as appropriate.

9 Section 4.2 presents general exposure concepts describing the relationship between
10 ambient pollutant concentrations and personal exposure. Section 4.3 describes exposure
11 measurement techniques and studies that measured personal, ambient, indoor, and
12 outdoor concentrations of O₃ and related pollutants. Section 4.4 presents material on
13 parameters relevant to exposure estimation, including activity patterns, averting behavior,
14 and population proximity to ambient monitors. Section 4.5 describes techniques for
15 modeling local O₃ concentrations, air exchange rates, microenvironmental concentrations,
16 and personal and population exposure. Section 4.6 discusses the implications of using
17 ambient O₃ concentrations to estimate exposure in epidemiologic studies, including
18 several factors that contribute to exposure error.

4.2 General Exposure Concepts

19 A theoretical model of personal exposure is presented to highlight measurable quantities
20 and the uncertainties that exist in this framework. An individual's time-integrated total
21 exposure to O₃ can be described based on a compartmentalization of the person's
22 activities throughout a given time period:

$$E_T = \int C_j dt$$

Equation 4-1

23 where E_T = total exposure over a time-period of interest, C_j = airborne O₃ concentration at
24 microenvironment j , and dt = portion of the time-period spent in microenvironment j .

1 [Equation 4-1](#) can be decomposed into a model that accounts for exposure to O₃, of
2 ambient (E_a) and nonambient (E_{na}) origin of the form:

$$E_T = E_a + E_{na}$$

Equation 4-2

3 Ambient O₃ is formed through photochemical reactions involving NO_x, VOCs, and other
4 compounds, as described in Chapter [3](#). Although nonambient sources of O₃ exist, such as
5 O₃ generators and laser printers, these sources are specific to individuals and may not be
6 important sources of population exposure. Ozone concentrations generated by ambient
7 and nonambient sources are subject to spatial and temporal variability that can affect
8 estimates of exposure and influence epidemiologic effect estimates. Exposure parameters
9 affecting interpretation of epidemiologic studies are discussed in Section [4.5](#).

10 This assessment focuses on the ambient component of exposure because this is more
11 relevant to the NAAQS review. Assuming steady-state outdoor conditions, E_a can be
12 expressed in terms of the fraction of time spent in various outdoor and indoor
13 microenvironments ([Wallace et al., 2006](#); [Wilson et al., 2000](#)):

$$E_a = \sum f_o C_o + \sum f_i F_{inf,i} C_{o,i}$$

Equation 4-3

14 where f = fraction of the relevant time period (equivalent to dt in [Equation 4-1](#)), subscript
15 o = index of outdoor microenvironments, subscript i = index of indoor
16 microenvironments, subscript o,i = index of outdoor microenvironments adjacent to a
17 given indoor microenvironment i , and $F_{inf,i}$ = infiltration factor for indoor
18 microenvironment i . [Equation 4-3](#) is subject to the constraint $\sum f_o + \sum f_i = 1$ to reflect the
19 total exposure over a specified time period, and each term on the right hand side of the
20 equation has a summation because it reflects various microenvironmental exposures.
21 Here, “indoors” refers to being inside any aspect of the built environment, e.g., home,
22 office buildings, enclosed vehicles (automobiles, trains, buses), and/or recreational
23 facilities (movie theaters, restaurants, bars). “Outdoor” exposure can occur in parks or
24 yards, on sidewalks, and on bicycles or motorcycles. Assuming steady state ventilation
25 conditions, the infiltration factor is a function of the penetration (P) of O₃ into the
26 microenvironment, the air exchange rate (a) of the microenvironment, and the rate of O₃
27 loss (k) in the microenvironment; $F_{inf} = Pa/(a + k)$.

1 In epidemiologic studies, the central-site ambient concentration, C_a , is often used in lieu
2 of outdoor microenvironmental data to represent these exposures based on the availability
3 of data. Thus it is often assumed that $C_o = C_a$ and that the fraction of time spent outdoors
4 can be expressed cumulatively as f_o ; the indoor terms still retain a summation because
5 infiltration differs among different microenvironments. If an epidemiologic study
6 employs only C_a , then the assumed model of an individual's exposure to ambient O_3 , first
7 given in [Equation 4-3](#), is re-expressed solely as a function of C_a :

$$E_a = (f_o + \sum f_i \mathcal{F}_{inf_i}) C_a$$

Equation 4-4

8 The spatial variability of outdoor O_3 concentrations due to meteorology, topography,
9 varying precursor emissions and O_3 formation rates; the design of the epidemiologic
10 study; and other factors determine whether or not [Equation 4-4](#) is a reasonable
11 approximation for [Equation 4-3](#). These equations also assume steady-state
12 microenvironmental concentrations. Errors and uncertainties inherent in use of [Equation](#)
13 [4-4](#) in lieu of [Equation 4-3](#) are described in Section [4.6](#) with respect to implications for
14 interpreting epidemiologic studies. Epidemiologic studies often use concentration
15 measured at a central site monitor to represent ambient concentration; thus α , the ratio
16 between personal exposure to ambient O_3 and the ambient concentration of O_3 , is defined
17 as:

$$\alpha = \frac{E_a}{C_a}$$

Equation 4-5

18 Combination of [Equation 4-4](#) and [Equation 4-5](#) yields:

$$\alpha = f_o + \sum f_i \mathcal{F}_{inf_i}$$

Equation 4-6

19 *where* α varies between 0 and 1. If a person's exposure occurs in a single
20 microenvironment, the ambient component of a microenvironmental O_3 concentration
21 can be represented as the product of the ambient concentration and F_{inf} . Wallace et al.
22 ([2006](#)) note that time-activity data and corresponding estimates of F_{inf} for each
23 microenvironmental exposure are needed to compute an individual's α with accuracy. In

1 epidemiologic studies, α is assumed to be constant in lieu of time-activity data and
2 estimates of F_{inf} , which can vary with building and meteorology-related air exchange
3 characteristics. If important local outdoor sources and sinks exist that are not captured by
4 central site monitors, then the ambient component of the local outdoor concentration may
5 be estimated using dispersion models, land use regression models, receptor models, fine
6 scale CTMs or some combination of these techniques. These techniques are described in
7 Section [4.5](#).

4.3 Exposure Measurement

8 This section describes techniques that have been used to measure microenvironmental
9 concentrations of O₃ and personal O₃ exposures as well as results of studies using those
10 techniques. Previous studies from the 2006 O₃ AQCD are described along with newer
11 studies that evaluate indoor-outdoor concentration relationships, associations between
12 personal exposure and ambient monitor concentration, and multipollutant exposure to
13 other pollutants in conjunction with O₃. Tables are provided to summarize important
14 study results.

4.3.1 Personal Monitoring Techniques

15 As described in the 2006 O₃ AQCD, passive samplers have been developed and deployed
16 to measure personal exposure to O₃ ([Grosjean and Hisham, 1992](#); [Kanno and
17 Yanagisawa, 1992](#)). Widely used versions of these samplers utilize a filter coated with
18 nitrite, which is converted to nitrate by O₃ and then quantified by a technique such as ion
19 chromatography ([Koutrakis et al., 1993](#)). This method has been licensed and marketed by
20 Ogawa, Inc., Japan ([Ogawa & Co, 2007](#)). The cumulative sampling and the detection
21 limit of the passive badges makes them mainly suitable for monitoring periods of 24
22 hours or greater, which limits their ability to measure short-term daily fluctuations in
23 personal O₃ exposure. Longer sampling periods give lower detection limits; use of the
24 badges for a 6-day sampling period yields a detection limit of 1 ppb, while a 24-hour
25 sampling period gives a detection limit of approximately 5-10 ppb. This can result in a
26 substantial fraction of daily samples being below the detection limit ([Sarnat et al., 2006a](#);
27 [Sarnat et al., 2005](#)), which is a limitation of past and current exposure studies.

28 Development of improved passive samplers capable of shorter-duration monitoring with
29 lower detection limits would enable more precise characterization of personal exposure in
30 multiple microenvironments with relatively low participant burden.

1 The nitrite-nitrate conversion reaction has also been used as the basis for an active
2 sampler consisting of a nitrite-coated glass tube through which air is drawn by a pump
3 operating at 65 mL/min ([Geyh et al., 1999](#); [Geyh et al., 1997](#)). The reported detection
4 limit is 10 ppb-h, enabling the quantification of O₃ concentrations measured over a few
5 hours rather than a full day ([Geyh et al., 1999](#)).

6 A portable active O₃ monitor based on the UV photometric technique used for stationary
7 monitors (Chapter [3](#)) has recently been approved as a FEM (75 FR 22126). This monitor
8 includes a Nafion tube in the inlet line to equilibrate humidity, reducing the effect of
9 humidity changes in different microenvironments ([Wilson and Birks, 2006](#)). Its size and
10 weight (approximately 10×20×30 cm; 2 kg) make it suitable for use in a backpack
11 configuration. The monitors are currently used by the U.S. National Park service as
12 stationary monitors to measure O₃ in several national parks (Chapter [3](#)). Future
13 improvements and continued miniaturization of real-time O₃ monitors can yield highly
14 time-resolved personal measurements to further evaluate O₃ exposures in specific
15 situations, such as near roadways or while in transit.

4.3.2 Indoor-Outdoor Concentration Relationships

16 Several studies summarized in the 2006 O₃ AQCD, along with some newer studies, have
17 evaluated the relationship between indoor O₃ concentration and the O₃ concentration
18 immediately outside the indoor microenvironment. These studies show that the indoor
19 concentration is often substantially lower than the outdoor concentration unless indoor
20 sources are present. Low indoor O₃ concentrations can be explained by reactions of O₃
21 with surfaces and airborne constituents. Studies have shown that O₃ is deposited onto
22 indoor surfaces where reactions produce secondary pollutants such as formaldehyde
23 ([Reiss et al., 1995b](#); [Reiss et al., 1995a](#)). However, the indoor-outdoor relationship is
24 greatly affected by the air exchange rate; under conditions of high air exchange rate, such
25 as open windows, the indoor O₃ concentration may approach the outdoor concentration.
26 Thus, in rooms with open windows, the indoor-outdoor (I/O) ratio may approach 1.0.
27 [Table 4-1](#) summarizes I/O ratios and correlations reported by older and more recent
28 studies, with discussion of individual studies in the subsequent text. In general, I/O ratios
29 range from about 0.1 to 0.4, with some evidence for higher ratios during the O₃ season
30 when concentrations are higher.

31 O₃ concentrations near and below the monitor detection limit cause uncertainty in I/O
32 ratios, because small changes in low concentration values cause substantial variation in
33 resulting ratios. This problem is particularly acute in the non-ozone season when ambient
34 O₃ concentrations are low. Further improvements in characterization of

1 microenvironmental O₃ concentrations and I/O ratios will rely on improved monitoring.
 2 Until new monitoring techniques are available and can be used in the field, past studies
 3 summarized in the 2006 O₃ AQCD remain relevant to consider along with more recent
 4 studies in evaluating the relationship between indoor and outdoor O₃ concentrations.

Table 4-1 Relationships between indoor and outdoor ozone concentration

| Study | Location | Years/Season | Population | Sample duration | Ratio ^a | Correlation | Micro-environment | Comment |
|---------------------------------------|---|------------------------------------|------------|-----------------|---|-------------|-------------------|--|
| Geyh et al. (2000) | Upland, Southern California | June - September 1995 and May 1996 | Children | 6 days | 0.24 | NR | Home | Air-conditioned Ratio: Indoor mean/outdoor mean |
| | | October 1995-April 1996 | | | 0.15 | | | |
| | Mountain Communities, Southern California | June - September 1995 and May 1996 | Children | 6 days | 0.36 | NR | Home | Opening windows Ratio: indoor mean/outdoor mean |
| | | October 1995-April 1996 | | | 0.08 | | | |
| Avol et al. (1998a) | Southern California | February-December, 1994 | NR | 24 h | 0.37 SD: 0.25 | 0.58 | Home | Ratio: each pair of measurements |
| | | Summer | | | 0.43 SD: 0.29 | | | |
| | | Non-summer | | | 0.32 SD: 0.21 | | | |
| Romieu et al. (1998a) | Mexico City, Mexico | September 1993 - July 1994 | Children | 7 or 14 days | 0.20 SD: 0.18 0.15 ^b Range: 0.01-1.00 | NR | Home | Ratio: each pair of measurements |
| Lee et al. (2004a) | Nashville, TN | Summer 1994 | Children | 1 week | 0.1 SD: 0.18 | NR | Home | Ratio: Indoor mean/outdoor mean |

| Study | Location | Years/Season | Population | Sample duration | Ratio ^a | Correlation | Micro-environment | Comment |
|--|------------------------------|----------------------------|--------------------------------|--------------------------|--------------------|-------------|-------------------|---|
| Héroux et al. (2010) | Regina, Saskatchewan, Canada | Summer 2007 | All age groups | 5 days | 0.13 | NR | Home | Ratio: Indoor mean/outdoor mean |
| Liu et al. (1995) | Toronto, Canada | Winter, 1992 | All age groups | 1 week | 0.07 | NR | Home | Ratio: each pair of measurements |
| | | | | | SD: 0.10 | | | |
| | | Summer, 1992 | | 0.40 | | | | |
| | | | | SD: 0.29 | | | | |
| | | Summer, 1992 | | 12 h | 0.30 | | Daytime | Ratio: each pair of measurements |
| | | Summer, 1992 | | | SD: 0.32 | | Nighttime | Ratio: each pair of measurements |
| | | Summer, 1992 | | | 0.43 | | | |
| | | | | | SD: 0.54 | | | |
| Romieu et al. (1998a) | Mexico City, Mexico | September 1993 - July 1994 | Children | 24 h/day, 14 days | 0.15 | NR | School | Ratio: each pair of measurements |
| | | | Children (during school hours) | 5 h/day, 5 days, 10 days | 0.30-0.40 | | | Immediately outside the schools |
| Blondeau et al. (2005) | La Rochelle, France | Spring, 2000 | Children | 2 weeks | Range: 0.00-0.45 | NR | School | No air conditioning Ratio: Indoor mean/outdoor mean |
| López-Aparicio et al. (2011) | Prague, Czech Republic | July 2009 | All age groups | 1 month | 0.10 | NR | Historic Library | No heating or air conditioning Ratio: Indoor mean/outdoor mean |
| | | Dec 2009 | | | 0.30 | | | |
| Riediker et al. (2003) | North Carolina | August - October 2001 | Adults | 9 h | 0.51 | NR | Vehicle | Ratio: Indoor mean/outdoor mean |
| | | | | | p-value: 0.000 | | | |

^aMean value unless otherwise indicated

^bMedian

NR = not reported

SD = standard deviation.

1 [Geyh et al. \(2000\)](#) measured 6-day indoor and outdoor concentrations at 116 homes in
2 southern California, approximately equally divided between the community of Upland
3 and several mountain communities. The extended sampling period resulted in a relatively
4 low detection limit (1 ppb) for the passive samplers used. The Upland homes were nearly
5 all air-conditioned, while the mountain community homes were ventilated by opening
6 windows. During the O₃ season, the indoor O₃ concentration averaged over all homes was

1 approximately 24% of the overall mean outdoor concentration in Upland (11.8 versus
2 48.2 ppb), while in the mountain communities, the indoor concentration was 36% of the
3 outdoor concentration (21.4 versus 60.1 ppb). This is consistent with the increased air
4 exchange rate expected in homes using window ventilation. In the non-ozone season,
5 when homes are likely to be more tightly closed to conserve heat, the ratios of indoor to
6 outdoor concentration were 0.15 (3.2 versus 21.1 ppb) and 0.08 (2.8 versus 35.7 ppb) in
7 Upland and the mountain communities, respectively. [Avol et al. \(1998a\)](#) observed a mean
8 I/O ratio of 0.37 for 239 matched 24-h samples collected between February and
9 December at homes in the Los Angeles area. The I/O ratio during summer was somewhat
10 higher than the non-summer I/O ratio (0.43 versus 0.32). The authors also reported a
11 correlation of 0.58 between the 24-h avg indoor concentration and the outdoor
12 concentration, which was only slightly higher than the correlation between the indoor
13 concentration and the concentration at the neighborhood fixed-site monitor (0.49).
14 Substantially higher summer I/O ratios were reported in a study in Toronto ([Liu et al.,](#)
15 [1995](#)), which found summer I/O ratios of 0.30-0.43, in comparison with a winter I/O ratio
16 of 0.07. [Romieu et al. \(1998a\)](#) reported a mean I/O ratio of 0.20 in 145 homes in
17 Mexico City for 7- or 14-day cumulative samples, with the highest ratios observed in
18 homes where windows were usually open during the day and where there was no
19 carpeting or air filters. Studies conducted in Nashville, TN and Regina, Saskatchewan
20 reported mean residential I/O ratios of approximately 0.1 ([Héroux et al., 2010](#); [Lee et al.,](#)
21 [2004a](#)).

22 Investigators have also measured I/O ratios for non-residential microenvironments,
23 including schools and vehicles. [Romieu et al. \(1998a\)](#) reported that O₃ concentrations
24 measured during school hours (10-day cumulative sample, 5 h/day) were 30-40% of
25 concentrations immediately outside the schools, while overall I/O ratios (14-day
26 cumulative sample, 24 h/day) were approximately 15%. The authors attribute this
27 discrepancy to increased air exchange during the school day due to opening doors and
28 windows. Air exchange was also identified as an important factor in the I/O ratios
29 measured at eight French schools ([Blondeau et al., 2005](#)). In this study, the I/O ratios
30 based on simultaneous continuous measurements ranged from 0-0.45, increasing with
31 decreasing building tightness. A historical library building in Prague, Czech Republic
32 with no heating or air conditioning (i.e., natural ventilation) was observed to have ratios
33 of one-month indoor and outdoor concentrations ranging from 0.10-0.30 during a nine-
34 month sampling campaign, with the highest ratios reported in Nov-Dec 2009 and the
35 lowest ratios during Jul-Aug 2009 ([López-Aparicio et al., 2011](#)). Indoor concentrations
36 were relatively constant (approximately 3-7 µg/m³ or 2-3 ppb), while outdoor
37 concentrations were lower in the winter (9-10 µg/ m³ or about 5 ppb) than in the summer
38 (35-45 µg/ m³ or about 20 ppb). This seasonal variation in outdoor concentrations
39 coupled with homogeneous indoor concentrations, together with increased wintertime air

1 exchange rate due to higher indoor-outdoor temperature differences, is likely responsible
2 for the observed seasonal pattern in I/O ratios.

3 Exposures in near-road, on-road and in-vehicle microenvironments are likely to be more
4 variable and lower in magnitude than those in other microenvironments due to reaction of
5 O₃ with NO and other combustion emissions. Depending on wind direction, O₃
6 concentrations near the roadway have been found to be 20-80% of ambient
7 concentrations at sites 400 meters or more distant from roads (Section [3.6.2.1](#)). A study
8 on patrol cars during trooper work shifts reported in-vehicle 9-h concentrations that were
9 approximately 51% of simultaneously measured roadside concentrations (mean of 11.7
10 versus 22.4 ppb) ([Riediker et al., 2003](#)).

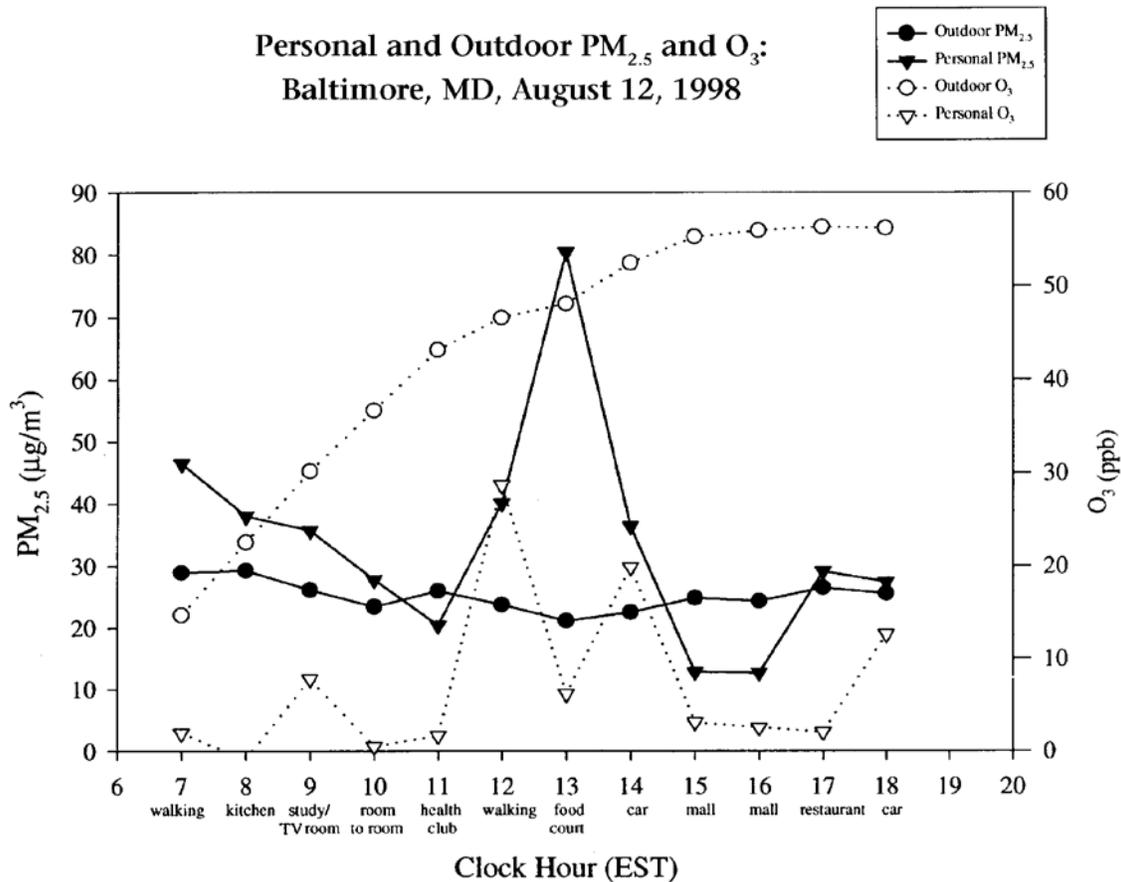
4.3.3 Personal-Ambient Concentration Relationships

11 Several factors influence the relationship between personal O₃ exposure and ambient
12 concentration. Due to the lack of indoor O₃ sources, along with reduction of ambient O₃
13 that penetrates into enclosed microenvironments, indoor and in-vehicle O₃ concentrations
14 are highly dependent on air exchange rate and therefore vary widely in different
15 microenvironments. Ambient O₃ varies spatially due to reactions with other atmospheric
16 species, especially near busy roadways where O₃ concentrations are decreased by
17 reaction with NO (Section [3.6.2.1](#)). This is in contrast with pollutants such as CO and
18 NO_x, which show appreciably higher concentrations near the roadway than several
19 hundred meters away ([Karner et al., 2010](#)). O₃ also varies temporally over multiple
20 scales, with generally increasing concentrations during the daytime hours, and higher O₃
21 concentrations during summer than in winter. An example of this variability is shown in
22 [Figure 4-1](#), taken from a personal exposure study conducted by [Chang et al. \(2000\)](#).

23 In this figure, hourly personal exposures are seen to vary from a few ppb in some indoor
24 microenvironments to tens of ppb in vehicle and outdoor microenvironments. The
25 increase in ambient O₃ concentration during the day is apparent from the outdoor
26 monitoring data. In comparison, ambient PM_{2.5} exhibits less temporal variability over the
27 day than O₃, although personal exposure to PM_{2.5} also varies by microenvironment. This
28 combined spatial and temporal variability for O₃ results in varying relationships between
29 personal exposure and ambient concentration.

30 Correlations between personal exposure to O₃ and corresponding ambient concentrations,
31 summarized in [Table 4-2](#), exhibit a wide range (generally 0.3-0.8, although both higher
32 and lower values have been reported), with higher correlations generally observed in
33 outdoor microenvironments, high building ventilation conditions, and during the summer
34 season. Low O₃ concentrations indoors and during the winter lead to a high proportion of

1 personal exposures below the sampler detection limit, which may partially explain the
 2 low correlations observed in some studies under those conditions. Studies report varying
 3 correlations over a range of averaging times, with no clear trend. Ratios of personal
 4 exposure to ambient concentration, summarized in [Table 4-3](#), are generally lower in
 5 magnitude (typically 0.1-0.3), and are also variable, with increasing time spent outdoors
 6 associated with higher ratios. The next two subsections describe studies that have
 7 reported personal-ambient correlations and slopes for a variety of seasons, locations, and
 8 populations.



Note: the notation below each clock hour shows the location or activity during that hour.

Source: Reprinted with permission of Air and Waste Management Association ([Chang et al., 2000](#)).

Figure 4-1 Variation in hourly personal and ambient concentrations of ozone and PM_{2.5} in various microenvironments during daytime hours.

1 Ozone concentrations near and below the passive sampler detection limit lead to
2 uncertainty in personal-ambient correlations and ratios. Correlations are reduced in
3 magnitude by values below the detection limit because noise obscures the underlying
4 signal in the data, while ratios tend to fluctuate widely at low concentration since small
5 changes in measured values cause large relative changes in resulting ratios. As with I/O
6 ratios, this problem is particularly acute in the non-ozone season when ambient O₃
7 concentrations are low. Improved characterization of the relationship between personal
8 exposure and ambient concentration will depend on the use of recent improved
9 monitoring techniques to accurately capture low O₃ concentrations, preferably at high
10 time resolution to facilitate evaluation of the effect of activity pattern on exposure
11 (Section [4.3.1](#)). While data from studies using new monitoring techniques become
12 available, past studies summarized in the 2006 O₃ AQCD remain relevant to consider
13 along with more recent studies in evaluating personal-ambient concentration
14 relationships.

15 **Personal-Ambient Correlations.** Correlations between personal exposure and
16 ambient O₃ concentrations have been evaluated in several research studies, many of
17 which were conducted prior to 2005 and are discussed in the 2006 O₃ AQCD. Some
18 studies evaluated subject-specific, or longitudinal correlations, which describe multiple
19 daily measurements for a single individual. These studies indicate the inter-individual
20 variability of personal-ambient correlations. Another type of correlation is a pooled
21 correlation, which combines data from multiple individuals over multiple monitoring
22 periods (e.g., days), providing an overall indicator of the personal-ambient relationship
23 for all study subjects. A third type of correlation is a community-average correlation,
24 which correlates average exposure across all study subjects with fixed-site monitor
25 concentrations. Community-average correlations are particularly informative for
26 interpreting time-series epidemiologic studies, in which ambient concentrations are used
27 as a surrogate for community-average exposure. However, few studies report this metric;
28 this represents another opportunity for improvement of future personal exposure studies.
29 [Table 4-2](#) summarizes studies reporting personal-ambient correlations, and the studies in
30 the table are discussed in the subsequent text.

31 The results of these studies generally indicate that personal exposures are moderately
32 well correlated with ambient concentrations, and that the ratio of personal exposure to
33 ambient concentration is higher in outdoor microenvironments and during the summer
34 season. In some situations, a low correlation was observed, and this may be due in part to
35 a high proportion of personal measurements below the detection limit of the personal
36 sampler. The effect of season is unclear, with mixed evidence on whether higher
37 correlations are observed during the O₃ season. [Chang et al. \(2000\)](#) measured hourly
38 personal exposures in multiple microenvironments and found that the pooled correlation

1 between personal exposure and ambient concentration was highest for outdoor
2 microenvironments ($r = 0.68-0.91$). In-vehicle microenvironments showed moderate to
3 high correlations ($0.57-0.72$). Correlations in residential indoor microenvironments were
4 very low ($r = 0.05-0.09$), with moderate correlations ($0.34-0.46$) in other indoor
5 microenvironments such as restaurants and shopping malls. [Liard et al. \(1999\)](#) evaluated
6 community-average correlations based on 4-day mean personal O_3 exposure
7 measurements for adults and children and found a relatively high correlation ($r = 0.83$)
8 with ambient concentrations, even though 31-82% of the personal measurements were
9 below the detection limit. [Sarnat et al. \(2000\)](#) studied a population of older adults in
10 Baltimore and found that longitudinal correlations between 24-h personal exposure and
11 ambient concentration varied by subject and season, with somewhat higher correlations
12 observed in this study during summer (mean = 0.20) than in winter (mean = 0.06). Some
13 evidence was presented that subjects living in well-ventilated indoor environments have
14 higher correlations than those living in poorly ventilated indoor environments, although
15 exceptions to this were also observed. [Ramírez-Aguilar et al. \(2008\)](#) measured 48- to
16 72-h personal exposures of four groups of asthmatic children aged 6-14 in Mexico City
17 during 1998-2000. A moderate pooled correlation ($r = 0.35$) was observed between these
18 exposures and corresponding ambient concentrations.

Table 4-2 Correlations between personal and ambient ozone concentration.

| Study | Location | Years/Season | Population | Sample duration | Correlation | Study Type | Comment |
|---|-----------------------|-------------------------------|-----------------------|-----------------|---------------------------------|--------------------|--------------------------|
| Chang et al. (2000) | Baltimore, MD | Summer 1998 | Older adults | 1 h | 0.91 | Pooled | Outdoor near roadway |
| | | Winter 1999 | | | 0.77 | | |
| | | Summer 1998 | | | 0.68 | | Outdoor away from road |
| | | Winter 1999 | | | 0.86 | | |
| | | Summer 1998 | | | 0.72 | | In vehicle |
| | | Winter 1999 | | | 0.57 | | |
| | | Summer 1998 | | | 0.09 | | Indoors-residence |
| | | Winter 1999 | | | 0.05 | | |
| | | Summer 1998 | | | 0.34 | | Indoors-other |
| | | Winter 1999 | | | 0.46 | | |
| Liard et al. (1999) | Paris, France | Summer 1996 | All age groups | 4 day | 0.83 | Community-averaged | |
| Sarnat et al. (2000) | Baltimore, MD | Summer | Older adults | 24 h | 0.20 | Longitudinal | |
| | | | | | SD: 0.28 95% CI: 0.06, 0.34 | | |
| | | Winter | | | 0.06 | | |
| | | | | | SD: 0.34 95% CI: -0.88, 0.24 | | |
| Linn et al. (1996) | Southern California | All seasons from 1992 to 1993 | Children | 24 h | 0.61 | Community-averaged | |
| Brauer and Brook (1997) | Vancouver, Canada | Summers 1992 and 1993 | Health clinic workers | 24 h | 0.60 | Pooled | 0-25% of time outdoors |
| | | | Camp counselors | 24 h | 0.42 | Pooled | 7.5-45% of time outdoors |
| | | | Farm workers | 24 h | 0.64 | Pooled | 100% of time outdoors |
| Ramírez-Aguilar et al. (2008) | Mexico City, Mexico | December 1998-April 2000 | Asthmatic children | 48 h to 72 h | 0.35 | Pooled | |
| Delfino et al. (1996) | San Diego, California | September and October 1993 | Asthmatic children | 12-h | 0.45 | Pooled | |
| | | | | | Range: 0.35-0.69 | | |

NR = not reported

1 Consistent with hourly microenvironment-specific results from the [Chang et al. \(2000\)](#)
2 study described above, studies have found moderate to high personal-ambient
3 correlations for individuals spending time outdoors. A moderate pooled correlation of
4 0.61 was reported between 24-h avg personal and central-site measurements by [Linn et](#)
5 [al. \(1996\)](#) for a population of southern California schoolchildren who spent an average of

1 101-136 minutes per day outdoors. The authors also report a correlation of 0.70 between
2 central-site measurements and concentrations outside the children's schools. Although
3 the average school outdoor concentration (34 ppb) was higher than the average central-
4 site concentration (23 ppb) and the average personal exposure concentration was lower
5 (5 ppb) than the central-site value, the similarity between the correlations in this study
6 indicate that central-site monitor concentrations can represent personal exposures in
7 addition to representing local outdoor concentrations. A study in Vancouver, BC
8 provided another illustration of the effect of outdoor microenvironments on personal-
9 ambient relationships by comparing three groups spending different amounts of time
10 outdoors: health clinic workers (0-25% of sampling period outdoors), camp counselors
11 (7.5-45% of sampling period outdoors), and farm workers (100% of sampling period
12 outdoors) ([Brauer and Brook, 1997](#)). Health clinic workers and camp counselors were
13 monitored 24 h/day, while farm workers were monitored during their work shift
14 (6-14 hours). In this study, the pooled correlations between personal exposure and fixed-
15 site concentration were not substantially different among the groups ($r = 0.60, 0.42,$ and
16 $0.64,$ respectively). The ratios of personal exposure to fixed-site monitor concentration
17 increased among the groups with increasing amount of time spent outdoors (0.35, 0.53,
18 and 0.96, respectively). This indicates that temporal variations in personal exposure to O₃
19 are driven by variations in ambient concentration, even for individuals that spend little
20 time outdoors.

21 **Personal-Ambient Ratios.** Studies indicate that the ratio between personal O₃
22 exposure and ambient concentration varies widely, depending on activity patterns,
23 housing characteristics, and season. Higher personal-ambient ratios are generally
24 observed with increasing time spent outside, higher air exchange rate, and in seasons
25 other than winter. [Table 4-3](#) summarizes the results of several such studies discussed in
26 the 2006 O₃ AQCD together with newer studies showing the same pattern of results.

27 [O'Neill et al. \(2003\)](#) studied a population of shoe cleaners working outdoors in
28 Mexico City and presented a regression model indicating a 0.56 ppb increase in 6-h
29 personal exposure for each 1 ppb increase in ambient concentration. Regression analyses
30 by ([2005; 2001](#)) for 24-h data from mixed populations of children and older adults in
31 Baltimore ([Sarnat et al., 2001](#)) and Boston ([Sarnat et al., 2005](#)) found differing results
32 between the two cities, with Baltimore subjects showing a near-zero slope (0.01) during
33 the summertime while Boston subjects showed a positive slope of 0.27 ppb personal
34 exposure per 1 ppb ambient concentration. In both cities, the winter slope was near zero.
35 The low slope observed in Baltimore may have been due to differences in time spent
36 outdoors, residential ventilation conditions, or other factors. [Xue et al. \(2005\)](#) measured
37 6-day personal exposure of children in southern California and found that the average
38 ratio of personal exposure to ambient concentration was relatively stable throughout the

1 year at 0.3. These authors also regressed personal exposures on ambient concentration
 2 after adjusting for time-activity patterns and housing characteristics and found a slope of
 3 0.54 ppb/ppb, with the regression R² value of 0.58. Unadjusted regression slopes were
 4 not presented. It should also be noted that the ratio and slope would not be expected to be
 5 identified unless the intercept and other regression parameters were effectively zero.

Table 4-3 Ratios of personal to ambient ozone concentration.

| Study | Location | Years/Season | Population | Sample duration | Ratio ^a | Slope | Intercept | Study Type | Comment |
|---|---------------------|-----------------------|---|-----------------|---------------------------------------|---------------------------|-----------|--------------|---------------------------|
| Sarnat et al. (2001) | Baltimore | Summer 1998 | Older adults and children | 24 h | NR | 0.01 | 1.84 | Longitudinal | t-value: 1.21 |
| | | Winter 1999 | Older adults, children, and individuals with COPD | | NR | 0.00 | 0.46 | | t-value: 0.03 |
| Brauer and Brook (1997) | Vancouver, Canada | Summers 1992 and 1993 | Health clinic workers | 24 h | 0.35 | NR | NR | Pooled | 0-25% of time outdoors |
| | | | Camp counselors | | 0.53 | NR | NR | Pooled | 7.5-45% of time outdoors |
| | | | Farm workers | | 0.96 | NR | NR | Pooled | 100% of time outdoors |
| O'Neill et al. (2003) | Mexico City, Mexico | April - July 1996 | Shoe cleaners | 6 h | 0.40 0.37 ^b SD: 0.22 | 0.56 95% CI: 0.43-0.69 | NR | Longitudinal | |
| Sarnat et al. (2005) | Boston | Summer | Older adults and children | 24 h | NR | 0.27 95% CI: 0.18-0.37 | NR | Longitudinal | |
| | | Winter | | | | NR | | | 0.04 95% CI: 0.00-0.07 |

| Study | Location | Years/Season | Population | Sample duration | Ratio ^a | Slope | Intercept | Study Type | Comment | | |
|---|-----------------------|-----------------------|--------------------|-----------------|--------------------|-----------------------|------------------|------------------|-----------------|--|--|
| Xue et al. (2005) | Southern California | June 1995 - May 1996 | Children | 6 day | 0.3 SD: 0.13 | NR | NR | Longitudinal | | | |
| Sarnat et al. (2006a) | Steubenville, OH | Summer | Older adults | 24 h | NR | 0.15 | NR | Longitudinal | All individuals | | |
| | | | | | | SE: 0.02 | | | | | |
| | | | | | | t-value: 7.21 | | | | | |
| | | R ² : 0.24 | | | | | | | | | |
| | | NR | | | 0.18 | NR | High-ventilation | | | | |
| | | | | | SE: 0.03 | | | | | | |
| | t-value: 7.34 | | | | | | | | | | |
| | R ² : 0.27 | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | NR | 0.08 | NR | Low-ventilation | | | |
| | | | | | | SE: 0.04 | | | | | |
| | | | | | | t-value: 1.89 | | | | | |
| | | | | | | R ² : 0.19 | | | | | |
| | | | | | | | | | | | |
| | | Fall | | | NR | 0.27 | NR | All individuals | | | |
| | | | | | | SE: 0.03 | | | | | |
| | | | | | | t-value: 8.64 | | | | | |
| | | | | | | R ² : 0.25 | | | | | |
| | | | | | | | | | | | |
| | | | | | NR | 0.27 | NR | High-ventilation | | | |
| | | | | | | SE: 0.04 | | | | | |
| | | | | | | t-value: 7.38 | | | | | |
| | | | | | | R ² : 0.33 | | | | | |
| | | | | | | | | | | | |
| | | | | | NR | 0.20 | NR | Low-ventilation | | | |
| | | | | | | SE: 0.05 | | | | | |
| | | | | | | t-value: 3.90 | | | | | |
| | | | | | | R ² : 0.12 | | | | | |
| Ramírez-Aguilar et al. (2008) | Mexico City, Mexico | Dec. 1998- Apr. 2000 | Asthmatic children | 48 h to 72 h | 0.23 | 0.17 | | Pooled | | | |
| | | | | | | SE: 0.02 | | | | | |
| | | | | | | 95% CI : 0.13-0.21 | | | | | |
| | | | | | | p-value: 0.00 | | | | | |

^a Mean value unless otherwise indicated

^b Median

NR = not reported

SD = standard deviation

1 A few additional studies have been published since the 2006 O₃ AQCD comparing
2 personal exposures with ambient concentrations, and these findings generally confirm the
3 conclusions of the 2006 O₃ AQCD that ventilation conditions, activity pattern, and season
4 may impact personal-ambient ratios. [Sarnat et al. \(2006a\)](#) measured 24-h personal
5 exposures for a panel of older adults in Steubenville, OH during summer and fall 2000.

1 Subjects were classified as high-ventilation or low-ventilation based on whether they
2 spent time in indoor environments with open windows. Regression of personal exposures
3 on ambient concentration found a higher slope for high-ventilation subjects compared
4 with low-ventilation subjects in both summer (0.18 versus 0.08) and fall (0.27 versus
5 0.20). [Suh and Zanobetti \(2010\)](#) reported an average 24-h personal exposure of 2.5 ppb as
6 compared to 24-h ambient concentration of 29 ppb for a group of individuals with either
7 recent MI or diagnosed COPD in Atlanta. A similar result was observed in Detroit, where
8 the mean 24-h personal exposure across 137 participants in summer and winter was
9 2.1 ppb, while the mean ambient concentration on sampling days was 25 ppb ([Williams
10 et al., 2009b](#)). Although no personal exposures were measured, [McConnell et al. \(2006\)](#)
11 found that average 24-h home outdoor O₃ concentrations were within 6 ppb of O₃
12 concentrations measured at central-site monitors in each of three southern California
13 communities, with a combined average home outdoor concentration of 33 ppb compared
14 to the central-site average of 36 ppb. In Mexico City, [Ramírez-Aguilar et al. \(2008\)](#)
15 regressed 48- to 72-h personal exposures of four groups of asthmatic children aged 6-14
16 with ambient concentrations and found slope of 0.17 ppb/ppb after adjustment for
17 distance to the fixed-site monitor, time spent outdoors, an interaction term combining
18 these two variables, and an interaction term representing neighborhood and study group.

4.3.4 Co-exposure to Other Pollutants and Environmental Stressors

19 Exposure to ambient O₃ occurs in conjunction with exposure to a complex mixture of
20 ambient pollutants that varies over space and time. Multipollutant exposure is an
21 important consideration in evaluating health effects of O₃ since these other pollutants
22 have either known or potential health effects that may impact health outcomes due to O₃.
23 The co-occurrence of high O₃ concentrations with high heat and humidity may also
24 contribute to health effects. This section presents data on relationships between overall
25 personal O₃ exposure and exposure to other ambient pollutants, as well as co-exposure
26 relationships for near-road O₃ exposure.

4.3.4.1 Personal Exposure to Ozone and Copollutants

27 Personal exposure to O₃ shows variable correlation with personal exposure to other
28 pollutants, with differences in correlation depending on factors such as instrument
29 detection limit, season, city-specific characteristics, time scale, and spatial variability of
30 the copollutant. [Suh and Zanobetti \(2010\)](#) reported Spearman rank correlation
31 coefficients during spring and fall between 24-h avg O₃ measurements and co-pollutants
32 of 0.14, 0.00, and -0.03 for PM_{2.5}, EC, and NO₂, respectively. Titration of O₃ near

1 roadway is likely to contribute to the low or slightly negative correlations with the
2 traffic-related pollutants EC and NO₂. The somewhat higher correlation with PM_{2.5} may
3 reflect the influence of air exchange rate and time spent outdoors on co-exposures to
4 ambient PM_{2.5} and O₃. Overall, the copollutant correlations are quite small, which may be
5 due to the very low personal exposures observed in this study (2-3 ppb), likely to be near
6 or below the detection limit of the passive sampler over a 24-h period. [Chang et al.](#)
7 [\(2000\)](#) measured hourly personal exposures to PM_{2.5} and O₃ in summer and winter in
8 Baltimore, Maryland. Correlations between PM_{2.5} and O₃ were 0.05 and -0.28 in summer
9 and winter, respectively. Results indicate personal O₃ exposures were not significantly
10 associated with personal PM_{2.5} exposures in either summer or winter. These non-
11 significant correlations may be attributed in part to the relatively low personal O₃
12 exposures observed in this study; in both summer and winter, the mean personal O₃
13 exposure was below the calculated limit of detection.

14 Studies conducted in Baltimore ([Sarnat et al., 2001](#)) and Boston ([Sarnat et al., 2005](#))
15 found differing results for the correlation between 24-h avg personal O₃ and personal
16 PM_{2.5} exposures, particularly during the winter season. [Sarnat et al. \(2001\)](#) found a
17 positive slope when regressing personal exposures of both total PM_{2.5} (0.21) and PM_{2.5} of
18 ambient origin (0.22) against personal O₃ exposures during the summer season, but
19 negative slopes (-0.05 and -0.18, respectively) during the winter season. The summertime
20 slope for personal PM_{2.5} exposure versus personal O₃ exposure was much higher for
21 children (0.37) than for adults (0.07), which may be the result of different activity
22 patterns. This team of researchers also found a positive, although higher, summer slope
23 between 24-h avg personal O₃ and personal PM_{2.5} in Boston (0.72) ([Sarnat et al., 2005](#)).
24 However, the winter slope was positive (1.25) rather than negative, as in Baltimore. In
25 both cities during both seasons, there was a wide range of subject-specific correlations
26 between personal O₃ and personal PM_{2.5} exposures, with some subjects showing
27 relatively strong positive correlations (>0.75) and others showing strong negative
28 correlations (<-0.50). The median correlation in both cities was slightly positive in the
29 summer and near zero (Boston) or slightly negative (Baltimore) in the winter. These
30 results indicate the potential effects of city-specific characteristics, such as housing stock
31 and building ventilation patterns, on relationships between O₃ and copollutants.

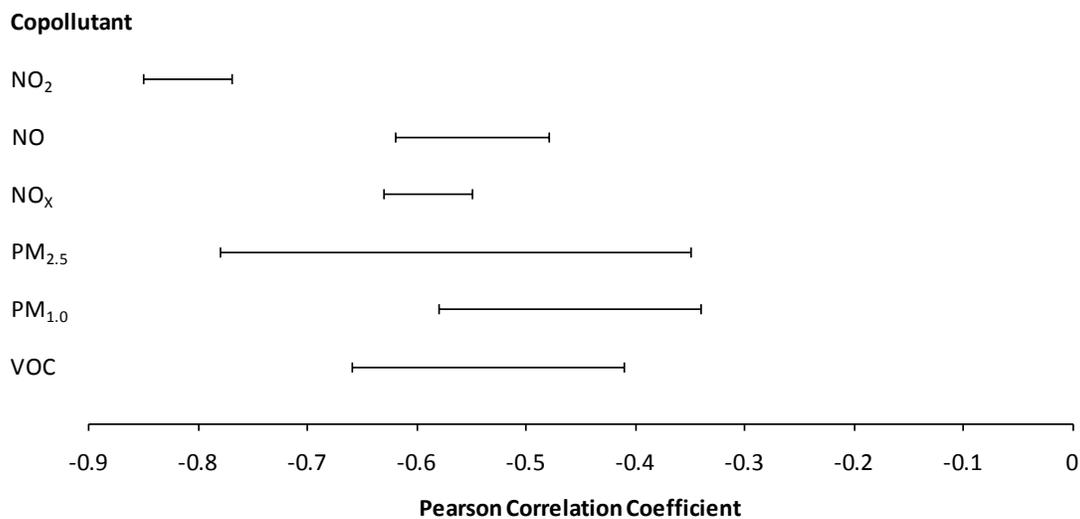
32 The lack of long-term exposure studies limits evaluation of long-term correlations
33 between O₃ exposure and copollutant exposure. However, some insight may be provided
34 by an analysis of correlations between O₃ and other criteria pollutants, such as is
35 provided in Section [3.6.4](#). Warm-season 8-h daily max O₃ concentrations are generally
36 positively correlated with co-located 24-h avg measurements of other criteria pollutants
37 ([Figure 3-57](#)). Median correlations range from approximately 0.15 to 0.55 for CO, SO₂,
38 NO₂, PM₁₀, and PM_{2.5}, in that order. In contrast, year-round 8-h daily max O₃ data show

1 negative median correlations with CO and NO₂, positive correlations with PM₁₀ and
2 PM_{2.5}, and essentially zero correlation with SO₂. This reflects mostly negative
3 correlations between O₃ and all pollutants during wintertime, as shown in [Figure 3-56](#).
4 Titration of O₃ near roadways also likely contributes to overall negative correlations with
5 NO₂ and CO. Positive correlations between O₃ and PM_{2.5} during the summertime can be
6 partly explained by meteorological conditions favoring increased formation of both
7 secondary PM and O₃. Strong positive correlations can influence the interpretation of
8 epidemiologic results, potentially complicating the ability to identify the independent
9 effect of a pollutant.

4.3.4.2 Near-Road Exposure to Ozone and Copollutants

10 [Beckerman et al. \(2008\)](#) measured both 1-week and continuous concentrations of O₃, NO,
11 NO₂, NO_x, PM_{2.5}, PM_{1.0}, and several VOCs (the BTEX compounds, MTBE, hexane, and
12 THC) in the vicinity of heavily traveled (annual average daily traffic [AADT] >340,000)
13 roadways in Toronto, Canada. Passive samplers were deployed for one week in August
14 2004. Ozone concentrations were negatively correlated with all pollutants, with the
15 exception of VOCs at one of the monitoring sites which were suspected of being
16 influenced by small area sources. Site specific correlations are given in [Figure 4-2](#).
17 Correlations were -0.77 to -0.85 for NO₂, -0.48 to -0.62 for NO, and -0.55 to -0.63 for
18 NO_x. Pooled correlations using data from both sites were somewhat lower in magnitude.
19 PM_{2.5} and PM_{1.0} correlations were -0.35 to -0.78 and -0.34 to -0.58, respectively. At the
20 monitoring site not influenced by small area sources, O₃-VOC correlations ranged from -
21 0.41 to -0.66.

22 [Beckerman et al. \(2008\)](#) also made on-road measurements of multiple pollutants with a
23 instrumented vehicle. Concentrations were not reported, but correlations between O₃ and
24 other pollutants were negative and somewhat greater in magnitude (i.e., more negative)
25 than the near-road correlations. SO₂, CO, and BC were measured in the mobile
26 laboratory, although not at the roadside, and they all showed negative correlations with
27 O₃ when the data were controlled for site. Correlations for continuous concentrations
28 between O₃ and co-pollutants were somewhat lower than the 1-week correlations, except
29 for O₃-PM_{2.5} correlations. Correlations were -0.90, -0.66, -0.77, and -0.89 for NO₂, NO,
30 NO_x, and PM_{1.0} respectively. The continuous O₃-PM_{2.5} correlation was -0.62, which is in
31 the range of the 1-week correlation.



Source: Data from: [Beckerman et al. \(2008\)](#)

Figure 4-2 Correlations between 1-week concentrations of ozone and copollutants measured near roadways.

4.3.4.3 Indoor Exposure to Ozone and Copollutants

1 Ambient O₃ that infiltrates indoors reacts with organic compounds and other chemicals to
 2 form oxidized products, as described in Section [3.2.3](#) as well as the 2006 O₃ AQCD. It is
 3 anticipated that individuals are exposed to these reaction products, although no evidence
 4 was identified regarding personal exposures. The reactions are similar to those occurring
 5 in the ambient air, as summarized in Chapter [3](#). For example, O₃ can react with terpenes
 6 and other compounds from cleaning products, air fresheners, and wood products both in
 7 the gas phase and on surfaces to form particulate and gaseous species, such as
 8 formaldehyde ([Chen et al., 2011](#); [Shu and Morrison, 2011](#); [Aoki and Tanabe, 2007](#); [Reiss
 9 et al., 1995b](#)). Ozone has also been shown to react with material trapped on HVAC filters
 10 and generate airborne products ([Bekö et al., 2007](#); [Hytinen et al., 2006](#)). Potential
 11 oxygenated reaction products have been found to act as irritants ([Anderson et al., 2007](#)),
 12 indicating that these reaction products may have health effects separate from those of O₃
 13 itself ([Weschler and Shields, 1997](#)). Ozone may also react to form other oxidants, which
 14 then go on to participate in additional reactions. [White et al. \(2010\)](#) found evidence that
 15 HONO or other oxidants may have been present during experiments to estimate indoor
 16 OH concentrations, indicating complex indoor oxidant chemistry. Rates of these reactions
 17 are dependent on indoor O₃ concentration, temperature, and air exchange rate, making
 18 estimation of exposures to reaction products difficult.

4.4 Exposure-Related Metrics

1 In this section, parameters are discussed that are relevant to the estimation of exposure,
2 but are not themselves direct measures of exposure. Time-location-activity patterns,
3 including behavioral changes to avoid exposure, have a substantial influence on exposure
4 and dose. Proximity of populations to ambient monitors may influence how well their
5 exposure is represented by measurements at the monitors, although factors other than
6 distance play an important role as well.

4.4.1 Activity Patterns

7 The activity pattern of individuals is an important determinant of their exposure.
8 Variation in O₃ concentrations among various microenvironments means that the amount
9 of time spent in each location, as well as the level of activity, will influence an
10 individual's exposure to ambient O₃. The effect of activity pattern on exposure is
11 explicitly accounted for in [Equation 4-3](#) by the fraction of time spent in different
12 microenvironments.

13 Activity patterns vary both among and within individuals, resulting in corresponding
14 variations in exposure across a population and over time. Large-scale human activity
15 databases, such as those developed for the National Human Activity Pattern Survey
16 (NHAPS) ([Klepeis et al., 2001](#)) or the Consolidated Human Activity Database (CHAD)
17 ([McCurdy et al., 2000](#)), which includes NHAPS data together with other activity study
18 results, have been designed to characterize exposure patterns among much larger
19 population subsets than can be examined during individual panel studies. The complex
20 human activity patterns across the population (all ages) are illustrated in [Figure 4-3](#)
21 ([Klepeis et al., 2001](#)), which is presented to illustrate the diversity of daily activities
22 among the entire population as well as the proportion of time spent in each
23 microenvironment. For example, about 25% of the individuals reported being outdoors or
24 in a vehicle between 2:00 and 3:00 p.m., when daily O₃ levels are peaking, although
25 about half of this time was spent in or near a vehicle, where O₃ concentrations are likely
26 to be lower than ambient concentrations.

27 Time spent in different locations has also been found to vary by age. [Table 4-4](#)
28 summarizes NHAPS data reported for four age groups, termed Very Young (0-4 years),
29 School Age (5-17 years), Working (18-64 years), and Retired (65+ years) ([Klepeis et al.,](#)
30 [1996](#)). The working population spent the least time outdoors, while the school age
31 population spent the most time outdoors. NHAPS respondents aged 65 and over spent
32 somewhat more time outdoors than adults aged 18-64, with a greater fraction of time

1 spent outdoors at a residence. Children aged 0-4 also spent most of their outdoor time in a
 2 residential outdoor location. On average, the fraction of time spent outdoors by school
 3 age respondents was 2.62 percentage points higher than working respondents,
 4 corresponding to approximately 38 minutes more time outdoors per day. Although not
 5 accounting for activity level, this increased time spent outdoors is consistent with
 6 evidence in Chapter 8 suggesting that younger and older age groups are more at risk for
 7 O₃-related health effects.

Table 4-4 Mean fraction of time spent in outdoor locations by various age groups in the NHAPS study

| Age Group | Residential-Outdoor | Other Outdoor | Total Outdoors |
|-----------|---------------------|---------------|----------------|
| 0-4 yr | 5.38% | 0.96% | 6.34% |
| 5-17 yr | 5.05% | 2.83% | 7.88% |
| 18-64 yr | 2.93% | 2.33% | 5.26% |
| 65+ yr | 4.48% | 1.27% | 5.75% |

Source: Data from [Klepeis et al. \(1996\)](#).

8 Together with location, exertion level is an important determinant of exposure. [Table 4-5](#)
 9 summarizes ventilation rates for different age groups at several levels of activity as
 10 presented in Table 6-2 of the EPA's *Exposure Factors Handbook* ([U.S. EPA, 2011b](#)).
 11 Most of the age-related variability is seen for moderate and high intensity activities,
 12 except for individuals under 1 year. For moderate intensity, ventilation rate increases with
 13 age through childhood and adulthood until age 61, after which a moderate decrease is
 14 observed. Ventilation rate is most variable for high intensity activities. Children aged 1 to
 15 <11 years have ventilation rates of approximately 40 L/min, while children aged 11+ and
 16 adults have ventilation rates of approximately 50 L/min. The peak is observed for the 51
 17 to <61 age group, at 53 L/min, with lower ventilation rates for older adults.

Table 4-5 Mean ventilation rates (L/min) at different activity levels for different age groups.

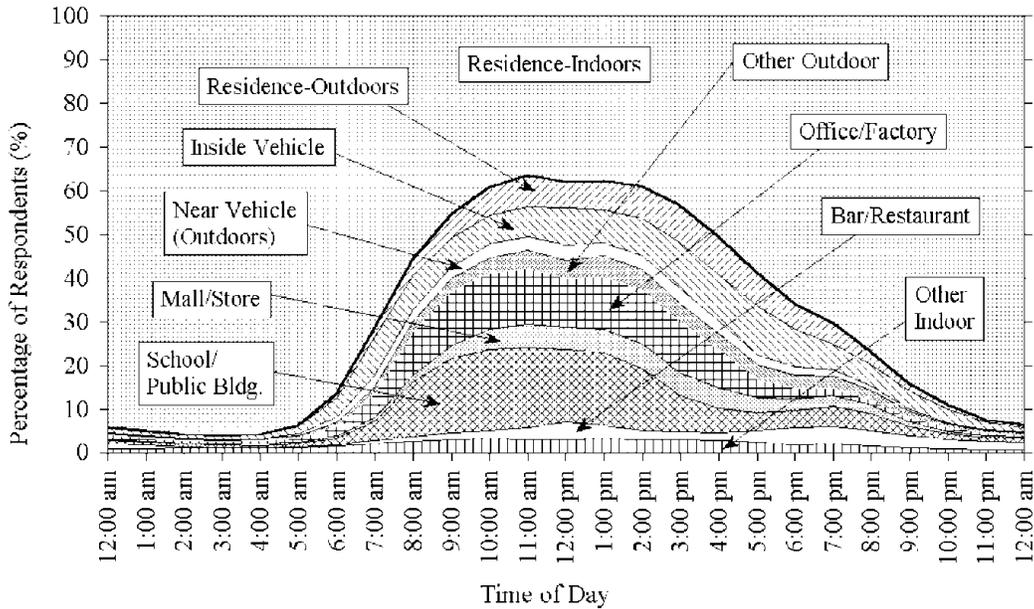
| Age Group | Sleep or Nap | Sedentary/Passive | Light Intensity | Moderate Intensity | High Intensity |
|----------------|--------------|-------------------|-----------------|--------------------|----------------|
| Birth to <1 yr | 3.0 | 3.1 | 7.6 | 14 | 26 |
| 1 to <2 yr | 4.5 | 4.7 | 12 | 21 | 38 |
| 2 to <3 yr | 4.6 | 4.8 | 12 | 21 | 39 |
| 3 to <6 yr | 4.3 | 4.5 | 11 | 21 | 37 |
| 6 to <11 yr | 4.5 | 4.8 | 11 | 22 | 42 |
| 11 to <16 yr | 5.0 | 5.4 | 13 | 25 | 49 |
| 16 to <21 yr | 4.9 | 5.3 | 12 | 26 | 49 |
| 21 to <31 yr | 4.3 | 4.2 | 12 | 26 | 50 |
| 31 to <41 yr | 4.6 | 4.3 | 12 | 27 | 49 |
| 41 to <51 yr | 5.0 | 4.8 | 13 | 28 | 52 |
| 51 to <61 yr | 5.2 | 5.0 | 13 | 29 | 53 |
| 61 to <71 yr | 5.2 | 4.9 | 12 | 26 | 47 |
| 71 to <81 yr | 5.3 | 5.0 | 12 | 25 | 47 |
| 81+ yr | 5.2 | 4.9 | 12 | 25 | 48 |

Source: Data from *Exposure Factors Handbook* ([U.S. EPA, 2011b](#)).

1 A dramatic increase in ventilation rate occurs as exercise intensity increases. For children
 2 and adults <31 years, high intensity activities result in nearly double the ventilation rate
 3 for moderate activity, which itself is nearly double the rate for light activity. Children
 4 have other important differences in ventilation compared to adults. As discussed in
 5 Chapter 5, children tend to have a greater oral breathing contribution than adults, and
 6 they breathe at higher minute ventilations relative to their lung volumes. Both of these
 7 factors tend to increase dose normalized to lung surface area.

8 Longitudinal activity pattern information is also an important determinant of exposure, as
 9 different people may exhibit different patterns of time spent outdoors over time due to
 10 age, gender, employment, and lifestyle-dependent factors. These differences may
 11 manifest as higher mean exposures or more frequent high-exposure episodes for some
 12 individuals. The extent to which longitudinal variability in individuals contributes to the
 13 population variability in activity and location can be quantified by the ratio of between-
 14 person variance to total variance in time spent in different locations and activities (the
 15 intraclass correlation coefficient, ICC). [Xue et al. \(2004\)](#) quantified ICC values in time-
 16 activity data collected by Harvard University for 160 children aged 7–12 years in
 17 Southern California ([Geyh et al., 2000](#)). For time spent outdoors, the ICC was
 18 approximately 0.15, indicating that 15% of the variance in outdoor time was due to

1 between-person differences. The ICC value might be different for other population
2 groups.



Source: Reprinted with permission of Nature Publishing Group ([Klepeis et al., 2001](#)).

Figure 4-3 Distribution of time that NHAPS respondents spent in ten microenvironments based on smoothed 1-min diary data.

3 The EPA's National Exposure Research Laboratory (NERL) has consolidated the most
4 important human activity databases into one comprehensive database called the
5 Consolidated Human Activity Database (CHAD). The current version of CHAD contains
6 data from nineteen human activity pattern studies (including NHAPS), which were
7 evaluated to obtain over 33,000 person-days of 24-h human activities in CHAD
8 ([McCurdy et al., 2000](#)). The surveys include probability-based recall studies conducted
9 by EPA and the California Air Resources Board, as well as real-time diary studies
10 conducted in individual U.S. metropolitan areas using both probability-based and
11 volunteer subject panels. All ages of both genders are represented in CHAD. The data for
12 each subject consist of one or more days of sequential activities, in which each activity is
13 defined by start time, duration, activity type, and microenvironment classification
14 (i.e., location). Activities vary from one minute to one hour in duration, with longer
15 activities being subdivided into clock-hour durations to facilitate exposure modeling.
16 CHAD also provides information on the level of exertion associated with each activity,

1 which can be used by exposure models, including the APEX model (Section [4.5.3](#)), to
2 estimate ventilation rate and pollutant dose.

4.4.2 Ozone Averting Behavior

3 Individuals can reduce their exposure to O₃ by altering their behaviors, such as by staying
4 indoors, being active outdoors when air quality is better, and by reducing activity levels
5 or time spent being active outdoors on high-O₃ days. To assist the public in avoiding
6 exposure to air pollution on days with high pollutant concentrations, EPA has developed
7 an information tool known as the Air Quality Index (AQI) to provide information to the
8 public on ambient levels of pollutants and the potential for individuals to experience
9 health effects ([U.S. EPA, 2011a](#)). The AQI describes the potential for health effects from
10 O₃ (and other individual pollutants) in six color-coded categories of air-quality, ranging
11 from good (green), moderate (yellow), unhealthy for sensitive groups (orange), unhealthy
12 (red), very unhealthy (purple), and hazardous (maroon). The levels are associated with
13 descriptors of the likelihood of health effects and the populations most likely to be
14 affected. For example, the orange level indicates that the general population is not likely
15 to be at risk, but susceptible groups may experience health effects. These advisories
16 explicitly state that children, older adults, people with lung disease, and those who are
17 active outdoors may be at greater risk from exposure to air pollution. Forecasted and
18 actual conditions typically are reported to the public during high-O₃ months through local
19 media outlets, using various versions of this air-quality categorization scheme. People are
20 advised to change their behavior to reduce exposure depending on predicted O₃
21 concentrations and the likelihood of risk. Behavioral recommendations include being
22 active outdoors when air quality is better, and reducing activity levels or the time spent
23 being active outdoors on high-O₃ days. Staying indoors to reduce exposure is only
24 recommended when the AQI is at or above the very unhealthy range.

25 Evidence of individual averting behaviors in response to advisories has been found in
26 several studies, especially for potentially susceptible populations, such as children, older
27 adults, and asthmatics. Reduced time spent outdoors was reported in an activity diary
28 study in 35 U.S. cities ([Mansfield et al., 2006](#)), which found that asthmatic children who
29 spent at least some time outdoors reduced their total time spent outdoors by an average of
30 30 min on a code red O₃ day relative to a code green, yellow, or orange day; however, the
31 authors noted that there was appreciable variation in both the overall amount of time
32 spent outdoors and the reduction in outdoor time on high ozone days among asthmatic
33 children. [Bresnahan et al. \(1997\)](#) examined survey data collected during 1985-86 from a
34 panel of adults in the Los Angeles area, many of whom had compromised respiratory
35 function, by an averting behavior model. A regression analysis indicated that individuals

1 with smog-related symptoms spent about 12 minutes less time outdoors over a two-day
2 period for each 10 ppb increase in O₃ concentration above 120 ppb. Considering that the
3 average daily maximum O₃ concentration at the time was approximately 180 ppb on days
4 when the then-current standard (1-h max of 120 ppb) was exceeded, this implies that
5 those individuals spent about 40 minutes less time outside per day on a typical high O₃
6 day compared to days with O₃ concentrations below the standard. However, the behavior
7 was not specifically linked to exceedances or air quality alerts.

8 The fraction of individuals who reduce time spent outdoors, or restrict their children's
9 outdoor activity, has been found to vary based on health status. In the [Bresnahan et al.
10 \(1997\)](#) study, 40 percent of respondents reported staying indoors on days when air quality
11 was poor. Individuals who reported experiencing smog-related symptoms were more
12 likely to take the averting actions, although the presence of asthma or other chronic
13 respiratory conditions did not have a statistically significant effect on behavior. A study
14 of parents of asthmatic children ([McDermott et al., 2006](#)) suggests that parents are aware
15 of the hazard of outdoor air pollution and the official alerts designed to protect them and
16 their children. It also suggests that a majority of parents (55%) comply with
17 recommendations of the alerts to restrict children's outdoor activity, with more parents of
18 asthmatics reporting awareness and responsiveness to alerts. However, only 7% of all
19 parents complied with more than one-third of the advisories issued ([McDermott et al.,
20 2006](#)). [Wen et al. \(2009\)](#) analyzed data from the 2005 Behavioral Risk Factor
21 Surveillance System (BRFSS) and indicated that people with asthma are about twice as
22 likely as people without asthma to reduce their outdoor activities based on either media
23 alerts of poor air quality (31% vs. 16%) or individual perception of air quality (26% vs.
24 12%). Respondents who had received advice from a health professional to reduce outdoor
25 activity when air quality is poor were more likely to report a reduction based on media
26 alerts, both for those with and without asthma. In a study of randomly selected
27 individuals in Houston, TX and Portland, OR, [Semenza et al. \(2008\)](#) found that a
28 relatively small fraction of survey respondents (9.7% in Houston, 10.5% in Portland)
29 changed their behaviors during poor air quality episodes. This fraction is appreciably
30 lower than the fraction reported for people with asthma in the [Wen et al. \(2009\)](#) study,
31 although it is similar to the fraction reported in that study for those without asthma. Most
32 of the people in the [Semenza et al. \(2008\)](#) study reported that their behavioral changes
33 were motivated by self-perception of poor air quality rather than an air quality advisory.
34 It should be noted that the [McDermott et al. \(2006\)](#), [Wen et al. \(2009\)](#), and [Semenza et al.
35 \(2008\)](#) studies evaluated air quality in general and therefore are not necessarily specific to
36 O₃.

37 Commuting behavior does not seem to change based on air quality alerts. A study in the
38 Atlanta area showed that advisories can raise awareness among commuters but do not

1 necessarily result in a change in an individual's travel behavior ([Henry and Gordon,](#)
2 [2003](#)). This finding is consistent with a survey for 1000 commuters in Denver, Colorado,
3 which showed that the majority (76%) of commuters heard and understood the air quality
4 advisories, but did not alter their commuting behavior ([Blanken et al., 2001](#)).

5 Some evidence is available for other behavioral changes in response to air quality alerts.
6 Approximately 40 percent of the respondents in the Los Angeles study by [Bresnahan et](#)
7 [al. \(1997\)](#) limited or rearranged leisure activities, and 20 percent increased use of air
8 conditioners. As with changes in time spent outdoors, individuals who reported
9 experiencing smog-related symptoms, but not those with asthma or chronic respiratory
10 conditions, were more likely to take the averting actions. Other factors influencing
11 behavioral changes, such as increased likelihood of averting behavior among high school
12 graduates, are also reported in the study. In a separate Southern California study,
13 attendance at two outdoor facilities (i.e., a zoo and an observatory) was reduced by
14 6-13% on days when smog alerts were announced, with greater decreases observed
15 among children and older adults ([Neidell, 2010, 2009](#)).

16 The studies discussed in this section indicate that averting behavior is dependent on
17 several factors, including health status and lifestage. People with asthma and those
18 experiencing smog-related symptoms reduce their time spent outdoors and are more
19 likely to change their behavior than those without respiratory conditions. Children and
20 older adults appear more likely to change their behavior than the general population.
21 Commuters, even when aware of air quality advisories, tend not to change their
22 commuting behavior.

4.4.3 Population Proximity to Fixed-Site Ozone Monitors

23 The distribution of O₃ monitors across urban areas varies between cities (Section [3.6.2.1](#)),
24 and the population living near each monitor varies as well. Monitoring sites in rural areas
25 are generally located in national or state parks and forests, and these monitors may be
26 relevant for exposures of exercising visitors as well as those who live in similar locations.
27 They also serve as an important source of data for evaluating ecological effects of O₃
28 (Chapter [9](#)). Rural monitors tend to be less affected than urban monitors by strong and
29 highly variable anthropogenic sources of species participating in the formation and
30 destruction of O₃ (e.g., onroad mobile sources) and more highly influenced by regional
31 transport of O₃ or O₃ precursors (Section [3.6.2.2](#)). This may contribute to less diel
32 variability in O₃ concentration than is observed in urban areas.

33 A variety of factors determine the siting of the O₃ monitors that are part of the SLAMS
34 network reporting to AQS. As discussed in Section [3.5.6](#), the number and location of

1 required O₃ monitors in an urban area depend on O₃ concentration and population, among
2 other factors. Areas classified as serious, severe, or extreme nonattainment have
3 additional monitoring requirements. Generally, high-O₃ urban areas with a population of
4 50,000 or greater are required to have at least one monitor; in low- or moderate-
5 concentration areas, the minimum population for a required monitor is 350,000. Most
6 large U.S. cities have several monitors, as shown in [Figure 3-76](#) through [Figure 3-95](#).

7 As an illustration of the location of O₃ monitors and their concentrations with respect to
8 population density, [Figure 4-4](#) through [Figure 4-6](#) present this information for Atlanta,
9 Boston, and Los Angeles, the three cities selected for detailed analysis in Chapter [3](#). They
10 represent a cross-section with respect to geographic distribution, O₃ concentration,
11 layout, geographic features, and other factors. The maps show the location of O₃
12 monitors, identified by the same letters as in Chapter [3](#) to facilitate intercomparisons,
13 along with the 2007-09 mean 8-h daily max O₃ concentration for perspective on the
14 variation in O₃ concentration across the urban area. Population density at the census
15 block group level is also presented on the maps.

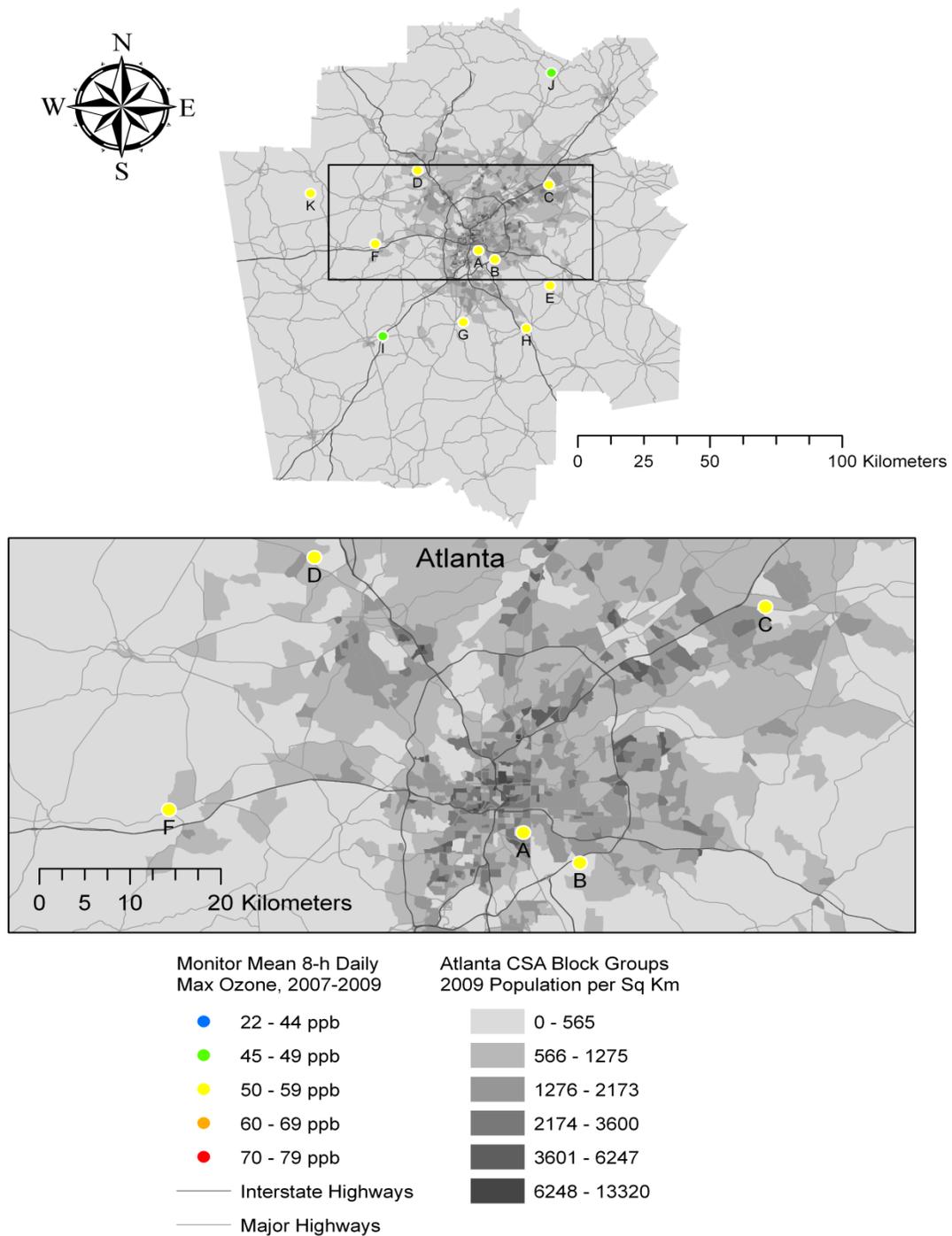


Figure 4-4 Map of the Atlanta CSA including ozone monitor locations and major roadways with respect to census block group population density estimates for 2009.

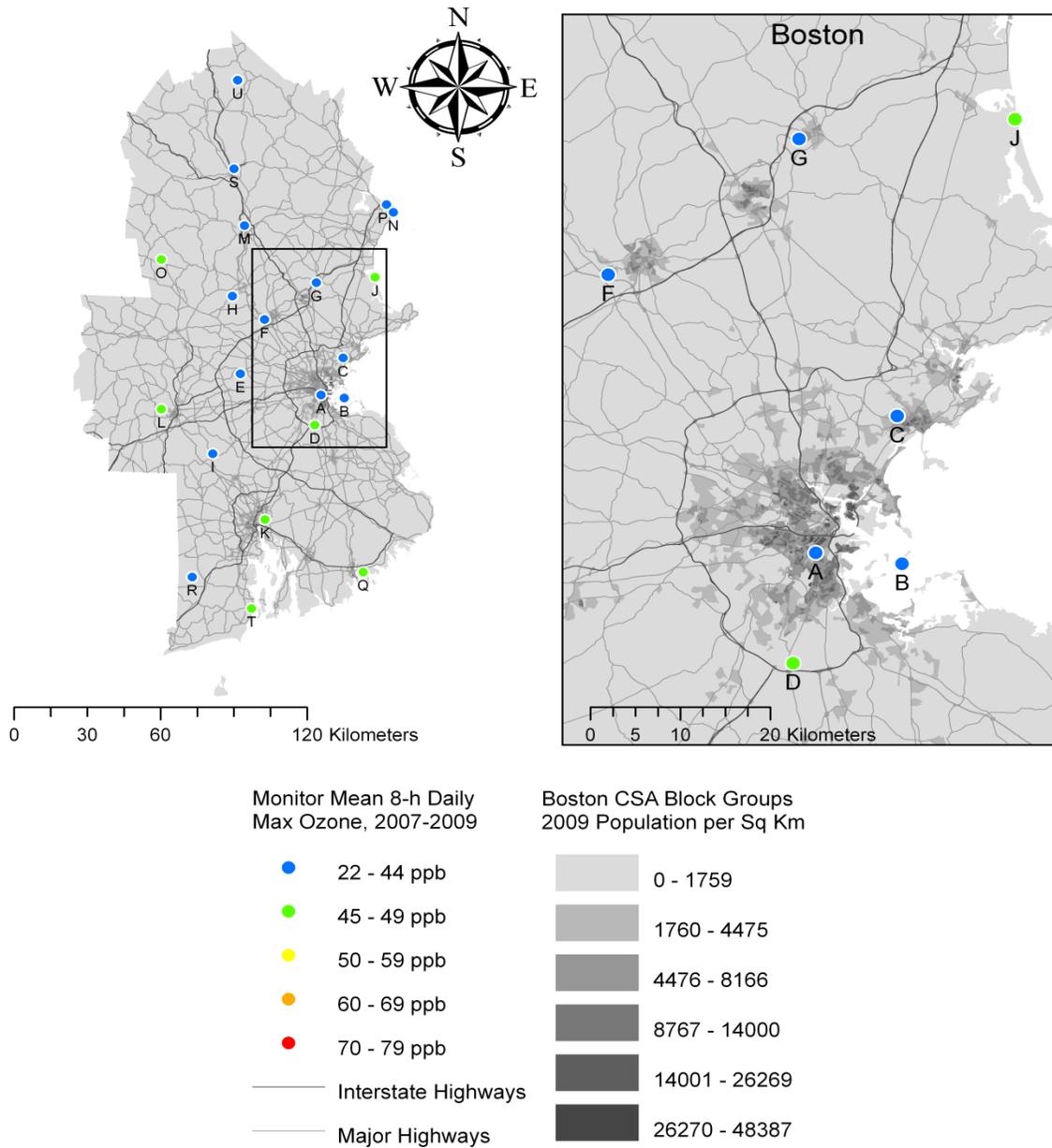


Figure 4-5 Map of the Boston CSA including ozone monitor locations and major roadways with respect to census block group population density estimates for 2009.

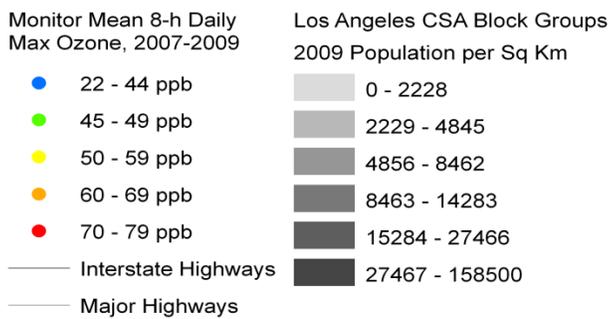
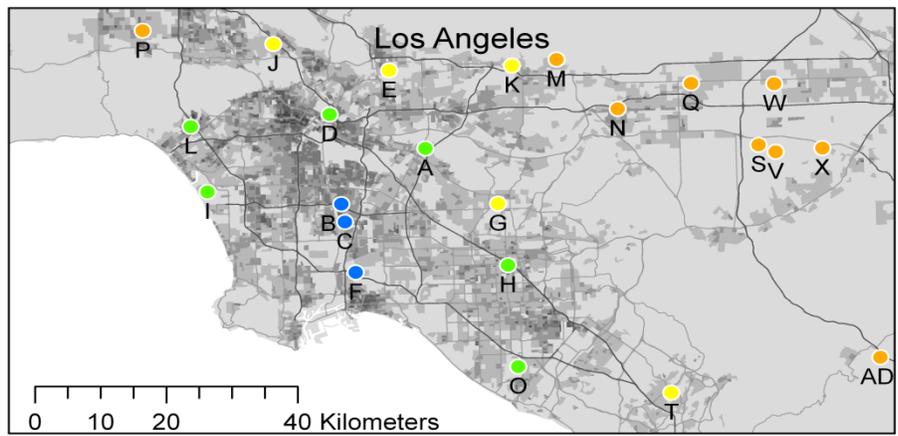
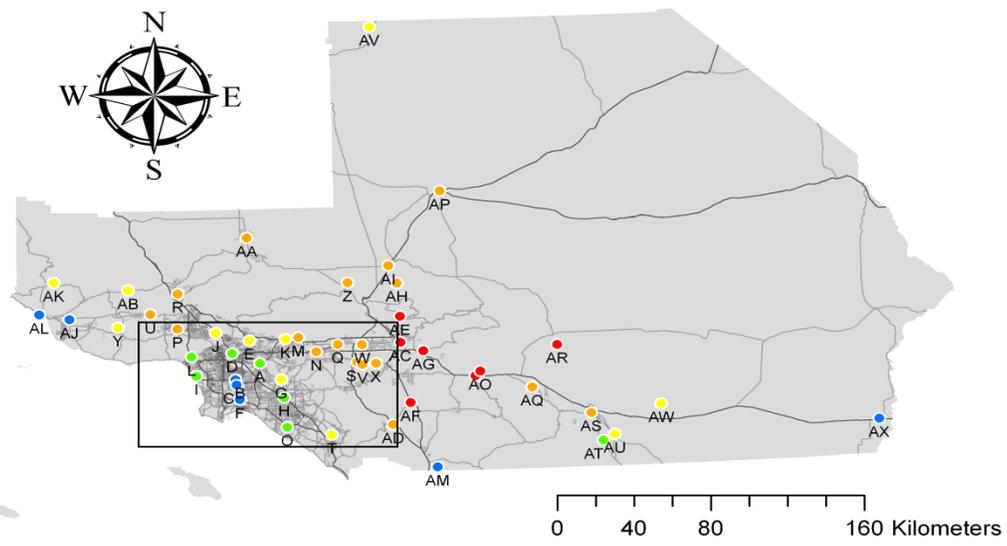


Figure 4-6 Map of the Los Angeles CSA including ozone monitor locations and major roadways with respect to census block group population density estimates for 2009.

1 Similarities and differences are apparent among the cities. The spatial distribution of
2 monitor locations in Atlanta and Boston is similar, with one site (site A) near the high
3 population density area and other monitors in surrounding areas of lower population
4 density. In Atlanta, the monitors near the city all have similar concentrations, while
5 somewhat lower concentrations are observed at sites I and J, which are located >50 km
6 from the city center. Boston shows a different spatial concentration pattern, with some
7 low and some high concentrations in urban and less-populated areas. The differences in
8 spatial concentration profiles between the two cities may be due to more consistent
9 terrain in Atlanta compared with Boston, which has a coastline, along with the downwind
10 influence of New York and other northeastern cities contributing to concentration
11 variability.

12 Los Angeles has a much more complex spatial pattern of monitors, population, and
13 geography. There are a large number of monitors located in multiple levels of population
14 density across the entire CSA, which includes substantial rural areas. Most monitors are
15 near at least moderate population density areas, but there are some high-density areas
16 without a monitor. Concentrations increase in a somewhat radial or west-east pattern
17 from the city, with lower concentrations near the port of Long Beach (monitors B, C, and
18 F). The highest concentrations are located near the San Bernadino forest (e.g., monitors
19 AG, AO, and AR), which have lower population density, but more potential for ecological
20 impacts. Low concentrations in highly populated areas near the coast likely reflect
21 titration by NO_x and other atmospheric constituents, while high downwind
22 concentrations reflect lack of local sources and increased photochemical processing time.

23 The location of these monitors relative to the location of dense population centers varies
24 among urban areas. NCore sites, a subset of the overall monitoring network, are designed
25 with population exposure as a monitoring objective, and the monitoring requirements in
26 40 CFR Part 58, Appendix D include population density as one of several factors that
27 would be considered in designing the O₃ monitoring program for an area. At least one site
28 for each MSA is designed to be a maximum concentration site, which could presumably
29 represent the location with the maximum exposure potential in the city. Sites may also be
30 required upwind and downwind of high-concentration urban areas.

31 All three cities have some high population density areas without an O₃ monitor. The
32 siting considerations for NCore monitors generally target the neighborhood (0.5-4 km) or
33 urban (4-50 km) scale to provide representative concentrations throughout the
34 metropolitan area; however, a middle-scale (0.1-0.5 km) site may be acceptable in cases
35 where the site can represent many such locations throughout a metropolitan area. In other
36 words, a monitor could potentially represent exposures in other similar areas of the city if
37 land use and atmospheric chemistry conditions are similar. This is supported by the

1 correlation analyses in Chapter 3. For example, in Los Angeles, monitors H and L are
2 located in medium-density areas and show moderately high correlation (0.78), although
3 they are some 50 km apart.

4 Although proximity to a monitor does not determine the degree to which that monitor
5 represents an individual's ambient exposure, it is one indicator. One way to calculate
6 monitor representativeness is to calculate the fraction of the urban population living
7 within a certain radius of a monitor. Table 4-6 presents the fraction of the population in
8 selected cities living within 1, 5, 10, and 20 km of an O₃ monitor. Values are presented
9 for both total population and for those under 18 years of age, a potentially susceptible
10 population to the effects of O₃. The data indicate that relatively few people live within
11 1 km of an O₃ monitor, while nearly all of the population in most cities lives within
12 20 km of a monitor. Looking at the results for a 5-km radius, corresponding roughly to
13 the neighborhood scale (Section 3.5.6.1), generally 20-30% of the population lives within
14 this distance from an O₃ monitor. Some cities have a greater population in this buffer,
15 such as Salt Lake City, while others have a lower percentage, such as Minneapolis and
16 Seattle. Percentages for children are generally similar to the total population, with no
17 clear trend.

18 Another approach is to divide the metropolitan area into sectors surrounding each
19 monitor such that every person in the sector lives closer to that monitor than any other.
20 This facilitates calculation of the fraction of the city's population represented (according
21 to proximity) by each monitor. In Atlanta, for example, the population fraction
22 represented by each of the 11 monitors in the city ranged from 2.9-22%. The two
23 monitors closest to the city center (sites A and B on Figure 4-4) accounted for 16% and
24 8% of the population, respectively. Site B has two listed monitoring objectives, highest
25 concentration and population exposure. The other monitor in Atlanta with a listed
26 objective of highest concentration is Site C, which represents the largest fraction of the
27 population (22%). The eight monitors with a primary monitoring objective of population
28 exposure account for 2.9-17% of the population per monitor.

Table 4-6 Fraction of the 2009 population living within a specified distance of an ozone monitor in selected U.S. cities.

| City | Population | | Within 1 km | | Within 5 km | | Within 10 km | | Within 20 km | |
|--------------------|------------|-----------|-------------|--------|-------------|--------|--------------|--------|--------------|--------|
| | Total | <18 yr | Total | <18 yr | Total | <18 yr | Total | <18 yr | Total | <18 yr |
| Atlanta CSA | 5,901,670 | 1,210,932 | 0.3% | 0.3% | 8% | 9% | 28% | 29% | 75% | 77% |
| Baltimore CSA | 8,421,016 | 1,916,106 | 1.3% | 1.1% | 25% | 24% | 57% | 55% | 89% | 89% |
| Birmingham CSA | 1,204,399 | 281,983 | 1.4% | 1.6% | 22% | 24% | 56% | 59% | 73% | 74% |
| Boston CSA | 7,540,533 | 1,748,918 | 0.9% | 0.9% | 17% | 16% | 49% | 47% | 85% | 85% |
| Chicago CSA | 9,980,113 | 2,502,454 | 1.5% | 1.5% | 28% | 29% | 63% | 65% | 89% | 91% |
| Dallas CSA | 6,791,942 | 1,530,877 | 0.4% | 0.4% | 13% | 13% | 45% | 44% | 87% | 87% |
| Denver CSA | 3,103,801 | 675,380 | 1.7% | 1.6% | 35% | 36% | 66% | 68% | 92% | 93% |
| Detroit CSA | 5,445,448 | 1,411,875 | 0.8% | 0.9% | 15% | 17% | 42% | 44% | 77% | 78% |
| Houston CSA | 5,993,633 | 1,387,851 | 1.5% | 1.8% | 26% | 28% | 54% | 57% | 83% | 84% |
| Los Angeles CSA | 18,419,720 | 4,668,441 | 1.6% | 1.7% | 28% | 29% | 77% | 79% | 98% | 98% |
| Minneapolis CSA | 3,652,490 | 872,497 | 0.3% | 0.3% | 5% | 4% | 16% | 16% | 57% | 56% |
| New York CSA | 22,223,406 | 5,284,875 | 1.5% | 1.7% | 23% | 23% | 51% | 50% | 91% | 91% |
| Philadelphia CSA | 6,442,836 | 1,568,878 | 0.9% | 1.0% | 22% | 24% | 55% | 56% | 89% | 89% |
| Phoenix CBSA | 4,393,462 | 873,084 | 2.0% | 2.4% | 35% | 41% | 74% | 79% | 96% | 97% |
| Pittsburgh CSA | 2,471,403 | 563,309 | 1.5% | 1.4% | 22% | 21% | 52% | 50% | 88% | 88% |
| Salt Lake City CSA | 1,717,045 | 460,747 | 3.0% | 3.0% | 41% | 38% | 79% | 79% | 95% | 95% |
| San Antonio CBSA | 2,061,147 | 484,473 | 0.5% | 0.5% | 12% | 12% | 42% | 43% | 78% | 80% |
| San Francisco CSA | 7,497,443 | 1,675,711 | 2.6% | 2.9% | 41% | 40% | 81% | 81% | 98% | 98% |
| Seattle CSA | 4,181,278 | 918,309 | 0.3% | 0.3% | 5% | 5% | 18% | 16% | 43% | 39% |
| St. Louis CSA | 2,914,754 | 720,746 | 1.3% | 1.5% | 17% | 18% | 52% | 53% | 80% | 82% |

1 Atlanta population fractions for children (<18 years of age) are similar to those for the
2 general population, but other populations show a different pattern of monitor
3 representativeness. Older adults (age 65 and up) were somewhat differently distributed
4 with respect to the monitors, with most monitors showing a difference of more than a
5 percentage point compared to the general population. Based on 2000 population data, the
6 fraction of older adults closest to the two city center monitors (A and B) was 4% higher
7 and 2% lower, respectively, than the fraction for the population as a whole. Site C
8 showed the highest differential, with 21% of the total population but only 15% of the
9 older adult population. This indicates the potential for monitors to differentially represent
10 potentially susceptible populations.

4.5 Exposure Modeling

1 In the absence of personal exposure measurements, modeling techniques are used to
2 estimate exposures, particularly for large populations for which individual-level
3 measurements would be impractical. Model estimates may be used as inputs to
4 epidemiologic studies or as stand-alone assessments of the level of exposure likely to be
5 experienced by a population under certain air quality conditions. This section describes
6 approaches used to improve exposure estimates, including concentration surface
7 modeling, which calculates local outdoor concentrations over a geographic area; air
8 exchange rate modeling, which estimates building ventilation based on housing
9 characteristics and meteorological parameters; and microenvironment-based exposure
10 modeling, which combines air quality data with demographic information and activity
11 pattern simulations to estimate time-weighted exposures based on concentrations in
12 multiple microenvironments. These models each have strengths and limitations, as
13 summarized in [Table 4-7](#). The remainder of this section provides more detail on specific
14 modeling approaches, as well as results of applying the models.

Table 4-7 Characteristics of exposure modeling approaches.

| Model Type | Model | Description | Strengths | Limitations |
|---|---|--|--|---|
| Concentration Surface | Spatial Interpolation (e.g., Inverse Distance Weighting, Kriging) | Measured concentrations are interpolated across an area to yield local outdoor concentration estimates | High concentration resolution; uses available data; requires low to moderate resources for implementation | Spatial heterogeneity not fully captured; a single high-concentration monitor can skew results; no location-activity information |
| | Chemistry-transport (e.g., CMAQ) | Grid-based O ₃ concentrations are calculated from precursor emissions, meteorology, and atmospheric chemistry and physics | First-principles characterization of physical and chemical processes influencing O ₃ formation | Grid cell resolution; resource-intensive; no location-activity information |
| | Land-use regression (LUR) | Merges concentration data with local-scale variables such as land use factors to yield local concentration surface | High concentration resolution | Reactivity and small-scale spatial variability of O ₃ ; location-specific, limiting generalizability; no location-activity information |
| Air Exchange Rate | Mechanistic (LBL, LBLX) | Uses database on building leakage tests to predict AER based on building characteristics and meteorological variables (including natural ventilation in LBLX) | Physical characterization of driving forces for air exchange | Moderate resource requirement; no location-activity information |
| | Empirical | Predicts AER based on factors such as building age and floor area | Low input data requirements | Cannot account for meteorology; no location-activity information |
| Integrated Microenvironmental Exposure and Dose | Population (APEX, SHEDS) | Stochastic treatment of air quality data, demographic variables, and activity pattern to generate estimates of microenvironmental concentrations, exposures, and doses | Probabilistic estimates of exposure and dose distributions for specific populations; consideration of nonambient sources; small to moderate uncertainty for exercising asthmatic children (APEX) | Resource-intensive; evaluation with measured exposures; underestimation of multiple high-exposure events in an individual (APEX) |

4.5.1 Concentration Surface Modeling

1 One approach to improve exposure estimates in urban areas involves construction of a
2 concentration surface over a geographic area, with the concentration at locations between
3 monitors estimated using a model to compensate for missing data. The calculated O₃
4 concentration surface can then be used to estimate exposures outside residences, schools,
5 workplaces, roadways, or other locations of interest. This technique does not estimate
6 exposure directly because it does not account for activity patterns or concentrations in
7 different microenvironments. This is an important consideration in the utility of these
8 methods for exposure assessment; while improved local-scale estimates of outdoor
9 concentrations may contribute to better assignment of exposures, information on activity

1 patterns is needed to produce estimates of personal exposure. There are three main types
2 of approaches: spatial interpolation of measured concentrations; statistical models using
3 meteorological variables, pollutant concentrations, and other predictors to estimate
4 concentrations at receptors in the domain; and rigorous first-principle models, such as
5 chemistry-transport models or dispersion models incorporating O₃ chemistry. Some
6 researchers have developed models that combine these techniques. The models may be
7 applied over urban, regional, or national spatial scales, and can be used to estimate daily
8 concentrations or longer-term averages. This discussion will focus on short-term
9 concentrations estimated across urban areas.

10 The 2006 O₃ AQCD discussed concentration surface models, focusing on chemistry-
11 transport models as well as geospatial and spatiotemporal interpolation techniques (e.g.,
12 [Christakos and Vyas, 1998a, b](#); [Georgopoulos et al., 1997](#)). Recent research has
13 continued to refine and extend the modeling approaches. A few recent papers have
14 compared different approaches for the same urban area.

15 [Marshall et al. \(2008\)](#) compared four spatial interpolation techniques for estimation of O₃
16 concentrations in Vancouver, BC. The investigators assigned a daily average O₃
17 concentration to each of the 51,560 postal-code centroids using one of the following
18 techniques: (1) the concentration from the nearest monitor within 10 km; (2) the average
19 of all monitors within 10 km; (3) the inverse-distance-weighted (IDW) average of all
20 monitors in the area; and (4) the IDW average of the 3 closest monitors within 50 km.
21 Method 1 (the nearest-monitor approach) and Method 4 (IDW-50 km) had similar mean
22 and median estimated annual- and monthly-average concentrations, although the 10th-
23 90th percentile range was smaller for IDW-50. This is consistent with the averaging of
24 extreme values inherent in IDW methods. The Pearson correlation coefficient between
25 the two methods was 0.93 for monthly-average concentrations and 0.78 for annual-
26 average concentrations. Methods 2 and 3 were considered sub-optimal and were excluded
27 from further analysis. In the case of Method 2, a single downtown high-concentration
28 monitor skewed the results in the vicinity, partially as a result of the asymmetric layout of
29 the coastal city of Vancouver. Method 3 was too spatially homogenous because it
30 assigned most locations a concentration near the regional average, except for locations
31 immediately adjacent to a monitoring site. CMAQ concentration estimates using a
32 4 km×4 km grid were also compared to the interpolation techniques in this study. Mean
33 and median concentrations from CMAQ were approximately 50% higher than Method 1
34 and Method 4 estimates for both annual and monthly average concentrations. This may
35 be due in part to the CMAQ grid size, which was too coarse to reveal near-roadway
36 decrements in O₃ concentration due to titration by NO. The IQR for the annual average
37 was similar between CMAQ and the interpolation techniques, but the monthly average
38 CMAQ IQR was approximately twice as large, indicating a seasonal effect.

1 [Bell \(2006\)](#) compared CMAQ estimates for northern Georgia with nearest-monitor and
2 spatial interpolation techniques, including IDW and kriging. The area-weighted
3 concentration estimates from CMAQ indicated areas of spatial heterogeneity that were
4 not captured by approaches based on the monitoring network. The author concluded that
5 some techniques, such as spatial interpolation, were not suitable for estimation of
6 exposure in certain situations, such as for rural areas. Using the concentration from the
7 nearest monitor resulted in an overestimation of exposure relative to model estimates.

8 Land use regression (LUR) models have been developed to estimate levels of air
9 pollutants, predominantly NO₂, as a function of several land use factors, such as land use
10 designation, traffic counts, home heating usage, point source strength, and population
11 density ([Ryan and LeMasters, 2007](#); [Gilliland et al., 2005](#); [Briggs et al., 1997](#)). LUR,
12 initially termed regression mapping ([Briggs et al., 1997](#)), is a regression derived from
13 monitored concentrations as a function of data from a combination of the land use
14 factors. The regression is then used for predicting concentrations at multiple locations
15 based on the independent variables at those particular locations without monitors. [Hoek
16 et al. \(2008\)](#) warn of several limitations of LUR, including distinguishing real
17 associations between pollutants and covariates from those of correlated copollutants,
18 limitations in spatial resolution from monitor data, applicability of the LUR model under
19 changing temporal conditions, and introduction of confounding factors when LUR is used
20 in epidemiologic studies. These limitations may partially explain the lack of LUR models
21 that have been developed for O₃ at the urban scale. [Brauer et al. \(2008\)](#) evaluated the use
22 of LUR and IDW-based spatial-interpolation models in epidemiologic analyses for
23 several different pollutants in Vancouver, BC and suggested that LUR is appropriate for
24 directly-emitted pollutants with high spatial variability, such as NO and BC, while IDW
25 is appropriate for secondary pollutants such as NO₂ and PM_{2.5} with less spatial variability.
26 Although O₃ is also a secondary pollutant, its reactivity and high small-scale spatial
27 variability near high-traffic roadways indicates this conclusion may not apply for O₃.

28 At a much larger spatial scale, EU-wide, [Beelen et al. \(2009\)](#) compared a LUR model for
29 O₃ with ordinary kriging and universal kriging, which incorporated meteorological,
30 topographical, and land use variables to characterize the underlying trend. The LUR
31 model performed reasonably well at rural locations (5-km resolution), explaining a higher
32 percentage of the variability ($R^2 = 0.62$) than for other pollutants. However, at the urban
33 scale (1-km resolution), only one variable was selected into the O₃ LUR model
34 (high-density residential land use), and the R^2 value was very low (0.06). Universal
35 kriging was the best method for the large-scale composite EU concentration map, for O₃
36 as well as for NO₂ and PM₁₀, with an R^2 value for O₃ of 0.70. The authors noted that
37 these methods were not designed to capture spatial variation in concentrations that are

1 known to occur within tens of meters of roadways (Section [3.6.2.1](#)), which could partially
2 explain poor model performance at the urban scale.

3 Titration of O₃ with NO emitted by motor vehicles tends to reduce O₃ concentrations near
4 roadways. [McConnell et al. \(2006\)](#) developed a regression model to predict residential O₃
5 concentrations in southern California using estimates of residential NO_x calculated from
6 traffic data with the CALINE4 line source dispersion model. The annual average model
7 results were well-correlated (R² = 0.97) with multi-year average monitoring data. The
8 authors estimated that local traffic contributes 18% of NO_x concentrations measured in
9 the study communities, with the remainder coming from regional background. Their
10 regression model indicates that residential NO_x reduces residential O₃ concentrations by
11 0.51 ppb (SE 0.11 ppb) O₃ per 1 ppb NO_x, and that a 10th-90th percentile increase in
12 local NO_x results in a 7.5 ppb decrease in local O₃ concentrations. This intra-urban
13 traffic-related variability in O₃ concentrations suggests that traffic patterns are an
14 important factor in the relationship between central site monitor and residential O₃, and
15 that differences in traffic density between the central site monitor and individual homes
16 could result in either an overestimate or underestimate of residential O₃.

17 A substantial number of researchers have used geostatistical methods and chemistry-
18 transport models to estimate O₃ concentrations at urban, regional, national, and
19 continental scales, both in the U.S. and in other countries (Section [3.3](#)). In addition to
20 short-term exposure assessment for epidemiologic studies, such models may also be used
21 for long-term exposure assessment, O₃ forecasts, or evaluating emission control
22 strategies. However, as discussed at the beginning of this section, caveats regarding the
23 importance of activity pattern information in estimating personal and population exposure
24 should be kept in mind.

4.5.2 Residential Air Exchange Rate Modeling

25 The residential air exchange rate (AER), which is the airflow into and out of a home, is
26 an important mechanism for entry of ambient O₃. As described in Section [4.3.2](#), the
27 indoor-outdoor relationship is greatly affected by the AER. Since studies show that
28 people spend approximately 66% of their time indoors at home ([Leech et al., 2002](#);
29 [Klepeis et al., 2001](#)), the residential AER is a critical parameter for exposure models,
30 such as APEX, SHEDS, and EMI (discussed in Section [4.5.3](#)) ([U.S. EPA, 2011c, 2009b](#);
31 [Burke et al., 2001](#)). Since the appropriate AER measurements may not be available for
32 exposure models, mechanistic and empirical (i.e., regression-based) AER models can be
33 used for exposure assessments. The input data for the AER models can include building
34 characteristics (e.g., age, number of stories, wind sheltering), occupant behavior

1 (e.g., window opening), climatic region, and meteorology (e.g., local temperature and
2 wind speed). Mechanistic AER models use these meteorological parameters to account
3 for the physical driving forces of the airflows due to pressure differences across the
4 building envelope from wind and indoor-outdoor temperature differences ([ASHRAE,
5 2009](#)). Empirical AER models do not consider the driving forces from the wind and
6 indoor-outdoor temperature differences. Instead, a scaling constant can be used based on
7 factors such as building age and floor area ([Chan et al., 2005b](#)).

8 Single-zone mechanistic models represent a whole-building as a single, well-mixed
9 compartment. These AER models, such as the Lawrence Berkeley Laboratory (LBL)
10 model, can predict residential AER using input data from whole-building pressurization
11 tests ([Sherman and Grimsrud, 1980](#)), or leakage area models ([Breen et al., 2010](#); [Sherman
12 and McWilliams, 2007](#)). Recently, the LBL air infiltration model was linked with a
13 leakage area model using population-level census and residential survey data ([Sherman
14 and McWilliams, 2007](#)) and individual-level questionnaire data ([Breen et al., 2010](#)). The
15 LBL model, which predicts the AER from air infiltration (i.e., small uncontrollable
16 openings in the building envelope) was also extended to include airflow from natural
17 ventilation (LBLX), and evaluated using window opening data ([Breen et al., 2010](#)). The
18 AER predictions from the LBL and LBLX models were compared to daily AER
19 measurements on seven consecutive days during each season from detached homes in
20 central North Carolina ([Breen et al., 2010](#)). For the individual model-predicted and
21 measured AER, the median absolute difference was 43% (0.17 h^{-1}) and 40% (0.17 h^{-1}) for
22 the LBL and LBLX models, respectively. Given the uncertainty of the AER
23 measurements (accuracy of 20-25% for occupied homes), these results demonstrate the
24 feasibility of using these AER models for both air infiltration (e.g., uncontrollable
25 openings) and natural ventilation (e.g., window opening) to help reduce the AER
26 uncertainty in exposure models. The capability of AER models could help support the
27 exposure modeling needs, as described in Section [4.5.3](#), which includes the ability to
28 predict indoor concentrations of ambient O_3 that may be substantial for conditions of high
29 AER such as open windows.

4.5.3 Microenvironment-Based Models

30 Population-based methods, such as the Air Pollution Exposure (APEX) and Stochastic
31 Human Exposure and Dose Simulation (SHEDS) integrated microenvironmental
32 exposure and dose models, involve stochastic treatment of the model inputs ([U.S. EPA,
33 2009b](#); [Burke et al., 2001](#)). These are described in detail in the 2008 NO_x ISA ([U.S. EPA,
34 2008b](#)), in AX3.6.1. Stochastic models utilize distributions of pollutant-related and
35 individual-level variables, such as ambient and local O_3 concentration contributions and

1 breathing rate respectively, to compute the distribution of individual exposures across the
2 modeled population. The models also have the capability to estimate received dose
3 through a dosimetry model. Using distributions of input parameters in the model
4 framework rather than point estimates allows the models to incorporate uncertainty and
5 variability explicitly into exposure estimates ([Zidek et al., 2007](#)). These models estimate
6 time-weighted exposure for modeled individuals by summing exposure in each
7 microenvironment visited during the exposure period.

8 The initial set of input data for population exposure models is ambient air quality data,
9 which may come from a monitoring network or model estimates. Estimates of
10 concentrations in a set of microenvironments are generated either by mass balance
11 methods, which can incorporate AER models (Section [4.5.3](#)), or microenvironmental
12 factors. Microenvironments modeled include indoor residences; other indoor locations,
13 such as schools, offices, and public buildings; and vehicles. The sequence of
14 microenvironments and exertion levels during the exposure period is determined from
15 characteristics of each modeled individual. The APEX model does this by generating a
16 profile for each simulated individual by sampling from distributions of demographic
17 variables such as age, gender, and employment; physiological variables such as height
18 and weight; and situational variables such as living in a house with a gas stove or air
19 conditioning. Activity and location (microenvironmental) patterns from a database such
20 as CHAD are assigned to the simulated individual in a longitudinal manner, using age,
21 gender, and biometric characteristics ([U.S. EPA, 2009a](#); [Glen et al., 2008](#)). Breathing
22 rates for each individual are calculated for each activity based on predicted energy
23 expenditures, and the corresponding dose may then be computed. APEX has an algorithm
24 to estimate O₃ dose and changes in FEV₁ resulting from O₃ exposure. Summaries of
25 individual- and population-level metrics are produced, such as maximum exposure or
26 dose, number of individuals exceeding a specified exposure/dose, and number of
27 person-days at or above benchmark exposure levels. The models also consider the
28 nonambient contribution to total exposure. Nonambient source terms are added to the
29 infiltration of ambient pollutants to calculate the total concentration in the
30 microenvironment. Output from model runs with and without nonambient sources can be
31 compared to estimate the ambient contribution to total exposure and dose.

32 [Georgopoulos et al. \(2005\)](#) used a version of the SHEDS model as the exposure
33 component of a modeling framework known as MENTOR (Modeling Environment for
34 Total Risk Studies) in a simulation of O₃ exposure in Philadelphia over a 2-week period
35 in July 1999. 500 individuals were sampled from CHAD in each of 482 census tracts to
36 match local demographic characteristics from U.S. Census data. Outdoor concentrations
37 over the modeling domain were calculated from interpolation of photochemical modeling
38 results and fixed-site monitor concentrations. These concentrations were then used as

1 input data for SHEDS. Median microenvironmental concentrations predicted by SHEDS
2 for nine simulated microenvironments were strongly correlated with outdoor
3 concentrations, a result consistent with the lack of indoor O₃ sources in the model. A
4 regression of median microenvironmental concentrations against outdoor concentrations
5 indicated that the microenvironmental concentrations were appreciably lower than
6 outdoor concentrations (regression slope = 0.26). 95th percentile microenvironmental
7 concentrations were also well correlated with outdoor concentrations and showed a
8 regression slope of 1.02, although some microenvironmental concentrations were well
9 below the outdoor values. This suggests that in most cases the high-end concentrations
10 were associated with outdoor microenvironments. Although the authors did not report
11 exposure statistics for the population, their dose calculations also indicated that O₃ dose
12 due to time spent outdoors dominated the upper percentiles of the population dose
13 distribution. They found that both the 50th and 95th percentile O₃ concentrations were
14 correlated with census-tract level outdoor concentrations estimated by photochemical
15 modeling combined with spatiotemporal interpolation, and attributed this correlation to
16 the lack of indoor sources of O₃. Relationships between exposure and concentrations at
17 fixed-site monitors were not reported.

18 An analysis has been conducted for the APEX model to evaluate the contribution of
19 uncertainty in input parameters and databases to the uncertainty in model outputs
20 ([Langstaff, 2007](#)). The Monte Carlo analysis indicates that the uncertainty in model
21 exposure estimates for asthmatic children during moderate exercise is small to moderate,
22 with 95% confidence intervals of at most ± 6 percentage points at exposures above 60,
23 70, and 80 ppb (8-h avg) However, APEX appears to substantially underestimate the
24 frequency of multiple high-exposure events for a single individual. The two main sources
25 of uncertainty identified were related to the activity pattern database and the spatial
26 interpolation of fixed-site monitor concentrations to other locations. Additional areas
27 identified in the uncertainty analysis for potential improvement include: further
28 information on children's activities, including longitudinal patterns in the activity pattern
29 database; improved information on spatial variation of O₃ concentrations, including in
30 near-roadway and indoor microenvironments; and data from personal exposure monitors
31 with shorter averaging times to capture peak exposures and lower detection limits to
32 capture low indoor concentrations. A similar modeling approach has been developed for
33 panel epidemiologic studies or for controlled human exposure studies, in which activity
34 pattern data specific to the individuals in the study can be collected. Time-activity data is
35 combined with questionnaire data on housing characteristics, presence of indoor or
36 personal sources, and other information to develop a personalized set of model input
37 parameters for each individual. This model, the Exposure Model for Individuals, has been
38 developed by EPA's National Exposure Research Laboratory ([U.S. EPA, 2011c](#);
39 [Zartarian and Schultz, 2010](#)).

4.6 Implications for Epidemiologic Studies

1 Exposure measurement error, which refers to the uncertainty associated with using
2 exposure metrics to represent the actual exposure of an individual or population, can be
3 an important contributor to variability in epidemiologic study results. Time-series studies
4 assess the daily health status of a population of thousands or millions of people over the
5 course of multiple years (i.e., thousands of days) across an urban area by estimating their
6 daily exposure using a short monitoring interval (hours to days). In these studies, the
7 community-averaged concentration of an air pollutant measured at central-site monitors
8 is typically used as a surrogate for individual or population ambient exposure. In
9 addition, panel studies, which consist of a relatively small sample (typically tens) of
10 study participants followed over a period of days to months, have been used to examine
11 the health effects associated with short-term exposure to ambient concentrations of air
12 pollutants ([Delfino et al., 1996](#)). Panel studies may also apply a microenvironmental
13 model to represent exposure to an air pollutant. A longitudinal cohort epidemiologic
14 study, such as the ACS cohort study, typically involves hundreds or thousands of subjects
15 followed over several years or decades ([Jerrett et al., 2009](#)). Concentrations are generally
16 aggregated over time and by community to estimate exposures.

17 Exposure error can under- or over-estimate epidemiologic associations between ambient
18 pollutant concentrations and health outcomes by biasing effect estimates toward or away
19 from the null, and tends to widen confidence intervals around those estimates ([Sheppard
20 et al., 2005](#); [Zeger et al., 2000](#)). Exposure misclassification can also tend to obscure the
21 presence of potential thresholds for health effects, as demonstrated by a simulation study
22 of nondifferential exposure misclassification ([Brauer et al., 2002](#)). The importance of
23 exposure misclassification varies with study design and is dependent on the spatial and
24 temporal aspects of the design. For example, the use of a community-averaged O₃
25 concentration in a time-series epidemiologic study may be adequate to represent the day-
26 to-day temporal concentration variability used to evaluate health effects, but may not
27 capture differences in the magnitude of exposure due to spatial variability. Other factors
28 that could influence exposure estimates include nonambient exposure, topography of the
29 natural and built environment, meteorology, measurement errors, use of ambient O₃
30 concentration as a surrogate for ambient O₃ exposure, and the presence of O₃ in a mixture
31 of pollutants. The following sections will consider various sources of error and how they
32 affect the interpretation of results from epidemiologic studies of different designs.

4.6.1 Non-Ambient Ozone Exposure

1 For other criteria pollutants, nonambient sources can be an important contributor to total
2 personal exposure. There are relatively few indoor sources of O₃; as a result, personal O₃
3 exposure is expected to be dominated by ambient O₃ in outdoor microenvironments and
4 in indoor microenvironments with high air exchange rates (e.g., with open windows).
5 Even in microenvironments where nonambient exposure is substantial, such as in a room
6 with an O₃ generator, this nonambient exposure is unlikely to be temporally correlated
7 with ambient O₃ exposure ([Wilson and Suh, 1997](#)), and therefore would not affect
8 epidemiologic associations between O₃ and a health effect ([Sheppard et al., 2005](#)). In
9 simulations of a nonreactive pollutant, [Sheppard et al. \(2005\)](#) concluded that nonambient
10 exposure does not influence the health outcome effect estimate if ambient and
11 nonambient concentrations are independent. Since personal exposure to ambient O₃ is
12 some fraction of the ambient concentration, it should be noted that effect estimates
13 calculated based on personal exposure rather than ambient concentration will be
14 increased in proportion to the ratio of ambient concentration to ambient exposure, and
15 daily fluctuations in this ratio can widen the confidence intervals in the ambient
16 concentration effect estimate, but uncorrelated nonambient exposure will not bias the
17 effect estimate ([Sheppard et al., 2005](#); [Wilson and Suh, 1997](#)).

4.6.2 Spatial and Temporal Variability

18 Spatial and temporal variability in O₃ concentrations can contribute to exposure error in
19 epidemiologic studies, whether they rely on central-site monitor data or concentration
20 modeling for exposure assessment. Spatial variability in the magnitude of concentrations
21 may affect cross-sectional and large-scale cohort studies by undermining the assumption
22 that intra-urban concentration and exposure differences are less important than inter-
23 urban differences. This issue may be less important for time-series studies, which rely on
24 day-to-day temporal variability in concentrations to evaluate health effects. Low inter-
25 monitor correlations contribute to exposure error in time-series studies, including bias
26 toward the null and increased confidence intervals.

4.6.2.1 Spatial Variability

27 Spatial variability of O₃ concentrations is highly dependent on spatial scale; in effect, O₃
28 is a regional pollutant subject to varying degrees of local variability. In the immediate
29 vicinity of roadways, O₃ concentrations are reduced due to reaction with NO and other
30 species (Section [4.3.4.2](#)); over spatial scales of a few kilometers, O₃ may be more

1 homogeneous due to its formation as a secondary pollutant; over scales of tens of
2 kilometers, atmospheric processing can result in higher concentrations downwind of an
3 urban area than in the urban core. Local-scale variations have a large impact on the
4 relative magnitude of concentrations among urban monitors, while conditions favoring
5 high or low rates of O₃ formation (e.g., temperature) vary over large spatial scales. This
6 suggests that neighborhood monitors are likely to track one another temporally, but miss
7 small-scale spatial variability in magnitude. This is supported by an analysis in Atlanta
8 that found correlations greater than 0.8 for daily O₃ concentration metrics (1-h max,
9 8-h max, and 24-h avg) measured at monitors 10-60 km apart ([Darrow et al., 2011a](#)). In
10 rural areas, a lower degree of fluctuation in O₃ precursors such as NO and VOCs is likely
11 to make the diel concentration profile less variable than in urban areas, resulting in more
12 sustained ambient levels. Spatial variability contributes to exposure error if the ambient
13 O₃ concentration measured at the central site monitor is used as an ambient exposure
14 surrogate and differs from the actual ambient O₃ concentration outside a subject's
15 residence and/or worksite (in the absence of indoor O₃ sources). Averaging data from a
16 large number of samplers will dampen intersampler variability, and use of multiple
17 monitors over smaller land areas may allow for more variability to be incorporated into
18 an epidemiologic analysis.

19 Community exposure may not be well represented when monitors cover large areas with
20 several subcommunities having different sources and topographies, such as the
21 Los Angeles CSA (Section [3.6.2.1](#) and Section [4.4.3](#)). Ozone monitors in Los Angeles
22 had a much wider range of intermonitor correlations (-0.06 to 0.97) than Atlanta (0.61 to
23 0.96) or Boston (0.56 to 0.97) using 2007-2009 data. Although the negative and near-zero
24 correlations in Los Angeles were observed for monitors located some distance apart
25 (>150 km), some closer monitor pairs had low positive correlations, likely due to changes
26 in land use, topography, and airflow patterns over short distances. Lower COD values,
27 which indicate less variability among monitors in the magnitude of O₃ concentrations,
28 were observed in Atlanta (0.05-0.13) and Boston (0.05-0.19) than Los Angeles
29 (0.05-0.56), although a single monitor (AM) was responsible for all Los Angeles COD
30 values above 0.40. The spatial and temporal variability in O₃ concentration in 24 MSAs
31 across the U.S. was also examined in the 2006 O₃ AQCD by using Pearson correlation
32 coefficients, values of the 90th percentile of the absolute difference in O₃ concentrations,
33 and CODs. No clear discernible regional differences across the U.S. were found in the
34 ranges of parameters analyzed.

35 An analysis of the impact of exposure error due to spatial variability and instrument
36 imprecision on time-series epidemiologic study results indicated that O₃ has relatively
37 low exposure error compared to other routinely monitored pollutants, and that the
38 simulated impact on effect estimates is minor. [Goldman et al. \(2011\)](#) computed

1 population-weighted scaled semivariances and Pearson correlation coefficients for daily
2 concentration metrics of twelve pollutants measured at multiple central-site monitors in
3 Atlanta. 8-h daily max O₃ exhibited the lowest semivariance and highest correlation of
4 any of the pollutants. Although this indicates some degree of urban-scale homogeneity
5 for O₃, the analysis did not account for near-road effects on O₃ concentrations.

6 Studies evaluating the influence of monitor selection on epidemiologic study results have
7 found that O₃ effect estimates are similar across different spatial averaging scales and
8 monitoring sites. A study in Italy compared approaches for using fixed-site monitoring
9 data in a case-crossover epidemiologic study of daily O₃ and mortality ([Zauli Sajani et
10 al., 2011](#)). O₃ effect estimates were found to be similar whether the nearest monitor was
11 used, or whether single-city, three-city, or six-city regional averages were used for
12 exposure assessment. In contrast, effect estimates for PM₁₀ and NO₂ increased with
13 increasing scale of spatial averaging. Confidence intervals increased with increasing
14 spatial scale for all pollutants. The authors attributed the consistency of O₃ effect
15 estimates to the relative spatial homogeneity of O₃ over multi-km spatial scales, and
16 pointed to the high (0.85-0.95) inter-monitor correlations to support this. The use of
17 background monitors rather than monitors influenced by local sources in this study
18 suggests that local-scale spatial variation in O₃, such as that due to titration by traffic
19 emissions, was not captured in the analyses. A multi-city U.S. study of asthmatic children
20 found comparable respiratory effect estimates when restricting the analysis to the
21 monitors closest to the child's zip code centroid as when using the average of all
22 monitors in the urban area ([Mortimer et al., 2002](#)), suggesting little impact of monitor
23 selection. [Sarnat et al. \(2010\)](#) studied the spatial variability of O₃, along with PM_{2.5}, NO₂,
24 and CO, in the Atlanta, GA, metropolitan area and evaluated how spatial variability
25 affects interpretation of epidemiologic results, using time-series data for circulatory
26 disease ED visits. The authors found that associations with ambient 8-h daily maximum
27 O₃ concentration were similar among all sites tested, including multiple urban sites and a
28 rural site some 38 miles from the city center. This result was also observed for 24-h PM_{2.5}
29 concentrations. In contrast, hourly CO and NO₂ showed different associations for the
30 rural site than the urban sites, although the urban site associations were similar to one
31 another for CO. This suggests that the choice of monitor may have little impact on the
32 results of O₃ time-series studies, consistent with the moderate to high inter-monitor
33 correlations observed in Atlanta (Chapter [3](#)).

34 One potential explanation for this finding from the study by [Sarnat et al. \(2010\)](#) is that
35 although spatial variability at different scales contributes to a complicated pattern of
36 variations in the magnitude of O₃ concentrations between near-road, urban core, and
37 urban downwind sites, day-to-day fluctuations in concentrations may be reflected across
38 multiple urban microenvironments. In addition, time-averaging of O₃ and PM_{2.5}

1 concentrations may smooth out some of the intra-day spatial variability observed with the
2 hourly CO and NO₂ concentrations. However, some uncertainty in observed effect
3 estimates due to spatial variability and associated exposure error is expected to remain,
4 including a potential bias towards the null.

4.6.2.2 Seasonality

5 The relationship between personal exposure and ambient concentration has been found to
6 vary by season, with at least three factors potentially contributing to this variation:
7 differences in building ventilation (e.g., air conditioning or heater use versus open
8 window ventilation), higher O₃ concentrations during the O₃ season contributing to
9 increased exposure and improved detection by personal monitors; and changes in activity
10 pattern resulting in more time spent outside. Evidence has been presented in studies
11 conducted in several cities regarding the effect of ventilation on personal-ambient and
12 indoor-outdoor O₃ relationships (see Section 4.3.2 and Section 4.3.3). More limited
13 evidence is available regarding the specific effects of O₃ detection limits and activity
14 pattern changes on O₃ relationships.

15 Several studies have found increased summertime correlations or ratios between personal
16 exposure and ambient concentration ([Sarnat et al., 2005](#); [Sarnat et al., 2000](#)) or between
17 indoor and outdoor O₃ concentrations ([Geyh et al., 2000](#); [Avol et al., 1998a](#)). However,
18 others have found higher ratios in fall than in summer ([Sarnat et al., 2006a](#)) or equivalent,
19 near-zero ratios in winter and summer ([Sarnat et al., 2001](#)), possibly because summertime
20 use of air conditioners decreases building air exchange rates. It should be noted that O₃
21 concentrations during winter are generally much lower than summertime concentrations,
22 possibly obscuring wintertime relationships due to detection limit issues. Studies
23 specifically evaluating the effect of ventilation conditions on O₃ relationships have found
24 increased correlations or ratios for individuals or buildings experiencing higher air
25 exchange rates ([Sarnat et al., 2006a](#); [Geyh et al., 2000](#); [Sarnat et al., 2000](#); [Romieu et al.,](#)
26 [1998a](#)).

27 Increased correlations or ratios between personal exposure and ambient concentration, or
28 between indoor and outdoor concentration, are likely to reduce error in exposure
29 estimates used in epidemiologic studies. This suggests that studies conducted during the
30 O₃ season or in periods when communities are likely to have high air exchange rates
31 (e.g., during mild weather) may be less prone to exposure error than studies conducted
32 only during winter. Year-round studies that include both the O₃ and non-O₃ seasons may
33 have an intermediate level of exposure error.

4.6.3 Exposure Duration

1 Epidemiologic studies of health effects associated with short-term and long-term
2 exposures use different air pollution metrics and thus have different sources of exposure
3 error. The following subsections discuss the impact of using different short-term and
4 long-term exposure metrics on epidemiologic results.

4.6.3.1 Short-Term Exposure

5 The averaging time of the daily exposure metrics used to evaluate daily aggregated health
6 data (e.g., 1-h or 8-h daily maximum vs. 24-h avg concentration) may also impact
7 epidemiologic results, since different studies report different daily metrics. Correlations
8 between 1-h daily max, 8-h daily max, and 24-h avg concentrations for U.S. monitoring
9 sites are presented in Section [3.6.1 \(Figure 3-23](#) and accompanying text). The two daily
10 peak values (1-h max and 8-h max) are well correlated, with a median (IQR) correlation
11 of 0.97 (0.96-0.98). The correlation between the 8-h max and 24-h avg are somewhat less
12 well correlated with a median (IQR) correlation of 0.89 (0.86-0.92). While this may
13 complicate quantitative comparisons between epidemiologic studies using different daily
14 metrics, as well as the interpretation of studies using metrics other than the current 8-h
15 standard, the high inter-metric correlations suggest it is a relatively small source of
16 uncertainty in comparing the results of studies using different metrics. This is supported
17 by a study comparing each of these metrics in a time-series study of respiratory ED visits
18 ([Darrow et al., 2011a](#)), which found positive associations for all metrics, with the
19 strongest association for the 8-h daily max exposure metric (Section [6.2.7.3](#)).

20 The ratios of 1-h daily max, 8-h daily max, and 24-h avg concentrations to one another
21 have been found to differ across communities and across time within individual
22 communities ([Anderson and Bell, 2010](#)). For example, 8:24 hour ratios ranged from
23 1.23-1.83, with a median of 1.53. Lower ratios were generally observed in the spring and
24 summer compared to fall and winter. O₃ concentration was identified as the most
25 important predictor of ozone metric ratios, with higher overall O₃ concentrations
26 associated with lower ratios. In communities with higher long-term ozone concentrations,
27 the lower 8:24 hour ratio is attributed to high baseline O₃, which results in elevated 24-h
28 average values. Differences in the representativeness of O₃ metrics introduces uncertainty
29 into the interpretation of epidemiologic results and complicates comparison of studies
30 using different metrics. Preferably, studies will report results using multiple metrics. In
31 cases where this does not occur, the results of the study by [Anderson and Bell \(2010\)](#) can
32 inform the uncertainty associated with using a standard increment to adjust effect
33 estimates based on different metrics so that they are comparable (Chapter [6](#)).

1 A study compared measures of spatial and temporal variability for 1-h daily max and
2 24-h daily avg O₃ concentrations in Brazil ([Bravo and Bell, 2011](#)). The 1-h daily max
3 value was found to have higher correlation between monitors (i.e., lower temporal
4 variability) and lower COD (a measure of spatiotemporal variability which incorporates
5 differences in concentration magnitude, with lower values indicating lower variability;
6 see Chapter 3) than the 24-h avg value. The range of correlation coefficients and COD
7 values was similar between the two metrics, although the variation was lower for the 1-h
8 daily max, as indicated by the R² value for the regression of correlation coefficient on
9 inter-monitor distance.

4.6.3.2 Long-Term Exposure

10 Long-term O₃ exposure studies are not available that permit evaluation of the relationship
11 between long-term O₃ concentrations and personal or population exposure. The value of
12 short-term exposure data for evaluating long-term concentration-exposure relationships is
13 uncertain. If the longer averaging time (annual vs. daily or hourly) smooths out short-
14 term fluctuations, long-term concentrations may be well-correlated with long-term
15 exposures. However, lower correlation between long-term exposures and ambient
16 concentration could occur if important exposure determinants change over a period of
17 several years, including activity pattern and residential air exchange rate.

18 A study in Canada suggests that an exposure metric based on a single year can represent
19 exposure over a multi-decade period. The authors compared exposure assessment
20 methods for long-term O₃ exposure and found that the annual average concentration in
21 the census tract of a subject's residence during 1980 and 1994 was well-correlated (0.76
22 and 0.82, respectively) with a concentration metric accounting for movement among
23 census subdivisions during 1980-2002 ([Guay et al., 2011](#)). This may have been due in
24 part to a relatively low rate of movement, with subjects residing on average for 71% of
25 the 22-year period in the same census subdivision they were in during 1980.

26 Analysis of the exposure assessment methodology in a recent study of mortality
27 associated with long-term O₃ exposure ([Jerrett et al., 2009](#)) is illustrative. In this study,
28 the authors computed quarterly averages of the daily 1-h max O₃ concentration, averaged
29 the two summer quarters together to produce an annual value, then calculated a 23-year
30 average value for each city in the study. Producing a single value for each city enables a
31 comparison of relatively cleaner cities with relatively more polluted cities. In this case,
32 the average was calculated using the 1-h daily max value; if the 24-h avg value had been
33 used, concentrations would have been lower and potentially more variable, based on
34 analyses in Chapter 3. According to

1 Table 3-7, the 2007-2009, 3-year average 1-h daily max value during the warm season
2 was approximately 50% higher than the corresponding 24-avg value on a nationwide
3 basis. Correlation between the two metrics varies by site, indicating the differential
4 influence of the overnight period on 24-h avg concentrations. The median correlation
5 between 1-h daily max and 24-h avg is 0.83, with an IQR of 0.78-0.88. It is not clear,
6 however, that a different exposure assignment method would yield different results.

7 Long-term O₃ trends, as discussed in Chapter 3, show gradually decreasing
8 concentrations. [Figure 3-48](#) shows that concentrations have decreased most for the 90th
9 percentile, with relatively little change among the 10th percentile monitors. The decrease
10 has been greater in the eastern U.S. than in the western part of the country (excluding
11 California). For the most part, the rank order of regions in terms of O₃ concentration has
12 remained the same, as shown in [Figure 3-50](#), with the Northeast, Southeast, and
13 California exhibiting the highest concentrations. The decreasing trend is consistent across
14 nearly all monitors in the U.S., with only 1-2% of monitors reporting an increase of more
15 than 5 ppb between the 2001-2003 and 2008-2010 time periods ([Figure 3-52](#) and
16 [Figure 3-53](#)). This provides some evidence that epidemiologic studies of long-term
17 exposure are not affected by drastic changes in O₃ concentration, such as a relatively
18 clean city becoming highly polluted or the reverse.

19 A few epidemiologic studies have evaluated the impact of distance to monitor on
20 associations between long-term O₃ concentration and reproductive outcomes, as
21 discussed in Chapter 7. It is not clear from this evidence whether using a local monitor
22 for these multi-month concentration averages improves exposure assessment. [Jalaludin et](#)
23 [al. \(2007\)](#) found somewhat higher effect estimates for women living within 5 km of a
24 fixed-site O₃ monitor than for all women in the Sydney metropolitan area, suggesting that
25 increased monitor proximity reduced exposure misclassification. In contrast, [Darrow et](#)
26 [al. \(2011b\)](#) found no substantial difference between effect estimates for those living
27 within 4 mi of a fixed-site monitor and those living in the five-county area around
28 Atlanta. This result could be due to spatial variability over smaller scales than the 4-mi
29 radius evaluated, time spent away from the residence impacting O₃ exposure, or
30 similarity in monitor location and representativeness across the urban area (see
31 [Figure 4-4](#)). At this time, the effect of exposure error on long-term exposure
32 epidemiologic studies is unclear.

4.6.4 Exposure to Copollutants and Ozone Reaction Products

33 Although indoor O₃ concentrations are usually well below ambient concentrations, the
34 same reactions that reduce O₃ indoors form particulate and gaseous species, including

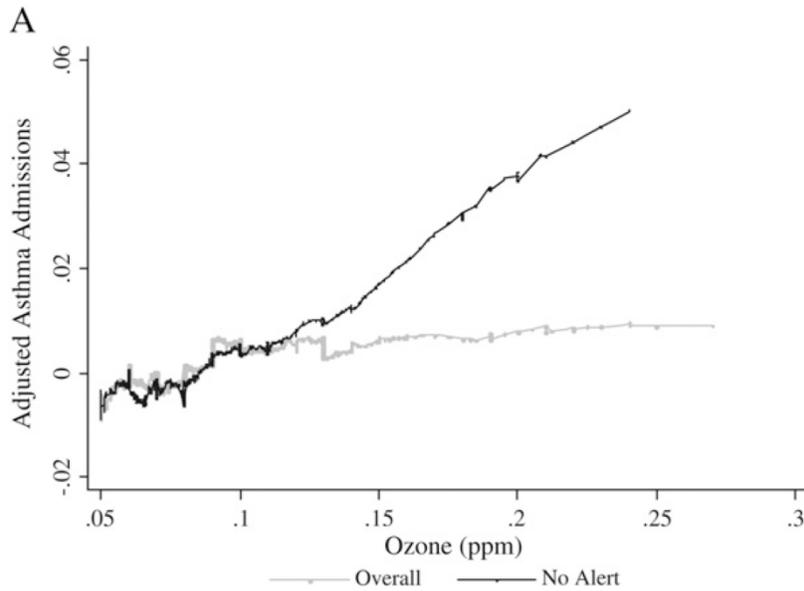
1 other oxidants, as summarized in Section [4.3.4.3](#). Exposures to these reaction products
2 would therefore be expected to be correlated with ambient O₃ concentrations, although no
3 evidence was identified regarding personal exposures. Such exposure could potentially
4 contribute to health effects observed in epidemiologic studies.

4.6.5 Averting Behavior

5 As described in Section [4.4.2](#), several recent studies indicate that some populations alter
6 their behavior on high ozone days to avoid exposure. Such behavioral responses to
7 information about forecasted air quality may introduce systematic measurement error in
8 air pollution exposure, leading to biased estimates of the impact of air pollution on health.
9 For example, studies have hypothesized that variation in time spent outdoors may be a
10 driving factor behind the considerable heterogeneity in ozone mortality impacts across
11 communities ([Bell et al., 2004](#)). If averting behavior reduces outdoor O₃ exposure, then
12 studies that do not account for averting behavior may produce effect estimates that are
13 biased towards the null (Section [6.2.7.2](#)).

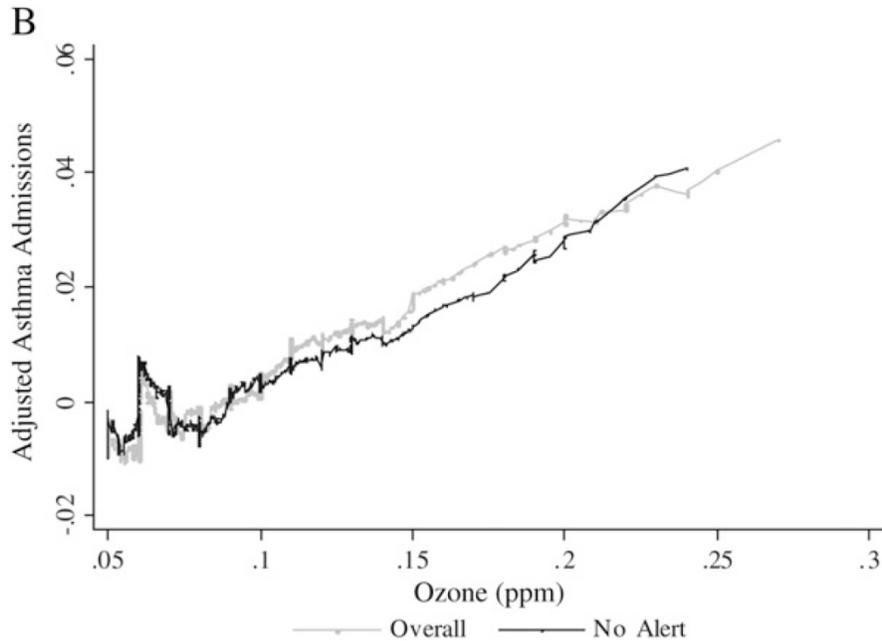
14 This is supported by an epidemiologic study that examined the association between
15 exposure to ambient ozone concentrations and asthma hospitalizations in Southern
16 California during 1989-1997, which indicates that controlling for avoidance behavior
17 increases the effect estimate for both children and older adults, but not for adults aged
18 20-64 ([Neidell and Kinney, 2010](#); [Neidell, 2009](#)). [Figure 4-7](#) and [Figure 4-8](#), reproduced
19 from [Neidell \(2009\)](#), show covariate-adjusted asthma hospital admissions as a function of
20 daily maximum 1-h O₃ concentration for all days (gray line) and days when no O₃ alert
21 was issued (black line). Stage 1 smog alerts were issued by the State of California for
22 days when ambient O₃ concentrations were forecast to be above 0.20 ppm; however, the
23 concentration-response functions are based on measured O₃ concentrations. For children
24 aged 5-19 ([Figure 4-7](#)), hospital admissions were higher on high-O₃ days when no alert
25 was issued, especially on days with O₃ concentrations above 0.15 ppm (150 ppb). The
26 concentration-response curves for all days and days with no alert diverge at measured O₃
27 concentrations between 0.10 and 0.15 ppm because smog alerts begin to be issued more
28 frequently in this range. This suggests that in the absence of information that would
29 enable averting behavior, children experience higher ozone exposure and subsequently a
30 greater number of asthma hospital admissions than on alert days with similar O₃
31 concentrations. The lower rate of admissions observed when alert days were included in
32 the analysis suggests that averting behavior reduced O₃ exposure and asthma hospital
33 admissions. In both cases, O₃ was found to be associated with asthma hospital
34 admissions, although the strength of the association is underestimated when not
35 accounting for averting behavior. A different result was observed when examining

1 associations for adults aged 20-64 (Figure 4-8), who had similar rates of hospital
2 admissions on non-alert days as on all days. The lack of change for adults aged 20-64,
3 which is primary employment age, may reflect lower response to air quality alerts due to
4 the increased opportunity cost of behavior change. The finding that air quality
5 information reduces the daily asthma hospitalization rate in these populations provides
6 additional support for a link between ozone and health effects.



Source: Reprinted with permission of the Board of Regents of the University of Wisconsin System, University of Wisconsin Press (Neidell, 2009).

Figure 4-7 Adjusted asthma hospital admissions by age on lagged ozone by alert status, ages 5-19.



Source: Reprinted with permission of the Board of Regents of the University of Wisconsin System, University of Wisconsin Press; [Neidell \(2009\)](#).

Figure 4-8 Adjusted asthma hospital admissions by age on lagged ozone by alert status, ages 20-64.

4.6.6 Exposure Estimation Methods in Epidemiologic Studies

1 Epidemiologic studies use a variety of methods to assign exposure. Study design, data
 2 availability, and research objectives are all important factors for epidemiologists when
 3 selecting an exposure assessment method. Common methods for assigning exposure
 4 using monitoring data include using a single fixed-site monitor to represent population
 5 exposure, averaging concentrations from multiple monitors, and selecting the closest
 6 monitor. Investigators may also use statistical adjustment methods, such as trimming
 7 extreme values, to prepare the concentration data set. Panel or small-scale cohort studies
 8 involving dozens of individuals may use more individualized concentration
 9 measurements, such as personal exposures, residential indoor or outdoor measurements,
 10 or concentration data from local study-specific monitors. For long-term epidemiologic
 11 studies, the lack of personal exposure data or dedicated measurements means that
 12 investigators must rely on fixed-site monitoring data. These data may be used directly,
 13 averaged across counties or other geographic areas, or used to construct geospatial or
 14 regression models to assign concentrations to unmonitored locations. Longer-term
 15 averages (months to years) are typically used (e.g., in studies discussed in
 16 Section [7.3.1.1](#)). Chapters 6 and 7 describe the exposure assessment methods used in the

1 epidemiologic studies described therein, providing additional detail on studies with
2 innovative or expanded techniques designed to improve exposure assessment and reduce
3 exposure error.

4 The use of O₃ measurements from central ambient monitoring sites is the most common
5 method for assigning exposure in epidemiologic studies. However, fixed-site
6 measurements do not account for the effects of spatial variation in O₃ concentration,
7 ambient and non-ambient concentration differences, and varying activity patterns on
8 personal exposures ([Brown et al., 2009](#); [Chang et al., 2000](#); [Zeger et al., 2000](#)). The use
9 of fixed-site concentrations results in minimal exposure error when: (1) O₃ concentrations
10 are uniform across the region; (2) personal activity patterns are similar across the
11 population; and (3) housing characteristics, such as air exchange rate and indoor reaction
12 rate, are constant over the study area. Since these factors vary by location and population,
13 there will be errors in the magnitude of total exposure based solely on ambient
14 monitoring data.

15 Modeled concentrations can also be used as exposure surrogates in epidemiologic studies,
16 as discussed in Section [4.5](#). Geostatistical spatial interpolation techniques, such as IDW
17 and kriging, can provide finer-scale estimates of local concentration over urban areas. A
18 microenvironmental modeling approach simulates exposure using empirical distributions
19 of concentrations in specific microenvironments together with human activity pattern
20 data. The main advantage of the modeling approach is that it can be used to estimate
21 exposures over a wide range of population and scenarios. A main disadvantage of the
22 modeling approach is that the results of modeling exposure assessment must be compared
23 to an independent set of measured exposure levels ([Klepeis, 1999](#)). In addition,
24 resource-intensive development of validated and representative model inputs is required,
25 such as human activity patterns, distributions of air exchange rate, and deposition rate.
26 Therefore, modeled exposures are used much less frequently in epidemiologic studies.

4.7 Summary and Conclusions

27 This section will briefly summarize and synthesize the main points of the chapter, with
28 particular attention to the relevance of the material for the interpretation of epidemiologic
29 studies.

30 Passive badge samplers are the most widely used technique for measuring personal O₃
31 exposure (Section [4.3.1](#)). The detection limit of the badges for a 24-h sampling period is
32 approximately 5-10 ppb, with lower detection limits at longer sampling durations. In low-
33 concentration conditions this may result in an appreciable fraction of 24-h samples being
34 below the detection limit. The use of more sensitive portable active monitors, including

1 some that have recently become available, may help overcome this issue and improve
2 personal monitoring in the future.

3 Since there are relatively few indoor sources of O₃, indoor O₃ concentrations are often
4 substantially lower than outdoor concentrations due to reactions of O₃ with indoor
5 surfaces and airborne constituents (Section 4.3.2). Air exchange rate is a key determinant
6 of the I/O ratio, which is generally in the range of 0.1-0.4 (Table 4-1), with some
7 evidence for higher ratios during the O₃ season when concentrations are higher.

8 Personal exposure is moderately correlated with ambient O₃ concentration, as indicated
9 by studies reporting correlations generally in the range of 0.3-0.8 (Table 4-2). Hourly
10 concentration correlations are more variable than those averaged over 24 hours or longer,
11 with correlations in outdoor microenvironments (0.7-0.9) much higher than those in
12 residential indoor (0.1) or other indoor (0.3-0.4) microenvironments. Some studies report
13 substantially lower personal-ambient correlations, a result attributable in part to low air
14 exchange rate and O₃ concentrations below the sampler detection limit, conditions often
15 encountered during wintertime. Low correlations may also occur for individuals or
16 populations spending substantial time indoors.

17 The ratio between personal exposure and ambient concentration varies widely depending
18 on activity patterns, housing characteristics, and season, with higher personal-ambient
19 ratios generally observed with increasing time spent outside, higher air exchange rate,
20 and in seasons other than winter (Table 4-3). Personal-ambient ratios are typically
21 0.1-0.3, although individuals spending substantial time outdoors (e.g., outdoor workers)
22 may have much higher ratios (0.5-0.9).

23 Personal exposure to other pollutants shows variable association with personal exposure
24 to O₃, with differences in copollutant relationships depending on factors such as season,
25 city-specific characteristics, activity pattern, and spatial variability of the copollutant
26 (Section 4.3.4). In near-road and on-road microenvironments, correlations between O₃
27 and traffic-related pollutants are moderately to strongly negative, with the most strongly
28 negative correlations observed for NO₂ (-0.8 to -0.9). This is consistent with the
29 chemistry of NO oxidation, in which O₃ is consumed to form NO₂. The more moderate
30 negative correlations observed for PM_{2.5}, PM_{1.0}, and VOC may reflect reduced
31 concentrations of O₃ in polluted environments due to other scavenging reactions. A
32 similar process occurs indoors, where infiltrated O₃ reacts with airborne or surface-
33 associated materials to form secondary compounds, such as formaldehyde. Although such
34 reactions decrease indoor O₃ exposure, they result in increasing exposure to other species
35 which may themselves have health effects.

1 Variations in ambient O₃ concentrations occur over multiple spatial and temporal scales.
2 Near roadways, O₃ concentrations are reduced due to reaction with NO and other species
3 (Section [4.3.4.2](#)). Over spatial scales of a few kilometers and away from roads, O₃ may
4 be somewhat more homogeneous due to its formation as a secondary pollutant, while
5 over scales of tens of kilometers, additional atmospheric processing can result in higher
6 concentrations downwind of an urban area. Although local-scale variability impacts the
7 magnitude of O₃ concentrations, O₃ formation rates are influenced by factors that vary
8 over larger spatial scales, such as temperature (Section [3.2](#)), suggesting that urban
9 monitors may track one another temporally but miss small-scale variability in magnitude.
10 The resulting uncertainty in exposure contributes to exposure measurement error in
11 epidemiologic studies.

12 Another factor that may influence epidemiologic results is the tendency for people to
13 avoid O₃ exposure by altering their behavior (e.g., reducing time spent outdoors) on high-
14 O₃ days. Activity pattern has a substantial effect on ambient O₃ exposure, with time spent
15 outdoors contributing to increased exposure (Section [4.4.2](#)). Averting behavior has been
16 predominantly observed among children, older adults, and people with respiratory
17 problems. Such effects are less pronounced in the general population, possibly due to the
18 opportunity cost of behavior modification. Evidence from one recent epidemiologic study
19 indicates increased asthma hospital admissions among children and older adults when O₃
20 alert days were excluded from the analysis (presumably thereby eliminating averting
21 behavior based on high O₃ forecasts). The lower rate of admissions observed when alert
22 days were included in the analysis suggests that estimates of health effects based on
23 concentration-response functions which do not account for averting behavior may be
24 biased towards the null.

25 The range of personal-ambient correlations reported by most studies (0.3-0.8) is similar
26 to that for NO₂ ([U.S. EPA, 2008b](#)) and somewhat lower than that for PM_{2.5} ([U.S. EPA,
27 2009d](#)). To the extent that relative changes in central-site monitor concentration are
28 associated with relative changes in exposure concentration, this indicates that ambient
29 monitor concentrations are representative of day-to-day changes in average total personal
30 exposure and in personal exposure to ambient O₃. The lack of indoor sources of O₃, in
31 contrast to NO₂ and PM_{2.5}, is partly responsible for low indoor-outdoor ratios (generally
32 0.1-0.4) and low personal-ambient ratios (generally 0.1-0.3), although it contributes to
33 increased personal-ambient correlations. The lack of indoor sources also suggests that
34 fluctuations in ambient O₃ may be primarily responsible for changes in personal
35 exposure, even under low-ventilation, low-concentration conditions. Nevertheless, low
36 personal-ambient correlations are a source of exposure error for epidemiologic studies,
37 tending to obscure the presence of potential thresholds, bias effect estimates toward the
38 null, and widen confidence intervals, and this impact may be more pronounced among

1 populations spending substantial time indoors. The impact of this exposure error may
2 tend more toward widening confidence intervals than biasing effect estimates, since
3 epidemiologic studies evaluating the influence of monitor selection indicate that effect
4 estimates are similar across different spatial averaging scales and monitoring sites.

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5 DOSIMETRY AND MODE OF ACTION

5.1 Introduction

1 This chapter has two main purposes. The first is to describe the principles that underlie
2 the dosimetry of O₃ and to discuss factors that influence it. The second is to describe the
3 modes of action leading to the health effects that will be presented in Chapters 6 and 7.
4 This chapter is not intended to be a comprehensive overview, but rather, it updates the
5 basic concepts derived from O₃ literature presented in previous documents ([U.S. EPA,](#)
6 [2006b](#), [1996a](#)) and introduces the recent relevant literature.

7 In Section [5.2](#), particular attention is given to dosimetric factors influencing individual
8 risk of developing effects from O₃ exposure. As there have been few O₃ dosimetry studies
9 published since the last AQCD, the reader is referred to previous documents ([U.S. EPA,](#)
10 [2006b](#), [1996a](#)) for more detailed discussion of the past literature. Evaluation of the
11 progress in the interpretation of past dosimetry studies, as well as studies published since
12 2005, in the areas of uptake, reactions, and models for O₃ dosimetry, is discussed.

13 Section [5.3](#) highlights findings of studies published since the 2006 O₃ AQCD, which
14 provide insight into the biological pathways by which O₃ exerts its actions. Since
15 common mechanisms lead to health effects from both short- and long-term exposure to
16 O₃, these pathways are discussed in Chapter [5](#) rather than in later chapters. The related
17 sections of Chapters 6 and 7 are indicated. Earlier studies that represent the current state
18 of the science are also discussed. Studies conducted at more environmentally-relevant
19 concentrations of O₃ are of greater interest, since mechanisms responsible for effects at
20 low O₃ concentrations may not be identical to those occurring at high O₃ concentrations.
21 Some studies at higher concentrations are included if they were early demonstrations of
22 key mechanisms or if they are recent demonstrations of potentially important new
23 mechanisms. The topics of dosimetry and mode of action are bridged by reactions of O₃
24 with components of the extracellular lining fluid (ELF), which play a role in both O₃
25 uptake and biological responses ([Figure 5-1](#)).

26 In addition, this chapter discusses interindividual variability in responses, and issues
27 related to species comparison of doses and responses (Section [5.4](#) and Section [5.5](#)). These
28 topics are included in this chapter because they are influenced by both dosimetric and
29 mechanistic considerations.

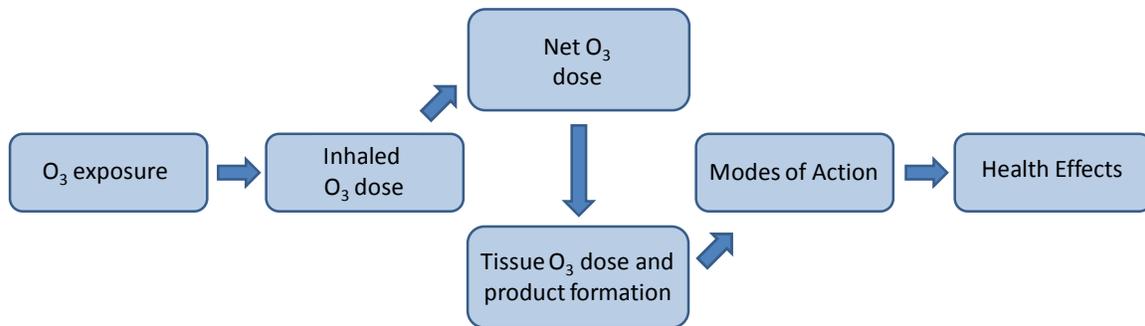


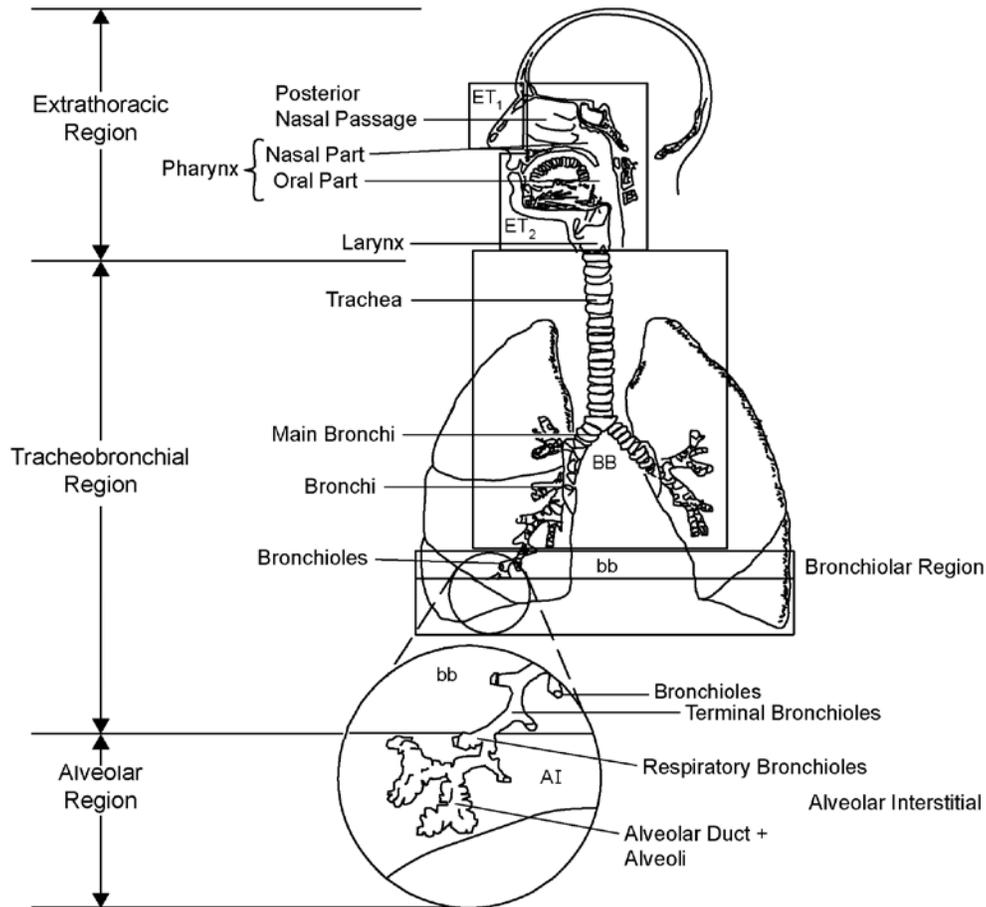
Figure 5-1 Schematic of the ozone exposure and response pathway. Ozone transport follows a path from exposure concentration, to inhaled dose, to net dose, to the local tissue dose. Chapter 5 discusses the concepts of dose and modes of action that result in the health effects discussed in Chapters 6 and 7.

5.2 Human and Animal Ozone Dosimetry

5.2.1 Introduction

1 Dosimetry refers to the measurement or estimation of the quantity of or rate at which a
 2 chemical and/or its reaction products are absorbed and retained at target sites. [Figure 5-1](#)
 3 illustrates the transport of O₃ or its reaction products from exposure to dose to the
 4 development of health effects. Ozone exposure has been defined in Section [4.2](#) and
 5 consists of contact between the human or animal and O₃ at a specific concentration for a
 6 specified period of time (i.e., exposure = concentration × time). The amount of O₃ present
 7 in a given volume of air for which animals and individuals are exposed is termed
 8 exposure concentration. Ozone exposure will result in some amount (dose) of O₃ crossing
 9 an exposure surface to enter a target area. The initial measure of dose after O₃ enters the
 10 RT is inhaled dose and is the amount or rate of O₃ that crosses the outer RT surface
 11 before crossing the ELF and is effectively $C \times t \times \dot{V}_E$. Ozone may then cross from the gas
 12 phase across the ELF interface where net dose may be measured. Net dose is the amount
 13 or rate of entry of O₃ across the gas/ELF interface. In modeling studies, the dose rate is
 14 often expressed as a flux per unit of surface area of a region of respiratory epithelium.
 15 Finally, O₃ or its reaction products may reach the tissues and tissue dose of O₃ can be
 16 reported. Tissue dose is the amount of O₃ or its reaction products absorbed and available
 17 for reacting with tissues and is difficult and rarely measured. In the literature, the
 18 exposure concentration and various measures of dose (i.e., net dose and inhaled dose) are
 19 often used as surrogates for tissue dose. However, ambient or exposure concentrations are

1 not a true measure of dose so understanding the relationship between ambient
2 concentrations and tissue dose allows for a greater appreciation of the dose-response from
3 O₃ exposure.



Note: Structures are anterior nasal passages, ET₁; oral airway and posterior nasal passages, ET₂; bronchial airways, BB; bronchioles, bb; and alveolar interstitial, AI.
Source: Based on [ICRP \(1994\)](#).

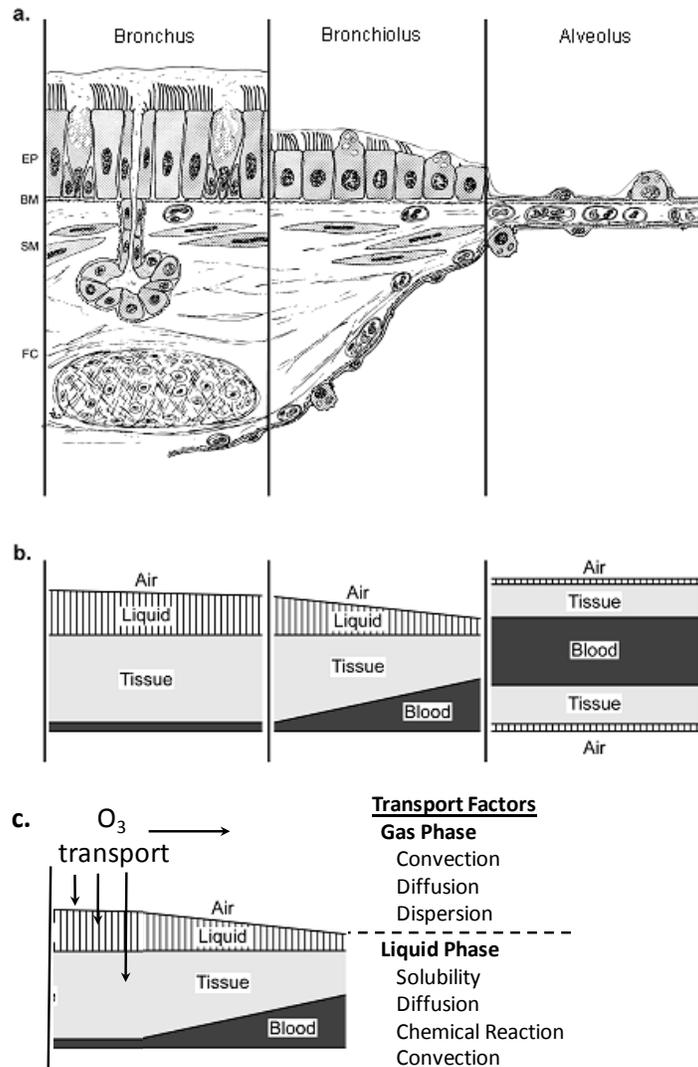
Figure 5-2 Representation of respiratory tract regions in humans.

4 Ozone is a highly reactive, though poorly water soluble, gas at physiological temperature.
5 The latter feature is believed to be the reason why it is able to penetrate into targets in the
6 lower respiratory tract (LRT). [Figure 5-2](#) presents the basic structure of the human
7 respiratory tract (RT). The lung can be divided into three major regions: the extrathoracic
8 (ET) region or upper respiratory tract (URT, from the nose/mouth to larynx); the
9 tracheobronchial (TB) tree (from trachea to the terminal bronchioles); and the alveolar or

1 pulmonary region (from the respiratory bronchioles to the terminal alveolar sacs). The
2 latter two regions comprise the LRT. Although the structure varies, the illustrated
3 anatomic regions are common to all mammalian species with the exception of the
4 respiratory bronchioles. Respiratory bronchioles, the transition region between ciliated
5 and fully alveolated airways, are found in humans, dogs, ferrets, cats, and monkeys.
6 Respiratory bronchioles are absent in rats and mice and abbreviated in hamsters, guinea
7 pigs, sheep, and pigs. The branching structure of the ciliated bronchi and bronchioles also
8 differs between species from being a rather symmetric and dichotomous branching
9 network of airways in humans to a more monopodial branching network in other
10 mammals.

11 [Figure 5-3](#) illustrates the structure of the LRT with progression from the large airways in
12 the TB region to the alveolus in the alveolar region. The fact that O₃ is so chemically
13 reactive has suggested to some that its tissue dose at the target sites exists in the form of
14 oxidation products such as aldehydes and peroxides (see Section [5.2.3](#)). Reaction
15 products are formed when O₃ interacts with components of the ELF such as lipids and
16 antioxidants. The ELF varies throughout the length of the RT with the bronchial tree
17 lined with a thin film of mucus and the alveolar region lined with a thinner layer of
18 surfactant solution ([Figure 5-3b](#)). Ozone dose is directly related to the coupled diffusion
19 and chemical reactions occurring in ELF, a process termed “reactive absorption.” Thus,
20 the O₃ dose depends on both the concentration of O₃ as well as the availability of
21 substrates within the ELF.

22 Ozone dose is affected by complex interactions between a number of other major factors
23 including RT morphology, breathing route, frequency, and volume, physicochemical
24 properties of the gas, physical processes of gas transport, as well as the physical and
25 chemical properties of the ELF and tissue layers ([Figure 5-3c](#)). The role of these
26 processes varies throughout the length of the RT and as O₃ moves from the gas to liquid
27 compartments of the RT.



Note: (a) Illustrates basic airway anatomy. Structures are epithelial cells, EP; basement membrane, BM; smooth muscle cells, SM; and fibrocartilaginous coat, FC. (b) Illustrates the relative amounts of liquid, tissue, and blood with distal progression. In the bronchi there is a thick surface lining over a relatively thick layer of tissues. With distal progress, the lining diminishes allowing increased access of compounds crossing the air-liquid interface to the tissues and the blood. (c) Presents the factors acting in the gas and liquid phases of O_3 transport.

Source: Panel (a) reprinted with permission of McGraw-Hill (Weibel, 1980).

Figure 5-3 Structure of lower airways with progression from the large airways to the alveolus.

- 1 Two types of measurements have been used to arrive at the O_3 dose to target sites during
- 2 breathing: (1) measurement of removal of O_3 from the air stream (termed “uptake”); and
- 3 (2) measurement of chemical reactions in tissues or with biomolecules known to be
- 4 present in tissues (termed “reactants”). The results of the above measurements have been
- 5 incorporated into mathematical models for the purpose of explaining, predicting, and

1 extrapolating O₃ dose in different exposure scenarios. Few new studies have investigated
2 the uptake of O₃ in the RT since the last O₃ assessment ([U.S. EPA, 2006b](#)). The studies
3 that have been conducted generally agree with the results presented in the past and do not
4 change the dosimetry conclusions of the last document.

5.2.2 Ozone Uptake

5 Past AQCDs provide information on the majority of literature relevant to understanding
6 the state of the science in O₃ dosimetry. Measurements of O₃ dose have been inferred
7 from simultaneous measurements of airflow and O₃ concentration at the airway opening
8 of the nose or mouth ([Nodelman and Ultman, 1999](#); [Wiester et al., 1996a](#)) as well as at
9 internal sampling catheters ([Gerrity et al., 1995](#); [Gerrity et al., 1988](#)). One method of
10 quantifying O₃ dose is to measure the amount of O₃ removed from the air stream during
11 breathing (termed “uptake”). The difference in the amount of O₃ inhaled and exhaled
12 relative to the amount of inhaled O₃ is termed fractional absorption. Uptake efficiency is
13 also reported and refers to the fraction of O₃ absorbed in a region as a function of the total
14 amount of O₃ entering the given region. Uptake studies have utilized bolus and
15 continuous O₃ breathing techniques as well as modeling to investigate these measures of
16 uptake and the distribution of O₃ uptake between the upper and lower respiratory tract. A
17 number of the studies that have measured the fractional absorption and uptake efficiency
18 of O₃ in the human RT, URT, and LRT are presented in [Table 5-1](#). For bolus exposure
19 studies that reported fractional absorption, the total RT uptake efficiency was estimated
20 as the sum of the products of the experimental bolus absorption and incremental volume
21 of a bolus into a breath divided by the tidal volume of the breath, or where available, was
22 taken from Table 1A of [Schlesinger et al. \(1997\)](#).

Table 5-1 Human respiratory tract uptake efficiency data

| Reference | Mouth/ Nose ^a | Inspiratory Flow (mL/sec) | V _T (mL) | f _B (bpm) ^b | Uptake Efficiency | | | |
|--|-----------------------------|---------------------------------|---------------------|--------------------------------------|----------------------------|---------------------|----------------------------|---------------------------|
| | | | | | URT, complete breath | URT, inspiration | LRT, complete breath | Total RT, tidal breath |
| Continuous Exposure | | | | | | | | |
| Gerrity et al. (1988) | OR | 509 | 832 | 18 | | 0.40 | 0.91 | |
| | N | 456 | 754 | 18 | | 0.36 | 0.91 | |
| | OR/N | 500 | 800 | 18 | | 0.43 | 0.91 | |
| | OR/N | 350 | 832 | 12 | | 0.41 | 0.93 | |
| | OR/N | 634 | 778 | 24 | | 0.38 | 0.89 | |
| Gerrity et al. (1994) | OR | 1,360 | 1,650 | 25 | | 0.37 | 0.43 | 0.81 |
| | OR | 1,360 | 1,239 | 35 | | 0.41 | 0.36 | 0.78 |
| Gerrity et al. (1995) | OR | 330 | 825 | 12 | | 0.27 | 0.95 | 0.91 |
| Wiester et al. (1996a) | OR | 539 | 631 | 16 | | | | 0.76 |
| | N | 514 | 642 | 16 | | | | 0.73 |
| Rigas et al. (2000) | Face mask | 480 | 1,100 | 27.6 | | | | 0.86 |
| Santiago et al. (2001) | N | 50 | | | | 0.80 ^c | | |
| | N | 250 | | | | 0.33 | | |
| Bolus Exposure | | | | | | | | |
| Hu et al. (1992) | Mouth-piece | 250 | 500 | | | 0.46 | | 0.88 |
| Kabel et al. (1994) | Mouth-piece | 250 | 500 | | | 0.50 | | 0.88 |
| | Mouth-piece | 250 | 500 | | | 0.53 | | 0.88 |
| | N | 250 | 500 | | | 0.78 | | 0.94 |
| Hu et al. (1994) | Mouth-piece | 150 | 500 | | | 0.65 | | 0.91 |
| | Mouth-piece | 250 | 500 | | | 0.51 | | 0.87 |
| | Mouth-piece | 500 | 500 | | | 0.26 | | 0.82 |
| | Mouth-piece | 750 | 500 | | | 0.16 | | 0.78 |
| | Mouth-piece | 1,000 | 500 | | | 0.11 | | 0.76 |
| Ultman et al. (1994) | Mouth-piece | 250 | 500 ^d | 15 | | 0.30 | | |
| | Mouth-piece | 250 | 500 | 15 | | 0.47 | | |

| Reference | Mouth/ Nose ^a | Inspiratory Flow (mL/sec) | V _T (mL) | f _B (bpm) ^b | Uptake Efficiency | | |
|--|-----------------------------|---------------------------------|---------------------|--------------------------------------|----------------------------|---------------------|----------------------------|
| | | | | | URT, complete breath | URT, inspiration | LRT, complete breath |
| Bush et al. (1996) | Mouth- piece | 250 | 500 | | 0.51 | | 0.89 |
| Nodelman and Ultman (1999) | Nasal Cannula | 150 | 500 | 18 | 0.90 | | 0.92 |
| | Nasal Cannula | 1,000 | 500 | 120 | 0.50 | | 0.84 |
| | Mouth- piece | 150 | 500 | 18 | 0.77 | | 0.91 |
| | Mouth- piece | 1,000 | 500 | 120 | 0.25 | | 0.75 |
| Ultman et al. (2004) | OR | 490 | 450 ^d | 32.7 | | | 0.87 |
| | OR | 517 | 574 | 27 | | | 0.91 |

^aOR = oral exposure during spontaneous breathing; N = nasal exposure during spontaneous breathing; OR/N = pooled data from oral and nasal exposure; mouthpiece = exposure by mouthpiece.

^bf_B is either measured or is computed from flows and V_T.

^cF_{URT} from [Santiago et al. \(2001\)](#) represents nasal absorption (F_{nose}).

^dV_T is computed from flow and f_B.

5.2.2.1 Gas Transport Principles

The three-dimensional transport of O₃ in the lumen of an airway is governed by diffusion and bulk flow or convection. When modeled as a one-dimensional process in which the radial profiles of axial velocity and O₃ concentration profiles are flat, O₃ transport along an airway lumen occurs by convection, axial diffusion and a coupled diffusion-reaction process called dispersion. Simultaneously, O₃ diffuses into the ELF where it undergoes radial diffusion and chemical reaction ([Figure 5-3c](#)) ([Miller, 1995](#)). The relative importance of these transport mechanisms varies among RT regions for a given level of ventilation. In the URT and major bronchi, bulk airflow tends to be the predominant mechanism for axial transport in the airway lumen. However, in the alveolar region of the lung, diffusion is the major gas transport mechanism.

Gas transport in the TB region occurs by a combination of bulk flow and mixing ([Ultman, 1985](#)). Mixing can occur by diffusion processes associated with the molecular nature of the gas and by convection, which depends on local velocity patterns. The complexity of the airway structure and surface affects the bulk airflow patterns so that not all nasal and lung surfaces receive the same O₃ exposure or dose ([Miller and Kimbell, 1995](#)). For example, it has been reported that the larger surface-to-volume ratio associated with the smaller airways in women enhances local O₃ uptake and reduces the distal penetration volume of O₃ into the RT of women relative to men ([Ultman et al., 2004](#)). Also, it was reported that changes in cross-sectional area available for gas diffusion are related to overall O₃ retention ([Reeser et al., 2005](#); [Ultman et al., 2004](#)).

1 The principal influence on mixing in the TB region comes from the axial velocity profile
2 and diffusion. When air flows through an airway, O₃ located near the tube center moves
3 faster than O₃ near the tube wall where frictional forces retard the flow. This
4 non-uniformity in the radial profile of velocity gives rise to an axial spreading or
5 dispersion of the O₃ that operates in parallel with bulk flow and axial diffusion (a process
6 caused by the ever-present Brownian motion of individual O₃ molecules). The shape of
7 the velocity profile is affected by the flow direction through bifurcating airway branches
8 ([Schroter and Sudlow, 1969](#)). The velocity profile is nearly parabolic during inhalation
9 but quite flat during exhalation. Thus, there tends to be greater axial dispersion during
10 inhalation than during exhalation. Dispersion also depends on the nature of the flow, that
11 is, whether it is laminar (i.e., streamlined) or turbulent (i.e., possessing random velocity
12 fluctuations). Because turbulent flow flattens velocity profiles, it may actually diminish
13 dispersion. In humans, turbulent flow persists only a few generations into the RT. The
14 persistence of turbulence into the RT also varies by species and flow rates. For example,
15 airflow is nonturbulent in the rat nose at any physiologic flow rate but may be highly
16 turbulent in the human nose during exercise ([Miller, 1995](#)). Diffusive forces and
17 resistance vary along the RT. Diffusive resistance increases with distal penetration into
18 the RT with a study reporting that the gas boundary layer contributes 53% of the overall
19 diffusive resistance in the URT, 78% in the proximal LRT, and 87% in the distal LRT
20 ([Hu et al., 1994](#)).

21 Conversely, the principal mechanism of gas mixing in the lung periphery is molecular
22 diffusion ([Engel, 1985](#)). While moving into more distal areas of the RT, the
23 cross-sectional area of the airways rapidly increases and linear velocities decrease,
24 leading to a greater role for molecular diffusion of gases. Gas molecules close to the
25 alveolar-capillary membrane have almost zero convective velocity with respect to the
26 membrane, and this creates a substantial boundary layer resistance to O₃ transfer across
27 the gas-eLF interface.

5.2.2.2 Target Sites for Ozone Dose

28 A primary uptake site of O₃ delivery to the lung epithelium is believed to be the
29 centriacinar region (CAR). The CAR refers to the zone at the junction of the TB airways
30 and the gas exchange region. This area is also termed the proximal alveolar region (PAR)
31 and is defined as the first generation distal to the terminal bronchioles. Contained within
32 the CAR, the respiratory bronchioles were confirmed as the site receiving the greatest O₃
33 dose (¹⁸O mass/lung weight) in resting O₃ exposed rhesus monkeys, when not considering
34 the nose ([Plopper et al., 1998](#)). Furthermore, the greatest cellular injury occurred in the
35 vicinity of the respiratory bronchioles and was dependent on the delivered O₃ dose to

1 these tissues (see also Section [5.4.1](#)). However, ¹⁸O label was detected to a lesser extent
2 in other regions of the TB airway tree, showing that O₃ is delivered to these
3 compartments as well, although in a smaller dose. These studies agree with earlier model
4 predictions showing that the tissue O₃ dose (O₃ flux to liquid-tissue interface) was low in
5 the trachea, increased to a maximum in the terminal bronchioles and the CAR, and then
6 rapidly decreased in the alveolar region ([Miller et al., 1985](#)). It was also predicted that the
7 net O₃ dose (total absorption, O₃ flux to air-liquid interface) gradually decreased with
8 distal progression from the trachea to the end of the TB region and then rapidly decreased
9 in the alveolar region. Despite the exclusion of the URT and appreciable O₃ reactions
10 with ELF constituents after the 16th generation, the results from the model agree with
11 experimental results showing that the greatest O₃ tissue dose was received in the CAR
12 ([Miller et al., 1985](#)).

13 Inhomogeneity in the RT structure may affect the dose delivered to this target site.
14 Models have predicted that the farther the PAR is from the trachea, the less the O₃ tissue
15 dose to the region. [Ultman and Anjilvel \(1990\)](#) and [Overton and Graham \(1989\)](#)
16 predicted approximately a 50 to 300% greater PAR dose for the shortest path relative to
17 the longest path in humans and rats, respectively. In addition, [Mercer et al. \(1991\)](#) found
18 that both path distance and ventilatory unit size affected dose. The variation of O₃ dose
19 among anatomically equivalent ventilatory units was predicted to vary as much as 6-fold,
20 as a function of path length from the trachea. This could have implications in regional
21 damage to the LRT, such that even though the average LRT dose may be at a level where
22 health effects would not be predicted, local regions of the RT may receive considerably
23 higher than average doses and therefore be at greater risk of effects.

5.2.2.3 Upper Respiratory Tract Ozone Removal and Dose

24 Total O₃ uptake in the entire RT in rats and guinea pigs ranges from 40-54% efficient
25 ([Hatch et al., 1989](#); [Wiester et al., 1988](#); [Wiester et al., 1987](#)), while in humans at rest it
26 ranges from 80-95% efficient ([Hu et al., 1992](#)). The URT provides a defense against O₃
27 entering the lungs by removing half of the O₃ that will be absorbed from the airstream. In
28 both animals and humans, about 50% of the O₃ that was absorbed in the RT was removed
29 in the head (nose, mouth, and pharynx), about 7% in the larynx/trachea, and about 43% in
30 the lungs ([Hu et al., 1992](#); [Hatch et al., 1989](#); [Miller et al., 1979](#)). However, experimental
31 studies in dogs have reported 75-100% uptake in the URT ([Yokoyama and Frank, 1972](#);
32 [Vaughan et al., 1969](#)). The fraction of O₃ taken up was inversely related to flow rate and
33 to inlet O₃ concentration ([Yokoyama and Frank, 1972](#); [Vaughan et al., 1969](#)). The
34 limiting factors in nasal O₃ uptake were simultaneous diffusion and chemical reaction of
35 O₃ in the nasal ELF layer ([Santiago et al., 2001](#)). The ELF layer in the nose is thicker

1 than in the rest of the RT, and mathematical estimates predicted that O₃ penetrates less
2 than the thickness of the ELF layer; reaction products are likely the agents damaging the
3 nasal tissue and not O₃ itself. It was hypothesized that the nasal non-linear kinetics of O₃
4 uptake fraction result from the depleting substrates in the nasal ELF becoming the
5 limiting factor of the reaction ([Santiago et al., 2001](#)).

6 Uptake efficiencies have been measured for various segments of the URT ([Table 5-1](#)).
7 [Gerrity et al. \(1995\)](#) reported unidirectional uptake efficiencies of O₃ inhaled from a
8 mouthpiece; of 17.6% from the mouth to vocal cords, 9.5% from the vocal cords to the
9 upper trachea (totaling 27.1%), 8.4% from the upper trachea to the main bifurcation
10 carina (totaling 35.5%), and essentially zero between the carina and the bronchus
11 intermedius (totaling 32.5%). These values are lower than those calculated by [Hu et al.](#)
12 [\(1992\)](#) that reported uptake efficiencies of 21, 36, 44, and 46% during a complete breath
13 in which an O₃ bolus penetrated between the mouth and the vocal cords, the upper
14 trachea, the main bifurcation carina, and the bronchus intermedius, respectively. The
15 lower efficiencies seen in [Gerrity et al. \(1995\)](#) may have resulted because these
16 investigators measurements were based on inhalation alone or was caused by O₃
17 scrubbing by the mouthpiece.

18 Past studies investigating nasal uptake of O₃ have shown that the nose partially protects
19 the LRT from damage from inspired O₃ ([Santiago et al., 2001](#); [Gerrity et al., 1988](#)).
20 [Sawyer et al. \(2007\)](#) further investigated nasal uptake of O₃ in healthy adults during
21 exercise. Fractional O₃ uptake, acoustic rhinometry (AR), and nasal NO measurements
22 were taken on ten adults (8 women, 2 men) exposed to 200 ppb O₃ before and after
23 moderate exercise at two flow rates (10 and 20 L/min). The percent nasal uptake of O₃
24 was ~50% greater at 10 L/min compared to 20 L/min both pre- and post-exercise.
25 However, the inhaled O₃ dose delivered to the LRT (i.e., flow rate × exposure
26 concentration × (1 - nasal absorbed fraction)) was 1.6-fold greater at the higher flow than
27 at the lower flow (2.5 compared to 0.9 ppm·L/min). These results are similar to those
28 published earlier that found air pollutant retention increased with increasing airflow by
29 more than what would be predicted by just the increased partial pressure difference of the
30 gas ([Aharonson et al., 1974](#)). Prior exercise did not affect O₃ uptake at either flow rate,
31 but did significantly increase nasal volume (V_n) and AR measurements of nasal
32 cross-sectional area (minimum cross-sectional area (MCA) that corresponds to the nasal
33 valve, CSA2 that corresponds to the anterior edge of the nasal turbinates, and CSA3 that
34 corresponds to the posterior edge of the nasal turbinates) (p ≤ 0.05) ([Sawyer et al., 2007](#)).
35 Conversely, exercise decreased nasal resistance (R_n) (p < 0.01) and NO production
36 (nonsignificant, p > 0.05). The change in V_n and CSA2:MCA ratio was correlated with
37 the percent change in nasal uptake, however the overall effect was small and sensitive to
38 elimination of outliers and gender segregation.

1 Overall, the majority of studies suggest that the URT removes about half of the O₃ that
2 will be absorbed by reactions in the nasal ELF. The exact uptake efficiency will change
3 due to variations in flow rate and inhaled concentration.

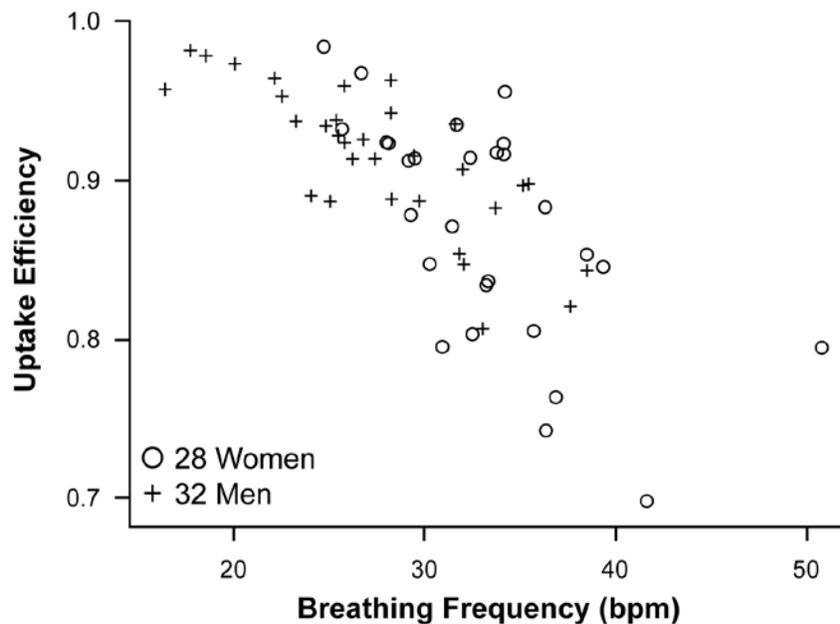
5.2.2.4 Lower Respiratory Tract Ozone Uptake and Dose

4 Approximately 43% of the O₃ absorption occurs in the LRT of both humans and animals.
5 Models predicted that the net O₃ dose decreases distally from the trachea toward the end
6 of the TB region and then rapidly decreases in the alveolar region ([Miller et al., 1985](#)).
7 Further, these models predicted low tissue O₃ dose in the trachea and large bronchi.

8 Uptake efficiency depends on a number of variables, including O₃ exposure
9 concentration, exposure time, and breathing pattern. For breaths of similar waveforms,
10 respiratory patterns are uniquely described by breathing frequency (f_B) and tidal volume
11 (V_T); by minute ventilation ($\dot{V}_E = f_B \times V_T$) and f_B ; or by \dot{V}_E and V_T . Simulations from the
12 [Overton et al. \(1996\)](#) single-path anatomical respiratory tract model, where the upper and
13 lower respiratory tracts were modeled but uptake by the URT was not considered,
14 predicted that fractional uptake and PAR O₃ dose increased with V_T when f_B was held
15 constant. Likewise, experimental studies found that O₃ uptake was positively correlated
16 with changes in V_T ([Ultman et al., 2004](#); [Gerrity et al., 1988](#)). Also, O₃ exposure led to a
17 reflex mediated increase in f_B and reduction in V_T , hypothesized to be protective by
18 decreasing the dose delivered to the lung at a particular \dot{V}_E ([Gerrity et al., 1994](#)). Nasal O₃
19 uptake efficiency was inversely proportional to flow rate ([Santiago et al., 2001](#)), so that
20 an increase in \dot{V}_E will increase O₃ delivery to the lower airways. At a fixed \dot{V}_E , increasing
21 V_T (corresponding to decreasing f_B) drove O₃ deeper into the lungs and increased total
22 respiratory uptake efficiency ([Figure 5-4](#)) ([Ultman et al., 2004](#); [Wiester et al., 1996a](#);
23 [Gerrity et al., 1988](#)). Modeling predicted a decrease in fractional uptake with increased f_B
24 when V_T was held constant, but an increase in PAR dose with increased f_B ([Overton et](#)
25 [al., 1996](#)). Similarly, increased f_B (80 - 160 bpm) and shallow breathing in rats decreased
26 midlevel tracheal ¹⁸O content and an increased ¹⁸O content in the mainstem bronchi
27 ([Alfaro et al., 2004](#)). This dependence may be a result of frequency-induced alterations in
28 contact time that affects the first-order absorption rate for O₃ ([Postlethwait et al., 1994](#)).
29 Also, an association of O₃ uptake efficiency was found with \dot{V}_E and exposure time.

30 Increasing flow leads to deeper penetration of O₃ into the lung, such that a smaller
31 fraction of O₃ is absorbed in the URT and uptake shifts to the TB airways and respiratory
32 airspaces ([Nodelman and Ultman, 1999](#); [Hu et al., 1994](#); [Ultman et al., 1994](#)). [Hu et al.](#)
33 [\(1994\)](#) and [Ultman et al. \(1994\)](#) found that O₃ absorption increased with volumetric
34 penetration (V_p) of a bolus of O₃ into the RT. Ozone uptake efficiency and V_p were not

1 affected by bolus O₃ concentration ([Kabel et al., 1994](#); [Hu et al., 1992](#)), indicating that
2 under these experimental conditions O₃ uptake was a linear absorption process, where the
3 diffusion and chemical reaction rates of O₃ were proportional to the O₃ concentration.
4 The absorption relationship would not be linear once interfacial mass transfer is
5 saturated. As mentioned above, a weak negative relationship between O₃ concentration
6 and uptake efficiency was reported for the nasal cavities by [Santiago et al. \(2001\)](#). [Rigas](#)
7 [et al. \(2000\)](#) also found a weak but significant negative dependence of O₃ concentration
8 on RT uptake efficiency in exercising individuals. This study also found that exposure
9 time had a small but significant influence on uptake efficiency; however, this negative
10 dependence may be an artifact of progressive depletion of reactive substrates from the
11 ELF.



Note: Subjects breathed 250 ppb O₃ oronasally via a breathing mask. The uptake efficiency was well correlated with breathing frequency ($r = -0.723$, $p < 0.001$) and tidal volume (not illustrated; $r = 0.490$, $p < 0.001$).

Source: Reprinted with permission of Health Effects Institute ([Ultman et al., 2004](#)).

Figure 5-4 Total ozone uptake efficiency as a function of breathing frequency at a constant minute ventilation of 30 L/min.

12 Past studies have shown that O₃-induced epithelial damage to the lung occurs with a
13 reproducible pattern of severity between daughter branches of individual bifurcations that
14 is dependent on the O₃ concentration-time profile of the inhaled gas. A 3-D
15 computational fluid dynamics model was created to investigate the O₃ transport in a

1 single airway bifurcation ([Taylor et al., 2007](#)). The model consisted of one parent branch
2 and two symmetrical daughter branches with a branching angle of 90° and a sharp carinal
3 ridge. Various flow scenarios were simulated using Reynolds numbers (Re) ranging from
4 100 to 500. The Re that corresponds to a certain airway generation is dependent upon
5 both lung size and \dot{V}_E , such that the range in Re from 100-500 would encompass
6 generations 1-5, 3-7, and 6-10 for an adult during quiet breathing, light exertion, and
7 heavy exercise, respectively, whereas the same Re range corresponds to generations 0-4,
8 1-6, and 4-8 for a 4-year-old child. This model predicted velocity distributions that were
9 consistent with earlier work of [Schroter and Sudlow \(1969\)](#), and also reported O_3
10 concentration and wall uptake distributions. The model predicted that during inspiration,
11 the velocity and O_3 concentration distribution were axisymmetric throughout the parent
12 branch, but skewed towards the inner wall within the daughter branches. During
13 expiration, the model predicted that the velocity and O_3 concentration distribution was
14 slightly skewed towards the outer walls of the daughter branches. Hot spots of wall flux
15 existed at the carina during inspiration and expiration with $Re > 100$. Additional hot spots
16 were found during expiration on the parent branch wall downstream of the branching
17 region.

18 Overall O_3 inhalation uptake in humans is over 80% efficient, but the exact efficiency
19 that determines how much O_3 is available at longitudinally distributed compartments in
20 the lung is sensitive to changes in V_T , f_B , and to a minor extent, exposure time.

5.2.2.5 Mode of Breathing

21 Ozone uptake and distribution is sensitive to the mode of breathing. Variability in TB
22 airways volume had a weaker influence on O_3 absorption during nasal breathing
23 compared to oral breathing. This could be a result of O_3 scrubbing in the nasal
24 passageways that are bypassed by oral breathing. Studies by Ultman and colleagues using
25 bolus inhalation demonstrated that O_3 uptake fraction was greater during nasal breathing
26 than during oral breathing at each V_p (e.g., 0.90 during nasal breathing and 0.80 during
27 oral breathing at 150 mL/sec and 0.45 during nasal breathing and 0.25 during oral
28 breathing at 1,000 mL/sec) ([Nodelman and Ultman, 1999](#); [Kabel et al., 1994](#); [Ultman et
29 al., 1994](#)). Therefore, oral breathing results in deeper penetration of O_3 into the RT with a
30 higher absorbed fraction in the TB and alveolar airways ([Nodelman and Ultman, 1999](#)).
31 Similar results were obtained from O_3 uptake studies in dogs ([Yokoyama and Frank,
32 1972](#)). Earlier human studies suggested that oral or oronasal breathing results in a higher
33 O_3 uptake efficiency than nasal breathing ([Wiester et al., 1996a](#); [Gerrity et al., 1988](#)).
34 Overall, the mode of breathing may have a seemingly small effect on the RT uptake

1 efficiency; however, it does play an important role in the distribution of O₃ deposited in
2 the distal airways.

5.2.2.6 Interindividual Variability in Dose

3 Similarly exposed individuals vary in the amount of actual dose delivered to the LRT
4 ([Santiago et al., 2001](#); [Rigas et al., 2000](#); [Bush et al., 1996](#)). Interindividual variability
5 accounted for between 10-50% of the absolute variability in O₃ uptake measurements
6 ([Santiago et al., 2001](#); [Rigas et al., 2000](#)). When concentration, time, and \dot{V}_E were held
7 constant, fractional absorption ranged from 0.80 to 0.91 ([Rigas et al., 2000](#)). It has been
8 hypothesized that interindividual variation in O₃ induced responses such as FEV₁ is the
9 result of interindividual variation in net dose or regional O₃ uptake among exposed
10 individuals.

11 Recent studies have reiterated the importance of intersubject variation in O₃ uptake. The
12 intersubject variability in nasal O₃ uptake determined by [Sawyer et al. \(2007\)](#) ranged
13 from 26.8 to 65.4% (pre- and post-exercise). A second study investigating the use of the
14 CO₂ expirogram to quantify pulmonary responses to O₃ found that intersubject variability
15 accounted for 50% of the overall variance in the study ([Taylor et al., 2006](#)).

16 Variability in net or tissue dose may be attributed to differences in the pulmonary
17 physiology, anatomy, and biochemistry. Since the URT and TB airways remove the
18 majority of inhaled O₃ before it reaches the gas exchange region, the volume and surface
19 area of these airways will influence O₃ uptake. Models predicted that fractional O₃ uptake
20 and PAR dose (flux of O₃ to the PAR surfaces divided by exposure concentration)
21 increase with decreasing TB volume and decreasing TB region expansion. On the
22 contrary, alveolar expansion had minimal effect on uptake efficiency as relatively little
23 O₃ reaches the peripheral lung ([Bush et al., 2001](#); [Overton et al., 1996](#)). Ozone uptake
24 was virtually complete by the time O₃ reaches the alveolar spaces of the lung
25 ([Postlethwait et al., 1994](#)). Experimental studies have found that differences in TB
26 volumes may account for 75% of the variation in absorption between subjects ([Ultman et
27 al., 2004](#)). In support of this concept, regression analysis showed that O₃ absorption was
28 positively correlated with anatomical dead space (V_D) and TB volume (i.e., V_D minus
29 V_{URT}), but not total lung capacity (TLC), forced vital capacity (FVC), or functional
30 residual capacity (FRC) ([Ultman et al., 2004](#); [Bush et al., 1996](#); [Hu et al., 1994](#);
31 [Postlethwait et al., 1994](#)). Variability in V_D was correlated more with the variability in the
32 TB volume than the URT volume. Similarly, uptake was correlated with changes in
33 individual bronchial cross-sectional area, indicating that changes in cross-sectional area
34 available for gas diffusion are related to overall O₃ retention ([Reeser et al., 2005](#); [Ultman](#)

1 [et al., 2004](#)). When coupled, these results suggest that the larger surface-to-volume ratio
2 associated with the smaller airways in women enhances local O₃ uptake, thereby reducing
3 the distal penetration volume of O₃ into the female respiratory system. When absorption
4 data were normalized to V_p/V_D, variability attributed to gender differences were not
5 distinguishable ([Bush et al., 1996](#)). These studies provide support to the RT anatomy,
6 especially the TB volume and surface area, playing a key role in variability of O₃ uptake
7 between individuals.

8 In addition, variability between individuals is influenced by age. [Overton and Graham](#)
9 [\(1989\)](#) predicted that the total mass of O₃ absorbed per minute (in units of: μg/min per
10 [μg/m³ of ambient O₃]) increased with age from birth to adulthood. This model predicted
11 that during quiet breathing the LRT distribution of absorbed O₃ and the CAR O₃ tissue
12 dose were not sensitive to age. However, during heavy exercise or work O₃ uptake was
13 dependent on age. A physiologically based pharmacokinetic model simulating O₃ uptake
14 predicted that regional extraction of O₃ was relatively insensitive to age, but extraction
15 per unit surface area was 2-fold to 8-fold higher in infants compared to adults, due to the
16 fact that children under age 5 have much a much smaller airway surface area in the
17 extrathoracic (nasal) and alveolar regions ([Sarangapani et al., 2003](#)). Additionally,
18 children tend to have a greater oral breathing contribution than adults at rest and during
19 exercise ([Bennett et al., 2008](#); [Becquemin et al., 1999](#); [James et al., 1997](#)). Normalized to
20 lung surface area, the dose rate to the lower airways of children compared to adults is
21 increased further because children breathe at higher minute ventilations relative to their
22 lung volumes.

23 Smoking history, with its known increase in mucus production, was not found to affect
24 the fractional uptake of a bolus of O₃ in apparently healthy smokers with limited smoking
25 history ([Bates et al., 2009](#)). Despite similar internal O₃ dose distribution, the smokers
26 exhibited greater pulmonary responses to O₃ bolus exposures, measured as FEV₁
27 decrements and increases in the normalized slope of the alveolar plateau (S_N). This was
28 contrary to previous studies conducted in smokers with a greater smoking history that
29 found decreased O₃ induced decrements in FEV₁ in smokers during continuous O₃
30 exposure ([Frampton et al., 1997a](#); [Emmons and Foster, 1991](#)).

5.2.2.7 Physical Activity

31 Exercise increases the overall exposure of the lung to inhaled contaminants due, in most
32 part, to the increased intake of air. Thus, human studies have used exercise, at a variety of
33 activity levels, to enhance the effects of O₃ ([Table 5-2](#)). Further explanation of the effects
34 of physical activity on ventilation can be found in Chapters 4 and 6. [Table 4-5](#) presents

1 the mean ventilation rates at different activity levels for different age groups. [Table 6-1](#)
2 provides activity levels as detailed in specific human exposure studies.

Table 5-2 General adult human inhalation rates by activity levels.

| Activity Level | Inhalation Rate |
|----------------|---|
| Light | 2 to 3 × resting \dot{V}_E ^a |
| Moderate | 4 to 6 × resting \dot{V}_E |
| Heavy | 7 to 8 × resting \dot{V}_E |
| Very Heavy | >9 × resting \dot{V}_E |

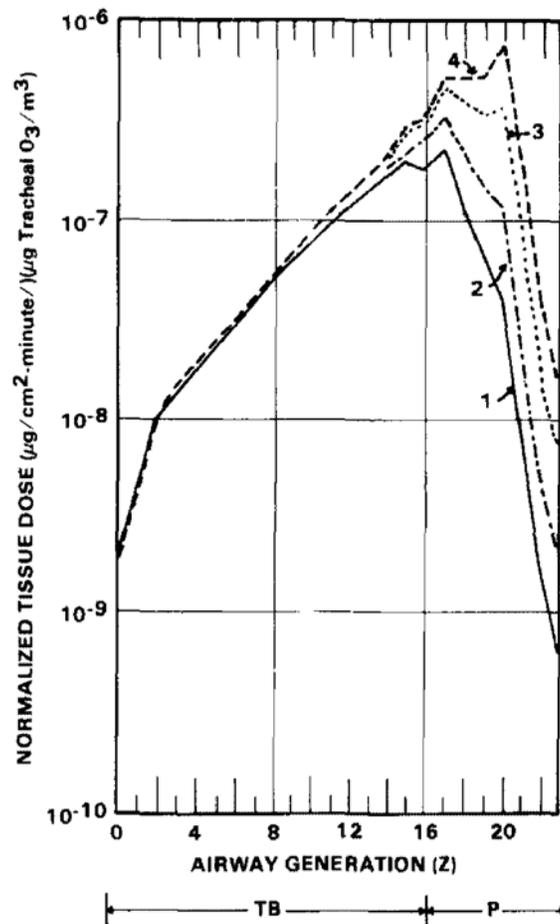
^aResting \dot{V}_E approximates 8 L/min

Source: [U.S. EPA \(1986\)](#).

3 As exercise increases from a light to moderate level, V_T increases. This increase in V_T is
4 achieved by encroaching upon both the inspiratory and expiratory reserve volumes of the
5 lung ([Dempsey et al., 1990](#)). After V_T reaches about 50% of the vital capacity, generally
6 during heavy exercise, further increases in ventilation are achieved by increasing f_B .
7 Ventilatory demands of very heavy exercise require airway flow rates that often exceed
8 10 times resting levels and V_T that approach 5 times resting levels ([Dempsey et al.,](#)
9 [2008](#)).

10 This increase in V_T and flow associated with exercise in humans shifts the net O_3 dose
11 further into the periphery of the RT causing a disproportionate increase in distal lung
12 tissue dose. In addition to increasing the bulk transport of O_3 into the lung, exercise also
13 leads to a switch from nasal to oronasal breathing. Higher ventilatory demand
14 necessitates a lower-resistance path through the mouth. Modeling heavy exercise by
15 increasing ventilatory parameters from normal respiration levels predicted a 10-fold
16 increase in total mass uptake of O_3 ([Miller et al., 1985](#)). This model also predicted that as
17 exercise and ventilatory demand increased, the maximum tissue dose, the O_3 reaching the
18 tissues, moved distally into the RT ([Figure 5-5](#)). By increasing flow to what is common
19 in moderate or heavy exercise (respiratory flow = 45-60 L/min compared to 15 L/min),
20 the URT absorbed a smaller fraction of the O_3 (~0.50 at low flow rate to 0.10 at high flow
21 rate); however, the trachea and more distal TB airways received higher doses during
22 higher flow rates than at lower flow rates (0.65 absorbed in the lower TB airways, and
23 0.25 absorbed in the alveolar zone with high flow compared to 0.5 in the TB with almost
24 no O_3 reaching the alveolar zone at low flow) ([Hu et al., 1994](#)). The same shift in the O_3
25 dose distribution more distally in the lung occurred in other studies mimicking the effects
26 of exercise ([Nodelman and Ultman, 1999](#)). Also, LRT uptake efficiency was sensitive to
27 age only under exercise conditions ([Overton and Graham, 1989](#)). The total mass of O_3

1 absorbed per minute ($\mu\text{g}/\text{min}$ per [$\mu\text{g}/\text{m}^3$ of ambient O_3]) was predicted to increase with
 2 age during heavy work or exercise. A recent study by [Sawyer et al. \(2007\)](#) approximated
 3 that doubling minute ventilation led to only a 1.6-fold higher delivered dose rate of O_3 to
 4 the lung (delivered dose was calculated as: flow rate \times [O_3 ppm] \times (100-percent nasal O_3
 5 uptake)). Past models have predicted the increase in uptake during exercise is distributed
 6 unevenly in the RT compartments and regions. Tissue and mucus layer dose in the TB
 7 region increased ~ 1.4 -fold during heavy exercise compared to resting conditions, whereas
 8 the alveolar region surfactant and tissue uptake increased by factors of 5.2 and 13.6,
 9 respectively ([Miller et al., 1985](#)).



Note: Curve 1: $V_T = 500$ mL; $f_B = 15$ breaths/min. Curve 2: $V_T = 1,000$ mL; $f_B = 15$ breaths/min. Curve 3: $V_T = 1,750$ mL; $f_B = 20.3$ breaths/min. Curve 4: $V_T = 2,250$ mL; $f_B = 30$ breaths/min. TB = tracheobronchial region; P = pulmonary region.
 Source: Reprinted with permission of Elsevier ([Miller et al., 1985](#)).

Figure 5-5 Modeled effect of exercise on tissue dose of the LRT.

5.2.2.8 Summary

1 In summary, O₃ uptake is affected by complex interactions between a number of factors
2 including RT morphology, breathing route, frequency, and volume, physicochemical
3 properties of the gas, physical processes of gas transport, as well as the physical and
4 chemical properties of the ELF and tissue layers. The role of these processes varies
5 throughout the length of the RT and as O₃ moves from the gas into liquid compartments
6 of the RT. The primary uptake site of O₃ delivery to the lung epithelium is believed to be
7 the CAR, however inhomogeneity in the RT structure may affect the dose delivered to
8 this target site with larger path lengths leading to smaller locally delivered doses. This
9 could have implications in regional damage to the LRT, such that even though the
10 average LRT dose may be at a level where health effects would not be predicted, local
11 regions of the RT may receive considerably higher than average doses and therefore be at
12 greater risk of effects. Recent studies have provided evidence for hot spots of O₃ flux
13 around bifurcations in airways. Experimental studies and models have suggested that the
14 net O₃ dose gradually decreases distally from the trachea toward the end of the TB region
15 and then rapidly decreases in the alveolar region. However, the tissue O₃ dose is low in
16 the trachea, increases to a maximum in the terminal bronchioles and the CAR, and then
17 rapidly decreases distally into the alveolar region.

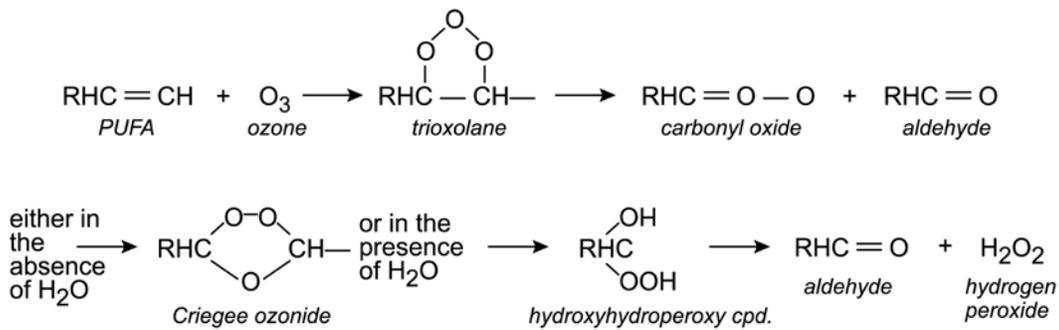
18 O₃ uptake efficiency is sensitive to a number of factors. Fractional absorption will
19 decrease with increased flow and increase proportional to V_T, so that at a fixed \dot{V}_E ,
20 increasing V_T (or decreasing f_B) drives O₃ deeper into the lungs and increases total
21 respiratory uptake efficiency. Individual total airway O₃ uptake efficiency is also
22 sensitive to large changes in O₃ concentration, exposure time, and \dot{V}_E . Major sources of
23 variability in absorption of O₃ include O₃ concentration, exposure time, f_B, \dot{V}_E , and V_T,
24 but the interindividual variation is the greatest source of variability uptake efficiency. The
25 majority of this interindividual variability is due to differences in TB volume and surface
26 area.

27 An increase in V_T and f_B are both associated with increased physical activity. These
28 changes and a switch to oronasal breathing during exercise results in deeper penetration
29 of O₃ into the lung with a higher absorbed fraction in the ET, TB, and alveolar airways.
30 For these reasons, increased physical activity acts to move the maximum tissue dose of
31 O₃ distally into the RT and into the alveolar region.

5.2.3 Ozone Reactions and Reaction Products

1 Ozone dose is affected by the chemical reactions or the products of these reactions that
2 result from O₃ exposure. The process by which O₃ moves from the airway lumen and into
3 the ELF is related to the coupled diffusion and chemical reactions occurring in ELF is
4 called “reactive absorption”. Ozone is chemically reactive with a wide spectrum of
5 biomolecules and numerous studies have evaluated the loss of specific molecules such as
6 GSH and the appearance of plausible products such as nonanal. Both in vitro and in vivo
7 studies contribute to the understanding of O₃ reactions and reaction products.

8 Ozone may interact with many of the components in the ELF including phospholipids,
9 neutral lipids like cholesterol, free fatty acids, proteins, and low molecular weight
10 antioxidants as has been demonstrated in in vitro studies ([Perez-Gil, 2008](#); [Uppu et al.,
11 1995](#)). It was estimated that 88% of the O₃ that does not come in contact with
12 antioxidants will react with unsaturated fatty acids in the ELF including those contained
13 within phospholipids or neutral lipids ([Uppu et al., 1995](#)). Ozone reacts with the double
14 bond of unsaturated fatty acids to form stable and less reactive ozonide, aldehyde, and
15 hydroperoxide reaction products via chemical reactions such as the Criegee ozonolysis
16 mechanism ([Figure 5-6](#)) ([Pryor et al., 1991](#)). Lipid ozonation products, such as the
17 aldehydes hexanal, heptanal, and nonanal, have been recovered after O₃ exposure in
18 human BAL fluid (BALF), rat BALF, isolated rat lung, and in vitro systems ([Frampton et
19 al., 1999](#); [Postlethwait et al., 1998](#); [Pryor et al., 1996](#)). Adducts of the aldehyde
20 4-hydroxynonenal were found in human alveolar macrophages after O₃ exposure in vivo
21 ([Hamilton et al., 1998](#)). Polyunsaturated fatty acid (PUFA) reactions are limited by the
22 availability of O₃ since lipids are so abundant in the ELF. Yields of O₃-induced aldehydes
23 were increased by the decrease in other substrates such as ascorbic acid (AH₂)
24 ([Postlethwait et al., 1998](#)). Free radicals are also generated during O₃-mediated oxidation
25 reactions with PUFA ([Pryor, 1994](#)). These reactions are reduced by the presence of the
26 lipid-soluble free radical scavenger α -tocopherol (α -TOH) ([Pryor, 1994](#); [Fujita et al.,
27 1987](#); [Pryor, 1976](#)). PUFA reactions may not generate sufficient bioactive materials to
28 account for acute cell injury, however only modest amounts of products may be
29 necessary to induce cytotoxicity ([Postlethwait and Ultman, 2001](#); [Postlethwait et al.,
30 1998](#)).



Note: Not all secondary reaction products are shown.
 Source: [U.S. EPA \(2006b\)](#).

Figure 5-6 Schematic overview of ozone interaction with PUFA in ELF and lung cells.

1 Cholesterol is the most abundant neutral lipid in human ELF. Reaction of cholesterol
 2 with O₃ results in biologically active cholesterol products such as the oxysterols,
 3 β-epoxide and 6-oxo-3,5-diol ([Murphy and Johnson, 2008](#); [Pulfer et al., 2005](#); [Pulfer and](#)
 4 [Murphy, 2004](#)). Product yields depend on ozonolysis conditions, however cholesterol
 5 ozonolysis products form in similar abundance to phospholipid-derived ozonolysis
 6 products in rat ELF ([Pulfer and Murphy, 2004](#)).

7 The ELF also contains proteins derived from blood plasma as well as proteins secreted by
 8 surface epithelial cells. Ozone reactions with proteins have been studied by their in vitro
 9 reactions as well as reactions of their constituent amino acids (the most reactive of which
 10 are cysteine, histidine, methionine, tyrosine, and tryptophan). Ozone preferentially reacts
 11 with biomolecules in the following order: thiosulfate > ascorbate > cysteine ≈ methionine
 12 > glutathione ([Kanofsky and Sima, 1995](#)). Rate constants for the reaction of amino acids
 13 with O₃ vary between studies due to differing reaction conditions and assumptions;
 14 however aliphatic amino acids were consistently very slow to react with O₃ (e.g., alanine:
 15 25-100 moles/L/sec) ([Kanofsky and Sima, 1995](#); [Ignatenko and Cherenkevich, 1985](#);
 16 [Pryor et al., 1984](#); [Hoigné and Bader, 1983](#)). [Uppu et al. \(1995\)](#) predicted that 12% of
 17 inhaled O₃ that does not react with antioxidants will react with proteins in the ELF.

18 Reactions of O₃ with low molecular weight antioxidants have been extensively studied.
 19 The consumption of antioxidants such as uric acid (UA), ascorbate (AH₂), and reduced
 20 glutathione (GSH) by O₃ was linear with time and positively correlated with initial
 21 substrate concentration and O₃ concentration ([Mudway and Kelly, 1998](#); [Mudway et al.,](#)
 22 [1996](#)). Endogenous antioxidants are present in relatively high concentrations in the ELF
 23 of the human airways (obtained as BALF) and display high (but not equal) intrinsic

1 reactivities toward O₃. In individual and in limited composite mixtures, UA was the most
2 reactive antioxidant tested, followed by AH₂ ([Mudway and Kelly, 1998](#)). GSH was
3 consistently less reactive than UA or AH₂ ([Mudway and Kelly, 1998](#); [Mudway et al.,
4 1996](#); [Kanofsky and Sima, 1995](#)). To quantify these reactions, [Kermani et al. \(2006\)](#)
5 evaluated the interfacial exposure of aqueous solutions of UA, AH₂, and GSH
6 (50-200 μM) with O₃ (1-5 ppm). Similar to the results of [Mudway and Kelly \(1998\)](#), this
7 study found the hierarchy in reactivity between O₃ and these antioxidants to be
8 UA ≥ AH₂ >> GSH. UA and AH₂ shared a 1:1 stoichiometry with O₃, whereas 2.5 moles of
9 GSH were consumed per mole of O₃. Using these stoichiometries, reaction rate constants
10 were derived ($5.8 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, $5.5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, and $57.5 \text{ M}^{-0.75} \text{ sec}^{-1}$ [$20.9 \text{ M}^{-1} \text{ sec}^{-1}$] for
11 the reaction of O₃ with UA, AH₂, and GSH, respectively). Other studies report reactive
12 rate constants that are two to three orders of magnitude larger, however these studies used
13 higher concentrations of O₃ and antioxidants under less physiologically relevant
14 experimental conditions ([Kanofsky and Sima, 1995](#); [Giamalva et al., 1985](#); [Pryor et al.,
15 1984](#)). However, O₃ acts through competition kinetics so the effective concentration of
16 the reactants present in the ELF will determine the reactions that occur in vivo. For
17 example, the pKa of GSH is about 8.7 so that at physiological pH very little is in the
18 reactive form of thiolate (GS⁻). On the other hand, ascorbic acid has a pKa of about 4.2 so
19 it exists almost entirely as ascorbate (AH⁻) in the ELF. Thus, the effective concentration
20 of GSH that is available to react with O₃ will be much lower than that of ascorbate in
21 ELF.

22 A series of studies used new techniques to investigate the reaction products resulting
23 from initial air-liquid interface interactions of O₃ with ELF components
24 (e.g., antioxidants and proteins) in ~1 millisecond ([Enami et al., 2009a, b, c, 2008a, b](#)).
25 Solutions of aqueous UA, AH₂, GSH, α-TOH, and protein cysteines (CyS) were sprayed
26 as microdroplets in O₃/N₂ mixtures at atmospheric pressure and analyzed by electrospray
27 mass spectrometry. These recent studies demonstrated different reactivity toward AH₂,
28 UA, and GSH by O₃ when the large surface to volume ratio of microdroplets promote an
29 interfacial reaction compared to previous studies using bulk liquid phase bioreactors. This
30 artificial system does not recapitulate the lung surface so caution must be taken in
31 translating the results of these studies to in vivo conditions.

32 As was seen in previous studies ([Kermani et al., 2006](#); [Kanofsky and Sima, 1995](#)), the
33 hierarchy of reactivity of these ELF components with O₃ was determined to be AH₂ ≈ UA
34 > CyS > GSH. There was some variance between the reaction rates and product formation
35 of UA, AH₂, and GSH with O₃ as investigated by Enami et al. versus O₃ reacting with
36 bulk liquid phase bioreactors as described previously. UA was more reactive than AH₂
37 toward O₃ in previous studies, but in reactions with O₃ with microdroplets, these
38 antioxidants had equivalent reactivity ([Enami et al., 2008b](#)). As O₃ is a kinetically slow

1 one-electron acceptor but very reactive O-atom donor, products of the interaction of O₃
2 with UA, AH₂, GSH, CyS, and α-TOH result from addition of *n* O-atoms (*n* = 1-4). These
3 products included epoxides (e.g., U-O[•]), peroxides (e.g., U-O₂[•]), and ozonides
4 (e.g., U-O₃[•]). For instance, GSH was oxidized to sulfonates (GSO₃⁻/GSO₃²⁻), not
5 glutathione disulfide (GSSG) by O₃ ([Enami et al., 2009b](#)). However, it is possible that
6 other oxidative species are oxidizing GSH in vivo, since sulfonates are not detected in O₃
7 exposed ELF whereas GSSG is. This is also supported by the fact that O₃ is much less
8 reactive with GSH than other antioxidants, such that <3% of O₃ will be scavenged by
9 GSH when in equimolar amounts with AH₂ ([Enami et al., 2009b](#)).

10 This series of studies also demonstrated that ozonolysis product yields and formation
11 were affected by pH. Acidified conditions (pH ≈ 3-4), such as those that may result from
12 acidic particulate exposure or pathological conditions like asthma (pH ≈ 6), decreased the
13 scavenging ability of UA and GSH for O₃; such that at low pH, the scavenging of O₃
14 must be taken over by other antioxidants, such as AH₂ ([Enami et al., 2009b](#), [2008b](#)).
15 Also, under acidic conditions (pH ≈ 5), the ozonolysis products of AH₂ shifted from the
16 innocuous dehydroascorbic acid to the more persistent products, AH₂ ozonide and
17 threonic acid ([Enami et al., 2008a](#)). It is possible that the acidification of the ELF by
18 acidic copollutant exposure will increase the toxicity of O₃ by preventing some
19 antioxidant reactions and shifting the reaction products to more persistent compounds.

20 Since ELF exists as a complex mixture, it is important to look at O₃ reactivity in substrate
21 mixtures. Individual antioxidant consumption rates decreased as the substrate mixture
22 complexity increased (e.g., antioxidant mixtures and albumin addition) ([Mudway and](#)
23 [Kelly, 1998](#)). However, O₃ reactions with AH₂ predominated over the reaction with
24 lipids, when exposed to substrate solution mixtures ([Postlethwait et al., 1998](#)). It was
25 suggested that O₃ may react with other substrates once AH₂ concentrations within the
26 reaction plane fall sufficiently. Additionally, once AH₂ was consumed, the absorption
27 efficiency diminished, allowing inhaled O₃ to be distributed to more distal airways
28 ([Postlethwait et al., 1998](#)). Multiple studies have concluded O₃ is more reactive with AH₂
29 and UA than with the weakly reacting GSH (or cysteine or methionine) or with amino
30 acid residues and protein thiols ([Kanofsky and Sima, 1995](#); [Cross et al., 1992](#)).

31 In a red blood cell (RBC) based system, AH₂ augmented the in vitro uptake of O₃ by
32 6-fold, as computed by the mass balance across the exposure chamber ([Ballinger et al.,](#)
33 [2005](#)). However, estimated in vitro O₃ uptake was not proportional to the production of
34 O₃-derived aldehydes from exposing O₃ to RBC membranes ([Ballinger et al., 2005](#)). In
35 addition, O₃ induced cell membrane oxidation that required interactions with AH₂ and
36 GSH, but not UA or the vitamin E analog Trolox. Further, aqueous phase reactions
37 between O₃ and bovine serum albumin did not result in membrane oxidation ([Ballinger et](#)

1 [al., 2005](#)). The presence of UA or bovine serum albumin protected against lipid and
2 protein oxidation resulting from the reaction of O₃ and AH₂ ([Ballinger et al., 2005](#)). This
3 study provided evidence that antioxidants may paradoxically facilitate O₃-mediated
4 damage. This apparent contradiction should be viewed in terms of the
5 concentration-dependent role of the ELF antioxidants. Reactions between O₃ and
6 antioxidant species exhibited a biphasic concentration response, with oxidation of protein
7 and lipid occurring at lower, but not higher, concentrations of antioxidant. In this way,
8 endogenous reactants led to the formation of secondary oxidation products that were
9 injurious and also led to quenching reactions that were protective. Moreover, the
10 formation of secondary oxidation products mediated by some antioxidants was opposed
11 by quenching reactions involving other antioxidants.

12 Alterations in ELF composition can result in alterations in O₃ uptake. Bolus O₃ uptake in
13 human subjects can be decreased by previous continuous O₃ exposure (120-360 ppb),
14 possibly due to depletion of compounds able to react with O₃ ([Rigas et al., 1997](#); [Asplund
15 et al., 1996](#)). Conversely, O₃ (360 ppb) bolus uptake was increased with prior NO₂
16 (360-720 ppb) or SO₂ (360 ppb) exposure ([Rigas et al., 1997](#)). It was hypothesized that
17 this increased fractional absorption of O₃ could be due to increased production of reactive
18 substrates in the ELF due to oxidant-induced airway inflammation.

19 Besides AH₂, GSH and UA, the ELF contains numerous antioxidant substances that
20 appear to be an important cellular defense against O₃ including α -TOH, albumin,
21 ceruloplasmin, lactoferrin, mucins, and transferrin ([Mudway et al., 2006](#); [Freed et al.,
22 1999](#)). The level and type of antioxidant present in ELF varies between species, regions
23 of the RT, and can be altered by O₃ exposure. Mechanisms underlying the regional
24 variability are not well-understood. It is thought that both plasma ultrafiltrate and locally
25 secreted substances contribute to the antioxidant content of the ELF ([Mudway et al.,
26 2006](#); [Freed et al., 1999](#)). In the case of UA, the major source appears to be the plasma
27 ([Peden et al., 1995](#)). Repletion of UA in nasal lavage fluid was demonstrated during
28 sequential nasal lavage in human subjects ([Mudway et al., 1999a](#)). When these subjects,
29 exercising at a moderate level, were exposed to 200 ppb O₃ for 2 hours, nasal lavage
30 fluid UA was significantly decreased while plasma UA levels were significantly
31 increased ([Mudway et al., 1999a](#)). The finding that UA, but not AH₂ or GSH, was
32 depleted in nasal lavage fluid indicated that UA was the predominant antioxidant with
33 respect to O₃ reactivity in the nasal cavity ([Mudway et al., 1999a](#)). However, in human
34 BALF samples, the mean consumption of AH₂ was greater than UA ([Mudway et al.,
35 1996](#)). In addition, concentrations of UA were increased by cholinergic stimulation of the
36 airways in human subjects, which suggested that increased mucosal gland secretions were
37 an important source ([Peden et al., 1993](#)). Using the O₃-specific antioxidant capacity assay
38 on human nasal lavage samples, [Rutkowski et al. \(2011\)](#) concluded that about 30% of the

1 antioxidant capacity of the nasal liquid lining layer was attributed to UA activity.
2 Additionally, more than 50% of the subject-to-subject differences in antioxidant capacity
3 were driven by differences in UA concentration. However, day-to-day within-subject
4 variations in measured antioxidant capacity were not related to the corresponding
5 variations in UA concentration in the nasal lavage fluid. Efforts to identify the
6 predominant antioxidant(s) in other RT regions besides the nasal cavity have failed to
7 yield definitive results.

8 Regulation of AH₂, GSH and α -TOH concentrations within the ELF is less clear than that
9 of UA ([Mudway et al., 2006](#)). In a sequential nasal lavage study in humans, wash-out of
10 AH₂ and GSH occurred, indicating the absence of rapidly acting repletion mechanisms
11 ([Mudway et al., 1999a](#)). Other studies demonstrated increases in BALF GSH and
12 decreases in BALF and plasma AH₂ levels several hours following O₃ exposure (200 ppb
13 for 2 h, while exercising at a moderate level) ([Mudway et al., 2001](#); [Blomberg et al.,](#)
14 [1999](#); [Mudway et al., 1999b](#)). Other investigators have demonstrated cellular uptake of
15 oxidized AH₂ by several cell types leading to intracellular reduction and export of
16 reduced AH₂ ([Welch et al., 1995](#)). Studies with rats exposed to 0.4-1.1 ppm O₃ for
17 1-6 hours have shown consumption of AH₂ that correlates with O₃ exposure ([Gunnison](#)
18 [and Hatch, 1999](#); [Gunnison et al., 1996](#); [Vincent et al., 1996b](#)).

19 A body of evidence suggests that reaction of O₃ within the ELF limits its diffusive
20 transport through the ELF; direct contact of O₃ with the apical membranes of the
21 underlying epithelial cells therefore might be negligible ([Ballinger et al., 2005](#); [Connor et](#)
22 [al., 2004](#); [Postlethwait and Ultman, 2001](#); [Pryor, 1992](#)). This conclusion is based on
23 computational analyses and in vitro studies. Direct confirmation using in vivo studies is
24 lacking. Nevertheless, when predicting exposure-related outcomes across species and
25 anatomic sites, whether O₃ directly contacts the apical membranes of the epithelial cells
26 is an important consideration, given that the extracellular surface milieu of the RT
27 appreciably varies in terms of the types and concentrations of the substrates present and
28 the thickness of the ELF.

29 For O₃ or its reaction products to gain access to the underlying cellular compartments, O₃
30 must diffuse at the air-liquid interface of the airway surface and travel through the ELF
31 layer. In vitro experiments have shown that O₃ disappearance from the gas phase depends
32 on the characteristics of the ELF substrates ([Postlethwait et al., 1998](#); [Hu et al., 1994](#)).
33 The ELF is comprised of the airway surface lining that includes the periciliary sol layer
34 and overlying mucus gel layer, and the alveolar surface lining that includes the subphase
35 of liquid and vesicular surfactant and the continuous surfactant monolayer ([Bastacky et](#)
36 [al., 1995](#)). There is a progressive decrease in ELF thickness and increase in interfacial
37 surface with progression from the TB region to the alveolus ([Mercer et al., 1992](#)). The

1 progressive thinning of the ELF while moving further down the RT decreases the radial
2 distance O_3 or its reaction products must travel to reach the cells lining the RT.

3 Taking into account the high reactivity and low water solubility of O_3 , calculations
4 suggest that O_3 will not penetrate ELF layers greater than $0.1 \mu\text{m}$ without being
5 transformed to other more long-lived reactive species, thus initiating a reaction cascade
6 ([Pryor, 1992](#)). These calculations utilize the Einstein-Smoluchowski equation ([Equation](#)
7 [5-1](#)) that combines Fick's second law of diffusion and a stochastic view of motion to
8 compare the half-life of O_3 in the ELF layer to the time it takes, t , for O_3 to travel a
9 distance, d , with a diffusion coefficient of D ($\sim 2 \times 10^{-5} \text{ cm}^2/\text{sec}$).

$$t = d^2/2D$$

Equation 5-1

10 The transit time through an ELF layer of 10^{-5} cm was estimated to be 2.5×10^{-6} seconds.
11 The half-life of O_3 can be approximated by dividing the pseudo-first order rate constant,
12 k_1 , into $\ln 2$. [Pryor \(1992\)](#) assumed the reaction rate constant 10^9 L/mol/sec for O_3 with
13 GSH and the concentration of GSH equaled 1 mM in the ELF. Using these values and
14 neglecting reactions of O_3 with other ELF species, the half-life of O_3 would be 7×10^{-7}
15 seconds. Under these assumptions of GSH concentration and ELF thickness, the half-life
16 of O_3 is about one third of the time necessary for O_3 to diffuse through the ELF layer.

17 Further, assuming that $0.5 \text{ ppm } O_3$ enters the trachea and the intrapulmonary gas-phase
18 concentration is reduced only 5 fold during transport to the terminal bronchioles, by using
19 a Henry's law constant and assuming equilibrium, the ELF O_3 concentration could be
20 calculated to be $< 1.4 \times 10^{-9} \text{ M}$ or approximately $0.0014 \mu\text{M}$. Further, assuming that
21 ascorbate = $100 \mu\text{M}$, GSH = $300 \mu\text{M}$, and uric acid = $250 \mu\text{M}$, while ignoring unsaturated
22 lipids and reactive proteins, the most facile reactants would equate to an approximately
23 500,000-fold excess over O_3 . If one then assumes a lumped reaction rate constant of
24 $10^7 \text{ M}^{-1} \text{ sec}^{-1}$, any O_3 in solution would be consumed by reaction almost instantaneously,
25 thereby constraining its diffusion as an unreacted species to within $< 0.1 \mu\text{m}$, which is less
26 than the thickness values estimated for distal airway ELF. If unsaturated lipids
27 ($\sim 10^6 \text{ M}^{-1} \text{ sec}^{-1}$) and proteins (for which the rate constant will vary depending on low
28 pKa thiolates and other amino acid-reactive sites) are included, the penetration depth is
29 further reduced.

30 Similarly, model calculations of the nasal cavity based on diffusion equations and
31 reaction rates of O_3 with model substrates predict an O_3 penetration distance ($0.5 \mu\text{m}$)
32 less than the thickness of the nasal lining layer ($10 \mu\text{m}$) ([Santiago et al., 2001](#)).

33 A computational fluid dynamics model was able to predict experimentally measured

1 O₃ uptake when nasal mucus layer thickness was considered ([Cohen-Hubal et al., 1996](#)),
2 reaffirming the importance of the resistance imparted by the ELF layer in dose and lesion
3 patterns in the nasal passage.

4 Despite calculations and in vitro studies suggesting that reactions of O₃ with underlying
5 epithelial cells may be negligible, there is some evidence that suggests direct interaction
6 of O₃ with epithelial cells is possible. While moving distally in the lung, the ELF
7 thickness decreases and becomes ultrathin in the alveolar region, possibly allowing for
8 direct interaction of O₃ with the underlying epithelial cells. One definitive study
9 conducted in excised rat lung measured alveolar lining layer thickness over relatively flat
10 portions of the alveolar wall to be 0.14 μm, to be 0.89 μm at the alveolar wall junctions,
11 and 0.09 μm over the protruding features ([Bastacky et al., 1995](#)). The area-weighted
12 average thickness of the alveolar lining fluid was found to be about 0.2 μm and the
13 alveolar lining layer was continuous over the entire alveolar surface measured. The
14 surface appeared smooth, and no epithelial surface features or macrophage features
15 protruded above the air-liquid interface. It was noted that measurements of alveolar lining
16 layer thickness were made in lungs prepared in a state of roughly 80% of total lung
17 capacity, and as a result, the values reported would be approaching the lowest values
18 possible during the respiratory cycle. However, 4% of the surface area in the alveolar
19 compartment was covered by alveolar lining fluid layer of less than 20 nm ([Bastacky et
20 al., 1995](#)), suggesting the possibility that unreacted O₃ could penetrate to the cell layer in
21 this region. Further it remains a possibility that airways macrophages may protrude into
22 the gas phase, allowing for direct contact between O₃ and airways epithelial cells.

23 Still, direct reaction of O₃ with alveolar epithelial cells or macrophages may be limited by
24 the presence of dipalmitoyl phosphatidylcholine (DPPC), the major component of
25 surfactant, which has been shown in vitro to inhibit uptake of O₃ into an aqueous
26 compartment containing ascorbate, glutathione, and uric acid ([Connor et al., 2004](#)).
27 Further, the amount of O₃ available to the alveolar compartment may be limited by
28 uptake of O₃ in nasal and TB compartments ([Figure 5-5](#)). In fact, the amount of ¹⁸O
29 reaction product was lower in the alveolar tissues than in TB tissues of rhesus monkeys
30 immediately following a 2 hour exposure to ¹⁸O-labeled O₃ (0.4 and 1 ppm) ([Plopper et
31 al., 1998](#)). These considerations illustrate the difficulty in determining whether O₃ reacts
32 directly with cells in the alveolar compartment.

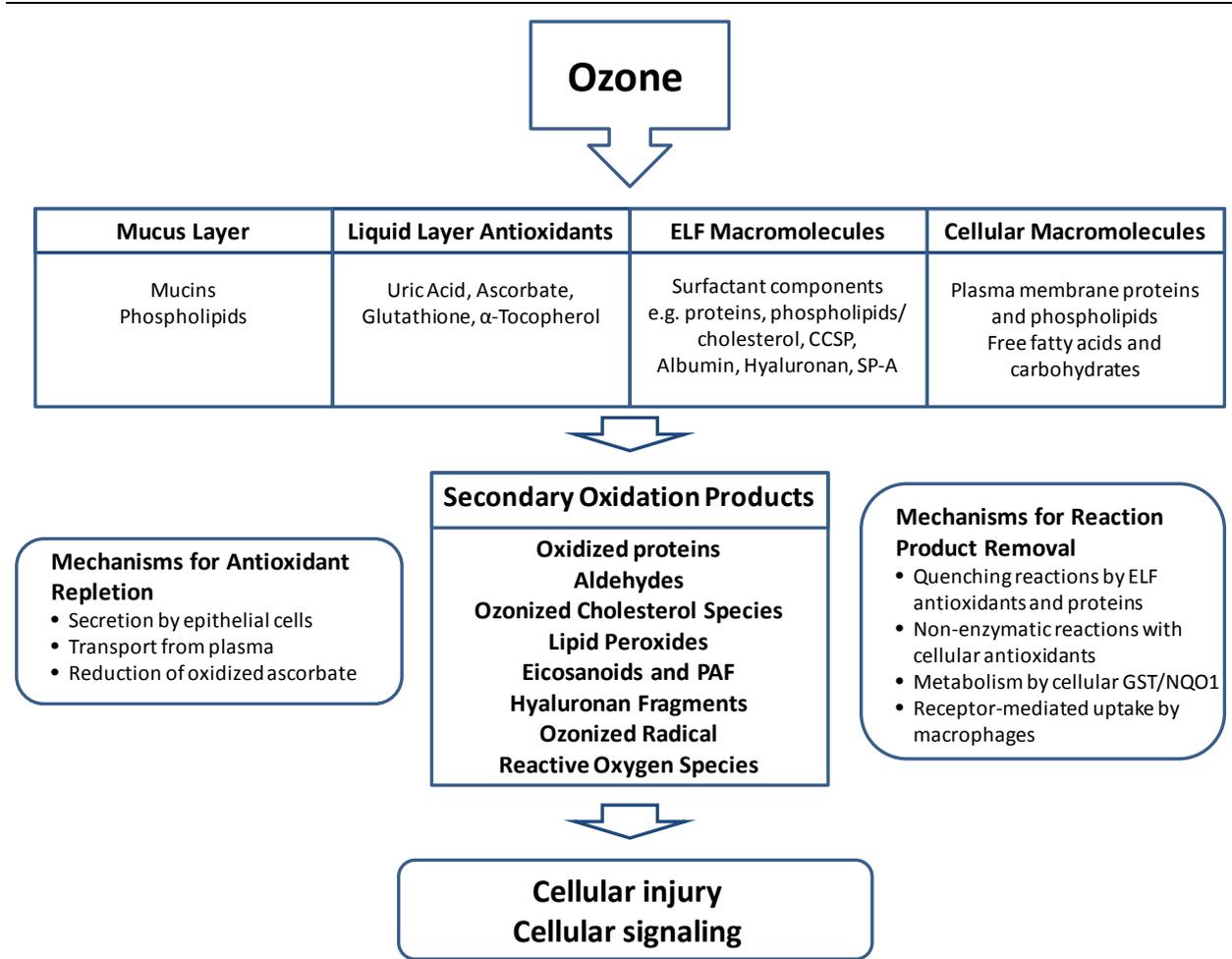
33 In some cases, however, with regard to the initiating mechanisms of cellular
34 perturbations, the precise reactive species that encounters the epithelia might or might not
35 have specificity to O₃ per se or to its secondary oxidants. Many of the measureable
36 products formed as a consequence of O₃ exposure have limited specificity to O₃, such as
37 4-hydroxynonenal that is formed by autoxidation, an event that can be initiated by O₃ but

1 also by a multitude of other oxidants. Although some classes of lipid oxidation products
2 (e.g., specific aldehydes, cholesterol products) are specific to O₃, measurement in either
3 BALF or in tissue does not necessarily provide insight on the compartment in which they
4 were formed (i.e., the ELF, cell membrane, intracellular space) because the ELF is a
5 dynamic compartment and, once formed, hydrophobic species can partition. Oxidation of
6 membrane components might produce similar cellular outcomes regardless of the
7 initiating oxidant. Lipid ozonides, which could be generated either within the ELF or
8 from ozonation of cell membrane unsaturated lipids, could bind to receptors, activate
9 signaling cascades, and act in other ways, making differences between pure extracellular
10 reaction and direct membrane reaction indistinguishable. Thus, in some cases
11 documenting whether O₃ per se reacts directly with cellular constituents might be
12 essential (despite the challenges of in vivo demonstrations), while in other cases precisely
13 where O₃ reacts might be of less concern with regard to characterizing mechanisms of
14 health outcomes.

15 Thus, components of the ELF are major targets for O₃ and the resulting secondary
16 oxidation products key mediators of toxicity in the airways (the role of reaction products
17 in O₃-induced toxicity is discussed in Section [5.3](#)). The reaction cascade resulting from
18 the interaction of O₃ with ELF substrates can then carry the oxidative burden deeper into
19 cells lining the RT to elicit the health effects observed.

5.2.3.1 Summary

20 The ELF is a complex mixture of lipids, proteins, and antioxidants that serve as the first
21 barrier and target for inhaled O₃ ([Figure 5-7](#)). The thickness of the lining fluid and mucus
22 layer is an important determinant of the dose of O₃ to the tissues. The antioxidant
23 substances present in the ELF appear in most cases to limit interaction of O₃ with
24 underlying tissues and to prevent penetration of O₃ deeper into the lung. The formation of
25 secondary oxidation products is likely related to the concentration of antioxidants present
26 and the quenching ability of the lining fluid. Mechanisms are present to replenish the
27 antioxidant substrate pools as well as to remove secondary reaction products from tissue
28 interactions. Important differences exist in the reaction rates for O₃ and these ELF
29 biomolecules and the reactivity of the resulting products. Overall, studies suggest that UA
30 and AH₂ are more reactive with O₃ than GSH, proteins, or lipids. In addition to
31 contributing to the driving force for O₃ uptake, formation of secondary oxidation
32 products may lead to increased cellular injury and cell signaling (discussed in
33 Section [5.3](#)). Studies indicate that the antioxidants might be participating in reactions
34 where the resulting secondary oxidation products might penetrate into the tissue layer and
35 lead to perturbations.



Note: Contents of this figure not discussed in Section 5.2 will be discussed in Section 5.3. Clara cell secretory protein, CCSP; Surfactant Protein-A, SP-A; Platelet activating factor, PAF. Ozone will react with components of the ELF to produce reaction products that may lead to cellular injury and cell signaling as discussed in Section 5.3.

Figure 5-7 Details of the ozone interaction with the airway ELF to form secondary oxidation products.

5.3 Possible Pathways/Modes of Action

5.3.1 Introduction

1 Mode of action refers to a sequence of key events and processes that result in a given
 2 toxic effect (U.S. EPA, 2005). Elucidation of mechanisms provides a more detailed
 3 understanding of these key events and processes (U.S. EPA, 2005). Moreover, toxicity
 4 pathways describe the processes by which perturbation of normal biological processes
 5 produce changes sufficient to lead to cell injury and subsequent events such as adverse

1 health effects ([U.S. EPA, 2009f](#)). The purpose of this section of Chapter 5 is to describe
2 the key events and toxicity pathways that contribute to health effects resulting from short-
3 term and long-term exposures to O₃. The extensive research carried out over several
4 decades in humans and in laboratory animals has yielded numerous studies on
5 mechanisms by which O₃ exerts its effects. This section will discuss some of the
6 representative studies with particular emphasis on studies published since the 2006 O₃
7 AQCD and on studies in humans that inform biological mechanisms underlying
8 responses to O₃.

9 It is well-appreciated that secondary oxidation products, which are formed as a result of
10 O₃ exposure, initiate numerous responses at the cellular, tissue and whole organ level of
11 the respiratory system. These responses include the activation of neural reflexes,
12 initiation of inflammation, alteration of epithelial barrier function, sensitization of
13 bronchial smooth muscle, modification of innate/adaptive immunity and airways
14 remodeling, as will be discussed below. These have the potential to result in effects on
15 other organ systems such as the cardiovascular, central nervous, hepatic and reproductive
16 systems or result in developmental effects. It has been proposed that lipid ozonides and
17 other secondary oxidation products, which are bioactive and cytotoxic in the respiratory
18 system, are responsible for systemic effects. However it is not known whether they gain
19 access to the vascular space ([Chuang et al., 2009](#)). Recent studies in animal models show
20 that inhalation of O₃ results in systemic oxidative stress. The following subsections
21 describe the current understanding of potential pathways and modes of action responsible
22 for the pulmonary and extrapulmonary effects of O₃ exposure.

5.3.2 Activation of Neural Reflexes

23 Acute O₃ exposure results in reversible effects on lung function parameters through
24 activation of neural reflexes. The involvement of bronchial C-fibers, a type of nociceptive
25 sensory nerve, has been demonstrated in dogs exposed through an endotracheal tube to
26 2-3 ppm O₃ for 20-70 minutes ([Coleridge et al., 1993](#); [Schelegle et al., 1993](#)). This vagal
27 afferent pathway was found to be responsible for O₃-mediated rapid shallow breathing
28 and other changes in respiratory mechanics in O₃-exposed dogs ([Schelegle et al., 1993](#)).
29 Ozone also triggers neural reflexes that stimulate the autonomic nervous system and alter
30 electrophysiologic responses of the heart. For example, bradycardia, altered HRV and
31 arrhythmia have been demonstrated in rodents exposed for several hours to 0.1-0.6 ppm
32 O₃ ([Hamade and Tankersley, 2009](#); [Watkinson et al., 2001](#); [Arito et al., 1990](#)). Another
33 effect is hypothermia, which in rodents occurred subsequent to the activation of neural
34 reflexes involving the parasympathetic nervous system ([Watkinson et al., 2001](#)). Vagal
35 afferent pathways originating in the RT may also be responsible for O₃-mediated

1 activation of nucleus tractus solitarius neurons that resulted in neuronal activation in
2 stress-responsive regions of the central nervous system (CNS) (rats, 0.5-2.0 ppm O₃ for
3 1.5-120 hours) ([Gackière et al., 2011](#)).

4 Recent studies in animals provide new information regarding the effects of O₃ on reflex
5 responses mediated by bronchopulmonary C-fibers. In ex vivo mouse lungs, O₃ exposure
6 (30 μM solubilized) selectively activated a subset of C-fiber receptors that are TRPA1
7 ion channels ([Taylor-Clark and Undem, 2010](#)). TRPA1 ion channels are members of the
8 TRP family of ion channels, which are known to mediate the responses of sensory
9 neurons to inflammatory mediators ([Caceres et al., 2009](#)). In addition to TRPA1 ion
10 channels possibly playing a key role in O₃-induced decrements in pulmonary function,
11 they may mediate allergic asthma ([Caceres et al., 2009](#)). Activation of TRPA1 ion
12 channels following O₃ exposure is likely initiated by secondary oxidation products such
13 as aldehydes and prostaglandins ([Taylor-Clark and Undem, 2010](#)) through covalent
14 modification of cysteine and lysine residues ([Trevisani et al., 2007](#)). Ozonation of
15 unsaturated fatty acids in the ELF was found to result in the generation of aldehydes
16 ([Frampton et al., 1999](#)) such as 4-hydroxynonenal and 4-oxononenal ([Taylor-Clark et al.,](#)
17 [2008](#); [Trevisani et al., 2007](#)). 4-oxononenal is a stronger electrophile than
18 4-hydroxynonenal and exhibits greater potency towards the TRPA1 channels ([Taylor-](#)
19 [Clark et al., 2008](#); [Trevisani et al., 2007](#)). In addition, PGE₂ is known to sensitize TRPA1
20 channels ([Bang et al., 2007](#)).

21 In humans exercising at a moderate level, the response to O₃ (500 ppb for 2 h) was
22 characterized by substernal discomfort, especially on deep inspiration, accompanied by
23 involuntary truncation of inspiration ([Hazucha et al., 1989](#)). This latter response led to
24 decreased inspiratory capacity and to decreased forced vital capacity (FVC) and forced
25 expiratory volume in one second (FEV₁), as measured by spirometry. These changes,
26 which occurred during O₃ exposure, were accompanied by decreased V_T and increased
27 respiratory frequency in human subjects. Spirometric changes in FEV₁ and FVC were not
28 due to changes in respiratory muscle strength ([Hazucha et al., 1989](#)). In addition,
29 parasympathetic involvement in the O₃-mediated decreases in lung volume was minimal
30 ([Mudway and Kelly, 2000](#)), since changes in FVC or symptoms were not modified by
31 treatment with bronchodilators such as atropine in human subjects exposed to 400 ppb O₃
32 for 2 hours while exercising at a heavy level ([Beckett et al., 1985](#)). However, the loss of
33 vital capacity was reversible with intravenous administration of the rapid-acting opioid
34 agonist, sufentanyl, in human subjects exercising at a moderate level and exposed to
35 420 ppb O₃ for 2 hours, which indicated the involvement of opioid receptor-containing
36 nerve fibers and/or more central neurons ([Passannante et al., 1998](#)). The effects of
37 sufentanyl may be attributed to blocking C-fiber stimulation by O₃ since activation of
38 opioid receptors downregulated C-fiber function ([Belvisi et al., 1992](#)). Thus, nociceptive

1 sensory nerves, presumably bronchial C-fibers, are responsible for O₃-mediated
2 responses in humans ([Passannante et al., 1998](#)). This vagal afferent pathway is
3 responsible for pain-related symptoms and inhibition of maximal inspiration in humans
4 ([Hazucha et al., 1989](#)).

5 There is some evidence that eicosanoids (see Section [5.3.3](#)) play a role in the neural
6 reflex since cyclooxygenase inhibition with indomethacin ([Alexis et al., 2000](#); [Schelegle
7 et al., 1987](#)) or ibuprofen, which also blocks some lipoxygenase activity ([Hazucha et al.,
8 1996](#)), before exposure to O₃ significantly blunted the spirometric responses. These
9 studies involved exposures of 1-2 hours to 350-400 ppb O₃ in human subjects exercising
10 at light, moderate and heavy levels. In the latter study, ibuprofen treatment resulted in
11 measurable decreases in BALF levels of PGE₂ and TXB₂ at 1-hour postexposure
12 ([Hazucha et al., 1996](#)). Although an earlier study demonstrated that PGE₂ stimulated
13 bronchial C-fibers ([Coleridge et al., 1993](#); [Coleridge et al., 1976](#)) and suggested that
14 PGE₂ mediated O₃-induced decreases in pulmonary function, no correlation was observed
15 between the degree of ibuprofen-induced inhibition of BALF PGE₂ levels and blunting of
16 the spirometric response to O₃ ([Hazucha et al., 1996](#)). These results point to the
17 involvement of a lipoxygenase product. Further, as noted above, PGE₂ may play a role in
18 the neural reflex by sensitizing TRPA1 channels. A recent study in human subjects
19 exercising at a moderate to high level and exposed for 1 hour to 350 ppb O₃ also provided
20 evidence that arachidonic acid metabolites, as well as oxidative stress, contribute to
21 human responsiveness to O₃ ([Alfaro et al., 2007](#)).

22 In addition to the spirometric changes, mild airways obstruction occurred in human
23 subjects exercising at a moderate level during O₃ exposure (500 ppb for 2 hours)
24 ([Hazucha et al., 1989](#)). This pulmonary function decrement is generally measured as
25 specific airway resistance (sRaw) which is the product of airway resistance and thoracic
26 gas volume. In several studies involving human subjects exercising at a moderate to
27 heavy level and exposed for 1-4 hours to 200-300 ppb O₃, changes in sRaw correlated
28 with changes in inflammatory and injury endpoints measured 18-hours postexposure, but
29 did not follow the same time course or change to the same degree as spirometric changes
30 (i.e., FEV₁, FVC) measured during exposure ([Balmes et al., 1996](#); [Aris et al., 1993](#);
31 [Schelegle et al., 1991](#)). In addition, a small but persistent increase in airway resistance
32 associated with narrowing of small peripheral airways (measured as changes in
33 isovolumetric FEF₂₅₋₇₅) was demonstrated in O₃-exposed human subjects (350 ppb for
34 130 minutes, moderate exercise level) ([Weinmann et al., 1995c](#); [Weinmann et al., 1995b](#)).
35 A similar study (400 ppb O₃ for 2 hours in human subjects exercising at a heavy level)
36 found decreases in FEF₂₅₋₇₅ concomitant with increases in residual volume, which is
37 suggestive of small airways dysfunction ([Kreit et al., 1989](#)). In separate studies, a
38 statistically significant increase in residual volume (500 ppb for 2 hours) ([Hazucha et al.,](#)

1 [1989](#)) and a statistically significant decrease in FEV₂₅₋₇₅ (160 ppb for 7.6 hours)
2 ([Horstman et al., 1995](#)) were observed following O₃ exposure in human subjects
3 exercising at moderate and light levels, respectively, providing further support for an
4 O₃-induced effect on small airways.

5 Mechanisms underlying this rapid increase in airway resistance following O₃ exposure
6 are incompletely understood. Pretreatment with atropine decreased baseline sRaw and
7 prevented O₃-induced increases in sRaw in human subjects exercising at a heavy level
8 (400 ppb for 0.5 hours) ([Beckett et al., 1985](#)), indicating the involvement of muscarinic
9 cholinergic receptors of the parasympathetic nervous system. Interestingly, atropine
10 pretreatment partially blocked the decrease in FEV₁, but had no effect on the decrease in
11 FVC, breathing rate, tidal volume or respiratory symptoms ([Beckett et al., 1985](#)). Using a
12 β-adrenergic agonist, it was shown that smooth muscle contraction, not increased airway
13 mucus secretion, was responsible for O₃-induced increases in airway resistance ([Beckett
14 et al., 1985](#)). Thus, pulmonary function decrements measured as FEV₁ may reflect both
15 restrictive (such as decreased inspiratory capacity) and obstructive (such as
16 bronchoconstriction) type changes in airway responses. This is consistent with findings of
17 [McDonnell et al. \(1983\)](#) who observed a relatively strong correlation between sRaw and
18 FEV₁ (r = -0.31, p = 0.001) and a far weaker correlation between sRaw and FVC
19 (r = -0.16, p = 0.10) in human subjects exercising at a heavy level and exposed for
20 2.5 hours to 120-400 ppb O₃.

21 Furthermore, tachykinins may contribute to O₃-mediated increases in airway resistance.
22 In addition to stimulating CNS reflexes, bronchopulmonary C-fibers mediate local axon
23 responses by releasing neuropeptides such as substance P (SP), neurokinin (NK) A and
24 calcitonin gene-related peptide (CGRP). Tachykinins bind to NK receptors resulting in
25 responses such as bronchoconstriction. Recent studies in animals demonstrated that NK-1
26 receptor blockade had no effect on O₃-stimulated physiologic responses such as V_T and f_B
27 in rats over the 8 hour exposure to 1 ppm O₃ ([Oslund et al., 2008](#)). However, SP and NK
28 receptors contributed to vagally-mediated bronchoconstriction in guinea pigs 3 days after
29 a single 4-hour exposure to 2 ppm O₃ ([Verhein et al., 2011](#)). In one human study in which
30 bronchial biopsies were performed and studied by immunohistochemistry, SP was
31 substantially diminished in submucosal sensory nerves 6 hours following O₃ exposure
32 (200 ppb for 2 hours, light exercise) ([Krishna et al., 1997](#)). A statistically significant
33 correlation was observed between loss of SP immunoreactivity from neurons in the
34 bronchial mucosa and changes in FEV₁ measured 1-hour postexposure ([Krishna et al.,
35 1997](#)). Another study found that SP was increased in lavage fluid of human subjects
36 immediately after O₃ challenge (250 ppb for 1 hour, heavy exercise) ([Hazbun et al.,
37 1993](#)). These results provide evidence that the increased airway resistance observed

1 following O₃ exposure is due to vagally-mediated responses and possibly by local axon
2 reflex responses through bronchopulmonary C-fiber-mediated release of SP.

3 A role for antioxidant defenses in modulating neural reflexes has been proposed given the
4 delay in onset of O₃-induced pulmonary function responses that has been noted in
5 numerous studies. Recently, this delay was characterized in terms of changes in f_B
6 ([Schelegle et al., 2007](#)). In humans exposed for 1-2 hours to 120-350 ppb O₃ while
7 exercising at a high level, no change in f_B was observed until a certain cumulative inhaled
8 dose of O₃ had been reached. Subsequently, the magnitude of the change in f_B was
9 correlated with the inhaled dose rate ([Schelegle et al., 2007](#)). These investigators
10 proposed that initial reactions of O₃ with ELF resulted in a time-dependent depletion of
11 ELF antioxidants, and that activation of neural reflexes occurred only after the
12 antioxidant defenses were overwhelmed ([Schelegle et al., 2007](#)).

5.3.3 Initiation of inflammation

13 As described previously (Section [5.2.3](#)), O₃ mainly reacts with components of the ELF
14 and cellular membranes resulting in the generation of secondary oxidation products.
15 Higher concentrations of these products may directly injure RT epithelium. Subsequent
16 airways remodeling may also occur (Section [5.3.7](#)) ([Mudway and Kelly, 2000](#)). Lower
17 concentrations of secondary oxidation products may initiate cellular responses including
18 cytokine generation, adhesion molecule expression, and modification of tight junctions
19 leading to inflammation and increased permeability across airway epithelium
20 (Section [5.3.4](#)) ([Dahl et al., 2007](#); [Mudway and Kelly, 2000](#)).

21 An important hallmark of acute O₃ exposure in humans and animals is neutrophilic
22 airways inflammation. Although neutrophil influx into nasal airways has been
23 demonstrated in human subjects (400 ppb O₃ 2 hours, heavy exercise) ([Graham and
24 Koren, 1990](#)), most studies of neutrophil influx have focused on the lower airways
25 ([Hazucha et al., 1996](#); [Aris et al., 1993](#)). The time course of this response in the lower
26 airways and its resolution appears to be slower than that of the decrements in pulmonary
27 function in exercising human subjects ([Hazucha et al., 1996](#)). In several studies, airways
28 neutrophilia was observed by 1-3 hours, peaked by 6 hours and was returning to baseline
29 levels at 18-24 hours in human subjects exercising at a heavy level and exposed for
30 1-2 hours to 300-400 ppb O₃ ([Schelegle et al., 1991](#); [Koren et al., 1989](#); [Seltzer et al.,
31 1986](#)). Neutrophils are thought to be injurious and a study in guinea pigs demonstrated
32 that the influx and persistence of neutrophils in airways following O₃ exposure correlated
33 with the temporal profile of epithelial injury (0.26-1 ppm O₃, 72 hours) ([Hu et al., 1982](#)).
34 However, neutrophils have also been shown to contribute to repair of O₃-injured

1 epithelium in rats exposed for 8 hours to 1 ppm O₃, possibly by removing necrotic
2 epithelial cells ([Mudway and Kelly, 2000](#); [Vesely et al., 1999](#)). Nonetheless, the degree
3 of airways inflammation due to O₃ is thought to have more important long-term
4 consequences than the more quickly resolving changes in pulmonary function since
5 airways inflammation is often accompanied by tissue injury ([Balmes et al., 1996](#)).

6 Ozone exposure results in alterations in other airways inflammatory cells besides
7 neutrophils, including lymphocytes, macrophages, monocytes and mast cells. Influx of
8 some of these cells accounts for the later (i.e., 18-20 hours) phase of inflammation
9 following O₃ exposure. Numbers of lymphocytes and total cells in BALF were decreased
10 early after O₃ exposure in human subjects exercising at a light to moderate level and
11 exposed for 2 hours to 200 ppb O₃, which preceded the neutrophil influx ([Mudway and
12 Kelly, 2000](#); [Blomberg et al., 1999](#); [Krishna et al., 1997](#)). The decrease in total cells was
13 thought to reflect decreases in macrophages, although it was not clear whether the cells
14 were necrotic or whether membrane adhesive properties were altered making them more
15 difficult to obtain by lavage ([Mudway and Kelly, 2000](#); [Blomberg et al., 1999](#); [Mudway
16 et al., 1999b](#); [Frampton et al., 1997b](#); [Pearson and Bhalla, 1997](#)). A recent study in human
17 subjects exercising at a moderate level and exposed for 6.6 hours to 80 ppb O₃
18 demonstrated an increase in numbers of sputum monocytes and dendritic-like cells with
19 increased expression of innate immune surface proteins and antigen presentation markers
20 ([Peden, 2011](#); [Alexis et al., 2010](#)) (see Section [6.2.3.1](#)). An increase in submucosal mast
21 cells was observed 1.5 hours after a 2 hour-exposure to 200 ppb O₃ ([Blomberg et al.,
22 1999](#)) and an increase in BAL mast cell number was observed 18 hours after a 4-hour
23 exposure to 220 ppb O₃ exposure in human subjects exercising at a moderate level
24 ([Frampton et al., 1997b](#)). Mast cells may play an important role in mediating neutrophil
25 influx since they are an important source of several pro-inflammatory cytokines and since
26 their influx preceded that of neutrophils in human subjects exercising at a moderate level
27 and exposed for 2 hours to 200 ppb O₃ ([Stenfors et al., 2002](#); [Blomberg et al., 1999](#)).
28 Further, a study using mast cell-deficient mice demonstrated decreased neutrophilic
29 inflammation in response to O₃ (1.75 ppm, 3 hours) compared with wild type mice
30 ([Kleeberger et al., 1993](#)). Influx of these inflammatory cell types in the lung is indicative
31 of O₃-mediated activation of innate immunity as will be discussed in Section [5.3.6](#).

32 Much is known about the cellular and molecular signals involved in inflammatory
33 responses to O₃ exposure ([U.S. EPA, 2006b](#)). Eicosanoids are one class of secondary
34 oxidation products that may be formed rapidly following O₃ exposure and that may
35 mediate inflammation. Eicosanoids are metabolites of arachidonic acid—a 20-carbon
36 PUFA—that are released from membrane phospholipids by phospholipase A₂-mediated
37 catalysis. Activation of phospholipase A₂ occurs by several cell signaling pathways and
38 may be triggered by O₃-mediated lipid peroxidation of cellular membranes ([Rashba-Step](#)

1 [et al., 1997](#)). Additionally, cellular phospholipases A2, C and D may be activated by lipid
2 ozonation products ([Kafoury et al., 1998](#)). While the conversion of arachidonic acid to
3 prostaglandins, leukotrienes and other eicosanoid products is generally catalyzed by
4 cyclooxygenases and lipoxygenases, non-enzymatic reactions also occur during oxidative
5 stress leading to the generation of a wide variety of eicosanoids and reactive oxygen
6 species. Further, the release of arachidonic acid from phospholipids is accompanied by
7 the formation of lysophospholipids that are precursors for platelet activating factors
8 (PAFs). Thus, formation of eicosanoids, reactive oxygen species and PAFs accompanies
9 O₃-mediated lipid peroxidation.

10 In addition, secondary reaction products may stimulate macrophages to produce
11 cytokines such as IL-1, IL-6 and TNF- α that in turn activate IL-8 production by epithelial
12 cells. Although IL-8 has been proposed to play a role in neutrophil chemotaxis,
13 measurements of IL-8 in BALF from humans exposed to O₃ found increases that were
14 too late to account for this effect ([Mudway and Kelly, 2000](#)). The time-course profiles of
15 PGE₂ and IL-6 responses suggest that they may play a role in neutrophil chemotaxis in
16 humans ([Mudway and Kelly, 2000](#)). However, pretreatment with ibuprofen attenuated
17 O₃-induced increases in BALF PGE₂ levels, but had no effect on neutrophilia in human
18 subjects exercising at a heavy level and exposed for 2 hour to 400 ppb O₃ ([Hazucha et al.,](#)
19 [1996](#)).

20 One set of studies in humans focused on the earliest phase of airways inflammation
21 (1-2 hours following exposure). Human subjects, exercising at a moderate level, were
22 exposed to 200 ppb O₃ for 2 hours and bronchial biopsy tissues were obtained 1.5 and
23 6 hours after exposure ([Bosson et al., 2009](#); [Bosson et al., 2003](#); [Stenfors et al., 2002](#);
24 [Blomberg et al., 1999](#)). Results demonstrated upregulation of vascular endothelial
25 adhesion molecules P-selectin and ICAM-1 at both 1.5 and 6 hours ([Stenfors et al., 2002](#);
26 [Blomberg et al., 1999](#)). Submucosal mast cell numbers were increased at 1.5 hours in the
27 biopsy samples without an accompanying increase in neutrophil number ([Blomberg et al.,](#)
28 [1999](#)). Pronounced neutrophil infiltration was observed at 6 hours in the bronchial
29 mucosa ([Stenfors et al., 2002](#)). Surprisingly, suppression of the NF- κ B and AP-1
30 pathways at 1.5 hours and a lack of increased IL-8 at 1.5 or 6 hours in bronchial
31 epithelium were observed ([Bosson et al., 2009](#)). The authors suggested that vascular
32 endothelial adhesion molecules, rather than redox sensitive transcription factors, play key
33 roles in early neutrophil recruitment in response to O₃.

34 Increases in markers of inflammation occurred to a comparable degree in human subjects
35 with mild (least sensitive) and more remarkable (more sensitive) spirometric responses to
36 O₃ (200 ppb, 4 hours, moderate exercise) ([Balmes et al., 1996](#)). Two other studies
37 (200 ppb for 4 hours with moderate exercise and 300 ppb for 1 hour with heavy exercise)

1 found that acute spirometric changes were not positively correlated with cellular and
2 biochemical indicators of inflammation ([Aris et al., 1993](#); [Schelegle et al., 1991](#)).
3 However inflammation was correlated with changes in sRaw ([Balmes et al., 1996](#)). In
4 another study, pretreatment with ibuprofen had no effect on neutrophilia although it
5 blunted the spirometric response in human subjects exercising at heavy level and exposed
6 for 2 hours to 400 ppb O₃ ([Hazucha et al., 1996](#)). Taken together, results from these
7 studies indicate different mechanisms underlying the spirometric and inflammatory
8 responses to O₃.

9 A common mechanism underlying both inflammation and impaired pulmonary function
10 was suggested by [Krishna et al. \(1997\)](#). This study, conducted in human subjects
11 exercising at a light level and exposed to 200 ppb O₃ for 2 hours, demonstrated a
12 correlation between loss of SP immunoreactivity from neurons in the bronchial mucosa
13 and numbers of neutrophils and epithelial cells (shed epithelial cells are an index of
14 injury) in the BALF 6-hours postexposure. Furthermore, the loss of SP immunoreactivity
15 was correlated with the observed changes in FEV₁. Another study found that SP was
16 increased in lavage fluid of exercising human subjects immediately after O₃ challenge
17 (250 ppb, 1 hour, heavy exercise) ([Hazbun et al., 1993](#)). SP is a neuropeptide released by
18 sensory nerves which mediates neurogenic edema and bronchoconstriction ([Krishna et
19 al., 1997](#)). Collectively, these findings suggest that O₃-mediated stimulation of sensory
20 nerves that leads to activation of central and local axon reflexes is a common effector
21 pathway leading to impaired pulmonary function and inflammation.

22 Studies in animal models have confirmed many of these findings and provided evidence
23 for additional mechanisms involved in O₃-induced inflammation. A study in mice (2 ppm
24 O₃, 3 hours) demonstrated that PAF may be important in neutrophil chemotaxis
25 ([Longphre et al., 1999](#)), while ICAM-1 and macrophage inflammatory protein-2 (MIP-2),
26 the rodent IL-8 homologue, have been implicated in a rat model (1 ppm O₃, 3 hours)
27 ([Bhalla and Gupta, 2000](#)). Key roles for CXCR2, a receptor for keratinocyte-derived
28 chemokine (KC) and MIP-2, and for IL-6 in O₃-mediated neutrophil influx were
29 demonstrated in mice (1 ppm O₃, 3 hours) ([Johnston et al., 2005a](#); [Johnston et al., 2005b](#)).
30 Activation of JNK and p38 pathways and cathepsin-S were also found to be important in
31 this response (3 ppm O₃, 3 hours) ([Williams et al., 2009a](#); [Williams et al., 2008a](#);
32 [Williams et al., 2007a](#)). Matrix metalloproteinase-9 (MMP-9) appeared to confer
33 protection against O₃-induced airways inflammation and injury in mice (0.3 ppm O₃,
34 6-72 hours) ([Yoon et al., 2007](#)). Interleukin-10 (IL-10) also appeared to be protective
35 since IL-10 deficient mice responded to O₃ exposure (0.3 ppm, 24-72 hours) with
36 enhanced numbers of BAL neutrophils, enhanced NF-κB activation and MIP-2 levels
37 compared with IL-10 sufficient mice ([Backus et al., 2010](#)).

1 In addition, lung epithelial cells may release ATP in response to O₃ exposure ([Ahmad et](#)
2 [al., 2005](#)). ATP and its metabolites (catalyzed by ecto-enzymes) can bind to cellular
3 purinergic receptors resulting in activation of cell signaling pathways ([Picher et al.,](#)
4 [2004](#)). One such metabolite, adenine, is capable of undergoing oxidation leading to the
5 formation of UA which, if present in high concentrations, could activate inflammasomes
6 and result in caspase 1 activation and the maturation and secretion of IL-1 β and IL-18
7 ([Dostert et al., 2008](#)). A recent study in human subjects exercising at a moderate level and
8 exposed for 2 hours to 400 ppb O₃ demonstrated a correlation between ATP metabolites
9 and inflammatory markers ([Esther et al., 2011](#)), which provides some support for this
10 mechanism.

11 Several recent studies have focused on the role of Toll-like receptor (TLR) and its related
12 adaptor protein MyD88 in mediating O₃-induced neutrophilia. [Hollingsworth et al. \(2004\)](#)
13 demonstrated airways neutrophilia that was TLR4-independent following acute (2 ppm,
14 3 hours) and subchronic (0.3 ppm, 72 hours) O₃ exposure in a mouse model. However,
15 [Williams et al. \(2007b\)](#) found that MyD88 was important in mediating O₃-induced
16 neutrophilia in mice (3 ppm, 3 hours), with TLR4 and TLR2 contributing to the speed of
17 the response. Moreover, MyD88, TLR2 and TLR4 contributed to inflammatory gene
18 expression in this model and O₃ upregulated MyD88, TLR4 and TLR4 gene expression
19 ([Williams et al., 2007a](#)). Neutrophilic inflammation was also found to be partially
20 dependent on MyD88 in mice exposed to 1 ppm O₃ for 3 hours ([Li et al., 2011](#)).

21 Hyaluronan was found to mediate a later phase (24 hours) of O₃-induced inflammation in
22 mice ([Garantziotis et al., 2010](#); [Garantziotis et al., 2009](#)). Hyaluronan is an extracellular
23 matrix component that is normally found in the ELF as a large polymer. Exposure to
24 2 ppm O₃ for 3 hours resulted in elevated levels of soluble low molecular weight
25 hyaluronan in the BALF 24-hours postexposure ([Garantziotis et al., 2010](#); [Garantziotis et](#)
26 [al., 2009](#)). Similar results were found in response to 3 hour exposure to 1 ppm O₃ ([Li et](#)
27 [al., 2011](#)). Ozone may have caused the depolymerization of hyaluronan to soluble
28 fragments that are known to be endogenous ligands of the CD44 receptor and TLR4 in
29 the macrophage ([Jiang et al., 2005](#)). Binding of hyaluronan fragments to the CD44
30 receptor activates hyaluronan clearance, while binding to TLR4 results in signaling
31 through MyD88 to produce chemokines that stimulate the influx of inflammatory cells
32 ([Jiang et al., 2005](#)). Activation of NF- κ B occurred in both airway epithelia and alveolar
33 macrophages 24-hours postexposure to O₃. Increases in BALF pro-inflammatory factors
34 KC, IL-1 β , MCP-1, TNF- α and IL-6 observed 24 hours following O₃ exposure were
35 found to be partially dependent on TLR4 ([Garantziotis et al., 2010](#)) while increases in
36 BAL inflammatory cells, which consisted mainly of macrophages, were dependent on
37 CD44 ([Garantziotis et al., 2009](#)). BAL inflammatory cells number and injury markers

1 following O₃ exposure were similar in wild-type and TLR4-deficient animals
2 ([Garantziotis et al., 2010](#)).

3 Since exposure to O₃ leads to airways inflammation characterized by neutrophilia, and
4 since neutrophil-derived oxidants often consume ELF antioxidants, concentrations of
5 ELF antioxidants have been examined during airways neutrophilia ([Long et al., 2001](#);
6 [Gunnison and Hatch, 1999](#); [Mudway et al., 1999b](#)). In human subjects exercising at a
7 moderate level and exposed to 200 ppb O₃ for 2 hours, UA, GSH and α-TOH levels
8 remained unchanged in BALF 6-hours postexposure while AH2 was decreased
9 significantly in both BALF and plasma ([Mudway et al., 1999b](#)). A second study
10 involving the same protocol reported a loss of AH2 from bronchial wash fluid and BALF,
11 representing proximal and distal airway ELF respectively, as well as an increase in
12 oxidized GSH in both compartments ([Mudway et al., 2001](#)). No change was observed in
13 ELF UA levels in response to O₃ ([Mudway et al., 2001](#)). Further, O₃ exposure (0.8 ppm,
14 4 hours) in female rats resulted in a 50% decrease in BALF AH2 immediately
15 postexposure ([Gunnison and Hatch, 1999](#)). These studies suggested a role for AH2 and
16 GSH in protecting against the oxidative stress associated with inflammation.

17 The relationship between inflammation, antioxidant status and O₃ dose has also been
18 investigated. The degree of inflammation in rats has been correlated with ¹⁸O-labeled O₃
19 dose markers in the lower lung. In female rats exposed to 0.8 ppm O₃ for 4 hours, BAL
20 neutrophil number and ¹⁸O reaction product were directly proportional ([Gunnison and
21 Hatch, 1999](#)). [Kari et al. \(1997\)](#) observed that a 3-week caloric restriction (75%) in rats
22 abrogated the toxicity of O₃ (2 ppm, 2 hours), measured as BALF increases in protein,
23 fibronectin and neutrophils, that was seen in normally fed rats. Accompanying this
24 resistance to O₃ toxicity was a reduction (30%) in the accumulation of ¹⁸O reaction
25 product in the lungs. These investigations also demonstrated an inverse relationship
26 between AH2 levels and O₃ dose and provided evidence for AH2 playing a protective
27 role following O₃ exposure in these studies. Pregnant and lactating rats had lower AH2
28 content in BALF and exhibited a greater increase in accumulation of ¹⁸O reaction
29 products compared with pre-pregnant rats in response to O₃ exposure ([Gunnison and
30 Hatch, 1999](#)). In the calorie restricted model, a 30% higher basal BALF AH2
31 concentration and a rapid accumulation of AH2 into the lungs to levels 60% above
32 normal occurred as result of O₃ exposure ([Kari et al., 1997](#)). However, this relationship
33 between AH2 levels and O₃ dose did not hold up in every study. Aging rats (9 and
34 24 months old) had 49% and 64% lower AH2 in lung tissue compared with month-old
35 rats but the aging-induced AH2 loss did not increase the accumulation of ¹⁸O reaction
36 products following O₃ exposure (0.4-0.8 ppm, 2-6 hours) ([Vincent et al., 1996b](#)).

1 A few studies have examined the dose- or concentration-responsiveness of airways
2 neutrophilia in O₃-exposed humans ([Holz et al., 1999](#); [Devlin et al., 1991](#)). No
3 concentration-responsiveness was observed in healthy human subjects exposed for 1 hour
4 to 125-250 ppb O₃ while exercising at a light level and a statistically significant increase
5 in sputum neutrophilia was observed only at the higher concentration ([Holz et al., 1999](#)).
6 However, concentration-dependent and statistically significant increases in BAL
7 neutrophils and the inflammatory mediator IL-6 were reported following exposure to 80
8 and 100 ppb O₃ for 6.6 hours in human subjects exercising at a moderate level ([Devlin et
9 al., 1991](#)). Additional evidence is provided by a meta-analysis of the O₃
10 dose-inflammatory response in controlled human exposure studies involving exposure to
11 80-600 ppb O₃ for 60-396 minutes and exercise levels ranging from light to heavy
12 ([Mudway and Kelly, 2004b](#)). Results demonstrated a linear relationship between inhaled
13 O₃ dose (determined as the product of concentration, ventilation and time) and BAL
14 neutrophils at 0-6 hours and 18-24 hours following O₃ exposure ([Mudway and Kelly,
15 2004b](#)).

5.3.4 Alteration of Epithelial Barrier Function

16 Following O₃ exposure, injury and inflammation can lead to altered airway barrier
17 function. Histologic analysis has demonstrated damage to tight junctions between
18 epithelial cells, suggesting an increase in epithelial permeability. In addition, the presence
19 of shed epithelial cells in the BALF and increased epithelial permeability, which is
20 measured as the flux of small solutes, have been observed and are indicative of epithelial
21 injury. This could potentially lead to the loss of ELF solutes that could diffuse down their
22 concentration gradient from the lung to the blood. Increases in vascular permeability, as
23 measured by BALF protein and albumin, have also been demonstrated ([Costa et al.,
24 1985](#); [Hu et al., 1982](#)).

25 An early study in sheep measured changes in airway permeability as the flux of inhaled
26 radiolabeled histamine into the plasma ([Abraham et al., 1984](#)). Exposure of sheep to
27 0.5 ppm O₃ for 2 hours via an endotracheal tube resulted in an increased rate of histamine
28 appearance in the plasma at 1 day postexposure. Subsequently, numerous studies have
29 measured epithelial permeability as the flux of the small solute ^{99m}Tc-DTPA that was
30 introduced into the air spaces in different regions of the RT. Increased pulmonary
31 epithelial permeability, measured as the clearance of ^{99m}Tc-DTPA from lung to blood,
32 was demonstrated in humans 1-2 hours following a 2-hour exposure to 400 ppb O₃ while
33 exercising at a heavy level ([Kehrl et al., 1987](#)). Another study in human subjects found
34 increased epithelial permeability 19-hours postexposure to 240 ppb O₃ for 130 minutes
35 while exercising at moderate level ([Foster and Stetkiewicz, 1996](#)). Increased bronchial

1 permeability was also observed in dogs 1-day postexposure (0.4 ppm O₃ by endotracheal
2 tube for 6 hours) and did not resolve for several days ([Foster and Freed, 1999](#)).

3 A role for tachykinins in mediating airway epithelial injury and decreased barrier
4 function has been suggested. [Nishiyama et al. \(1998\)](#) demonstrated that capsaicin, which
5 depletes nerve fibers of substance P, blocked the O₃-induced increase in permeability of
6 guinea pig tracheal mucosa (0.5-3 ppm O₃, 0.5 hours). Pretreatment with propranolol or
7 atropine failed to inhibit this response, suggesting that adrenergic and cholinergic
8 pathways were not involved. In another study, tachykinins working through NK-1 and
9 CGRP receptors were found to contribute to airway epithelial injury in O₃-exposed rats
10 (1 ppm, 8 hours) ([Oslund et al., 2009, 2008](#)).

11 [Kleeberger et al. \(2000\)](#) evaluated genetic susceptibility to O₃-induced altered barrier
12 function in recombinant inbred strains of mice. Lung hyperpermeability, measured as
13 BALF protein, was evaluated 72 hours after exposure to 0.3 ppm O₃ and found to be
14 associated with a functioning *Tlr4* gene. This study concluded that *Tlr4* was a strong
15 candidate gene for susceptibility to hyperpermeability in response to O₃ ([Kleeberger et
16 al., 2000](#)). A subsequent study by these same investigators found that *Tlr4* modulated
17 mRNA levels of the *Nos2* genes and suggested that the protein product of *Nos2*, iNOS,
18 plays an important role in O₂-induced lung hyperpermeability (0.3 ppm, 72 hours)
19 ([Kleeberger et al., 2001](#)). More recently, HSP70 was identified as part of the TLR4
20 signaling pathway (0.3 ppm, 6-72 hours) ([Bauer et al., 2011](#)).

21 Antioxidants have been shown to confer resistance to O₃-induced injury. In a recent
22 study, lung hyperpermeability in response to O₃ (0.3 ppm, 48 hours) was unexpectedly
23 reduced in mice deficient in the glutamate-cysteine ligase modifier subunit gene
24 compared with sufficient mice ([Johansson et al., 2010](#)). Since the lungs of these mice
25 exhibited 70% glutathione depletion, protection against O₃-induced injury was
26 unexpected ([Johansson et al., 2010](#)). However it was found that several other antioxidant
27 defenses, including metallothionein, were upregulated in response to O₃ to a greater
28 degree in the glutathione-deficient mice compared with sufficient mice ([Johansson et al.,
29 2010](#)). The authors suggested that resistance to O₃-induced lung injury was due to
30 compensatory augmentation of antioxidant defenses ([Johansson et al., 2010](#)). Antioxidant
31 effects have also been attributed to Clara cell secretory protein (CCSP) and surfactant
32 protein A (SP-A). CCSP was found to modulate the susceptibility of airway epithelium to
33 injury in mice exposed to O₃ (0.2 or 1 ppm for 8 hours) by an unknown mechanism
34 ([Plopper et al., 2006](#)). SP-A appeared to confer protection against O₃-induced airways
35 inflammation and injury in mice (2 ppm, 3 hours) ([Haque et al., 2007](#)).

36 Increased epithelial permeability has been proposed to play a role in allergic sensitization
37 ([Matsumura, 1970](#)), in activation of neural reflexes and in stimulation of smooth muscle

1 receptors ([Dimeo et al., 1981](#)). [Abraham et al. \(1984\)](#) reported a correlation between
2 airway permeability and airways hyperresponsiveness (AHR) in O₃-exposed sheep.
3 However a recent study in human subjects exposed to 220 ppb O₃ for 135 minutes while
4 exercising at a light to moderate level did not find a relationship between O₃-induced
5 changes in airway permeability and AHR ([Que et al., 2011](#)).

5.3.5 Sensitization of Bronchial Smooth Muscle

6 Bronchial reactivity is generally determined in terms of a response to a challenge agent.
7 Non-specific bronchial reactivity in humans is assessed by measuring the effect of
8 inhaling increasing concentrations of a bronchoconstrictive drug on lung mechanics
9 (sRaw or FEV₁). Methacholine is most commonly employed but histamine and other
10 agents are also used. Specific bronchial reactivity is assessed by measuring effects in
11 response to an inhaled allergen in individuals (or animals) already sensitized to that
12 allergen. An increase in sRaw in response to non-specific or specific challenge agents
13 indicates AHR.

14 In addition to causing mild airways obstruction as discussed above, acute O₃ exposure
15 results in reversible increases in bronchial reactivity by mechanisms that are not well
16 understood. In one study, bronchial reactivity of healthy subjects was significantly
17 increased 19-hours postexposure to O₃ (120-240 ppb O₃ for 2 hours with moderate
18 exercise) ([Foster et al., 2000](#)). These effects may be more considerable in human subjects
19 with already compromised airways (Section [5.4.2.2](#)).

20 Ozone may sensitize bronchial smooth muscle to stimulation through an exposure-related
21 effect on smooth muscle or through effects on the sensory nerves in the epithelium or on
22 the motor nerves innervating the smooth muscle ([O'Byrne et al., 1984](#); [O'Byrne et al.,
23 1983](#); [Holtzman et al., 1979](#)). It is also recognized that increased bronchial reactivity can
24 be both a rapidly occurring and a persistent response to O₃ ([Foster and Freed, 1999](#)).
25 Tachykinins and secondary oxidation products of O₃ have been proposed as mediators of
26 the early response and inflammation-derived products have been proposed as mediators
27 of the later response ([Foster and Freed, 1999](#)). Furthermore, bronchial reactivity may be
28 increased as a result of O₃-mediated generation of ROS.

29 Ozone-induced increases in epithelial permeability, which could improve access of
30 agonist to smooth muscle receptors, may be one mechanism of sensitization through a
31 direct effect on bronchial smooth muscle ([Holtzman et al., 1979](#)). As noted above, a
32 correlation between airway permeability and AHR has been reported in O₃-exposed sheep
33 ([Abraham et al., 1984](#)) but not in O₃-exposed human subjects ([Que et al., 2011](#)).

1 Neurally-mediated sensitization has been demonstrated. In human subjects exposed for
2 2 hours to 600 ppb O₃ while exercising at a light level, pretreatment with atropine
3 inhibited O₃-induced AHR, suggesting the involvement of cholinergic postganglionic
4 pathways ([Holtzman et al., 1979](#)). Animal studies have demonstrated that O₃-induced
5 AHR involved vagally-mediated responses (rabbits, 0.2 ppm O₃, 72 hours) ([Freed et al.,
6 1996](#)) and local axon reflex responses through bronchopulmonary C-fiber-mediated
7 release of SP (guinea pigs, 0.8 ppm O₃, 2 hours) ([Joad et al., 1996](#)). Further, pretreatment
8 with capsaicin to deplete nerve fibers of SP blocked O₃-mediated AHR (guinea pigs,
9 1-2 ppm O₃, 2-2.25 hours) ([Tepper et al., 1993](#)). Other investigators demonstrated that SP
10 released from airway nociceptive neurons in ferrets contributed to O₃-induced AHR
11 (2 ppm O₃, 3 hours) ([Wu et al., 2008c](#); [Wu et al., 2003](#)).

12 Some evidence suggests the involvement of arachidonic acid metabolites and neutrophils
13 in mediating O₃-induced AHR ([Seltzer et al., 1986](#); [Fabbri et al., 1985](#)). Increased BAL
14 neutrophils and cyclooxygenase products were found in one study demonstrating AHR in
15 human subjects exercising at a heavy level immediately postexposure to 600 ppb O₃ for
16 2 hours ([Seltzer et al., 1986](#)). Another study found that ibuprofen pretreatment had no
17 effect on AHR in human subjects exercising at a heavy level following exposure to
18 400 ppb O₃ for 2 hours, although spirometric responses were blunted ([Hazucha et al.,
19 1996](#)). This study measured arachidonic acid metabolites and provided evidence that that
20 the arachidonic acid metabolites whose generation was blocked by ibuprofen,
21 (i.e., prostaglandins, thromboxanes and some leukotrienes) did not play a role in AHR.
22 Experiments in dogs exposed for 2 hours to 2.1 ppm O₃ demonstrated a close correlation
23 between O₃-induced AHR and airways neutrophilic inflammation measured in tissue
24 biopsies ([Holtzman et al., 1983](#)). Furthermore, the increased AHR observed in dogs
25 following O₃ exposure (3 ppm, 2 hours) was inhibited by neutrophil depletion ([O'Byrne
26 et al., 1983](#)) and by pre-treatment with inhibitors of arachidonic acid metabolism. In one
27 of these studies, indomethacin pre-treatment did not prevent airways neutrophilia in
28 response to O₃ (3 ppm, 2 hours) providing evidence that the subset of arachidonic acid
29 metabolites whose generation was inhibitable by the cyclooxygenase inhibitor
30 indomethacin (i.e., prostaglandins and thromboxanes) was not responsible for neutrophil
31 influx ([O'Byrne et al., 1984](#)). It should be noted that these studies did not measure
32 whether the degree to which the inhibitor blocked arachidonic acid metabolism and thus
33 their results should be interpreted with caution. Taken together, these findings suggest that
34 arachidonic acid metabolites may be involved in the AHR response following O₃
35 exposure in dogs. Studies probing the role of neutrophils in mediating the AHR response
36 have provided inconsistent results ([Al-Hegelan et al., 2011](#)).

37 Evidence for cytokine and chemokine involvement in the AHR response to O₃ has been
38 described. Some studies have suggested a role for TNF- α (mice, 0.5 and 2 ppm O₃,

1 3 hours) ([Cho et al., 2001](#); [Shore et al., 2001](#)) and IL-1 (mice and ferrets, 2 ppm O₃,
2 3 hours) ([Wu et al., 2008c](#); [Park et al., 2004](#)). The latter study found that SP expression in
3 airway neurons was upregulated by IL-1 that was released in response to O₃. Other
4 studies in mice have demonstrated a key role for CXCR2, the chemokine receptor for the
5 neutrophil chemokines KC and MIP-2, but not for IL-6 in O₃-mediated AHR (1 ppm O₃,
6 3 hours) ([Johnston et al., 2005a](#); [Johnston et al., 2005b](#)). In contrast, CXCR2 and IL-6
7 were both required for neutrophil influx in this model ([Johnston et al., 2005a](#); [Johnston et
8 al., 2005b](#)), as discussed above. [Williams et al. \(2008b\)](#) demonstrated that the Th2
9 cytokine IL-13 contributed to AHR, as well as to airways neutrophilia, in mice (3 ppm
10 O₃, 3 hours).

11 Other studies have focused on the role of TLR4. [Hollingsworth et al. \(2004\)](#) measured
12 AHR, as well as airways neutrophilia, in mice 6 and 24 hours following acute (2 ppm O₃
13 for 3 hours) and subchronic (0.3 ppm for 3 days) exposure to O₃. TLR4 is a key
14 component of the innate immune system and is responsible for the immediate
15 inflammatory response seen following challenge with endotoxin and other pathogen-
16 associated substances. In this study, a functioning TLR4 was required for the full AHR
17 response following O₃ exposure but not for airways neutrophilia ([Hollingsworth et al.,
18 2004](#)). These findings are complemented by an earlier study demonstrating that O₃ effects
19 on lung hyperpermeability required a functioning TLR4 (mice, 0.3 ppm O₃, 72 hours)
20 ([Kleeberger et al., 2000](#)). [Williams et al. \(2007b\)](#) found that TLR2, TLR4 and the TLR
21 adaptor protein MyD88 contributed to AHR in mice (3 ppm O₃, 3 hours). Ozone was also
22 found to upregulate MyD88, TLR4 and TLR4 gene expression in this model ([Williams et
23 al., 2007b](#)). Furthermore, a recent study reported O₃-induced AHR that required TLR4
24 and MyD88 in mice exposed to 1 ppm O₃ for 3 hours ([Li et al., 2011](#)).

25 A newly recognized mechanistic basis for O₃-induced AHR is provided by studies
26 focusing on the role of hyaluronan following O₃ exposure in mice ([Garantziotis et al.,
27 2010](#); [Garantziotis et al., 2009](#)). Hyaluronan is an extracellular matrix component that is
28 normally found in the ELF as a large polymer. Briefly, TLR4 and CD44 were found to
29 mediate AHR in response to O₃ and hyaluronan. Exposure to 2 ppm O₃ for 3 hours
30 resulted in enhanced AHR and elevated levels of soluble low molecular weight
31 hyaluronan in the BALF 24-hours postexposure ([Garantziotis et al., 2010](#); [Garantziotis et
32 al., 2009](#)). Ozone may have caused the depolymerization of hyaluronan to soluble
33 fragments that are known to be endogenous ligands of the CD44 receptor and TLR4 in
34 the macrophage ([Jiang et al., 2005](#)). In the two recent studies, O₃-induced AHR was
35 attenuated in CD44 and TLR4-deficient mice ([Garantziotis et al., 2010](#); [Garantziotis et
36 al., 2009](#)). Hyaluronan fragment-mediated stimulation of AHR was found to require
37 functioning CD44 receptor and TLR4 ([Garantziotis et al., 2010](#); [Garantziotis et al., 2009](#)).
38 In contrast, high-molecular-weight hyaluronan blocked AHR in response to O₃

1 ([Garantziotis et al., 2009](#)). In another study high-molecular-weight hyaluronan enhanced
2 repair of epithelial injury ([Jiang et al., 2005](#)). These studies provide a link between innate
3 immunity and the development of AHR following O₃ exposure, and indicate a role for
4 TLR4 in increasing airways responsiveness. While TLR4-dependent responses usually
5 involve activation of NF-κB and the upregulation of proinflammatory factors, the precise
6 mechanisms leading to AHR are unknown ([Al-Hegelan et al., 2011](#)).

7 In guinea pigs, AHR was found to be mediated by different pathways at 1- and 3-days
8 postexposure to a single exposure of O₃ (2 ppm for 4 hours) ([Verhein et al., 2011](#); [Yost et
9 al., 2005](#)). At 1 day, AHR was due to activation of airway parasympathetic nerves rather
10 than to an exposure-related effect on smooth muscle ([Yost et al., 2005](#)). This effect
11 occurred as a result of O₃-stimulated release of major basic protein from eosinophils
12 ([Yost et al., 2005](#)). Major basic protein is known to block inhibitory M2 muscarinic
13 receptors that normally dampen acetylcholine release from parasympathetic nerves ([Yost
14 et al., 2005](#)). The resulting increase in acetylcholine release caused an increase in smooth
15 muscle contraction following O₃ exposure ([Yost et al., 2005](#)). Eosinophils played a
16 different role 3-days postexposure to O₃ in guinea pigs ([Yost et al., 2005](#)). Ozone-
17 mediated influx of eosinophils into lung airways resulted in a different population of cells
18 present 3-days postexposure compared to those present at 1 day ([Yost et al., 2005](#)). At
19 this time point, eosinophil-derived major basic protein increased smooth muscle
20 responsiveness to acetylcholine which also contributed to AHR ([Yost et al., 2005](#)).
21 However, the major effect of eosinophils was to protect against vagal hyperreactivity
22 ([Yost et al., 2005](#)). The authors suggested that these beneficial effects were due to the
23 production of nerve growth factor ([Yost et al., 2005](#)). Further work by these investigators
24 demonstrated a key role for IL-1β in mediating AHR 3-days postexposure to O₃ ([Verhein
25 et al., 2011](#)). In this study, IL-1β increased nerve growth factor and SP that acted through
26 the NK1 receptor to cause vagally-mediated bronchoconstriction ([Verhein et al., 2011](#)).
27 The mechanism by which SP caused acetylcholine release from parasympathetic nerves
28 following O₃ exposure was not determined ([Verhein et al., 2011](#)). Taken together, the
29 above study results indicate that mechanisms involved in O₃-mediated AHR can vary
30 over time postexposure and that eosinophils and SP can play a role. Results of this animal
31 model may provide some insight into allergic airways disease in humans that is
32 characterized by eosinophilia (Section [5.4.2.2](#)).

5.3.6 Modification of Innate/Adaptive Immune System Responses

33 Host defense depends on effective barrier function and on innate immunity and adaptive
34 immunity ([Al-Hegelan et al., 2011](#)). The effects of O₃ on barrier function in the airways
35 was discussed above (Section [5.3.4](#)). This section focuses on the mechanisms by which

1 O₃ impacts innate and adaptive immunity. Both tissue damage and foreign pathogens are
2 triggers for the activation of the innate immune system. This results in the influx of
3 inflammatory cells such as neutrophils, mast cells, basophils, eosinophils, monocytes and
4 dendritic cells and the generation of cytokines such as TNF- α , IL-1, IL-6, KC and IL-17.
5 Further, innate immunity encompasses the actions of complement and collections, and
6 the phagocytic functions of macrophages, neutrophils and dendritic cells. Airway
7 epithelium also contributes to innate immune responses. Innate immunity is highly
8 dependent on cell signaling networks involving TLR4. Adaptive immunity provides
9 immunologic memory through the actions of B and T-cells. Important links between the
10 two systems are provided by dendritic cells and antigen presentation. Recent studies
11 demonstrate that exposure to O₃ modifies cells and processes which are required for
12 innate immunity, contributes to innate-adaptive immune system interaction and primes
13 pulmonary immune responses to endotoxin.

14 Ozone exposure of human subjects resulted in recruitment of activated innate immune
15 cells to the airways. Healthy individuals were exposed to 80 ppb O₃ for 6.6 hours while
16 exercising at a moderate level and airways inflammation was characterized in induced
17 sputum 18-hours postexposure ([Alexis et al., 2010](#)). Previous studies demonstrated that
18 induced sputum contains liquid and cellular constituents of the ELF from central
19 conducting airways ([Alexis et al., 2001b](#)) and also identified these airways as a site of
20 preferential O₃ absorption during exercise ([Hu et al., 1994](#)). Ozone exposure resulted in
21 increased numbers of neutrophils, airway monocytes and dendritic-like cells in sputum
22 ([Alexis et al., 2010](#)). In addition, increased expression of cell surface markers
23 characteristic of innate immunity and antigen presentation (i.e., CD-14 and HLA-DR)
24 was demonstrated on airway monocytes ([Alexis et al., 2010](#)). Enhanced antigen
25 presentation contributes to exaggerated T-cell responses and promotes Th2 inflammation
26 and an allergic phenotype ([Lay et al., 2007](#)). Upregulation of pro-inflammatory cytokines
27 was also demonstrated in sputum of O₃-exposed subjects ([Alexis et al., 2010](#)). One of
28 these cytokines, IL-12p70, correlated with numbers of dendritic-like cells in the sputum,
29 and is an indicator of dendritic cell activation ([Alexis et al., 2010](#)). These authors have
30 previously reported that exposure of human subjects exercising at a light to moderate
31 level to 400 ppb O₃ for 2 hours resulted in activation of monocytes and macrophages
32 ([Lay et al., 2007](#)), which could play a role in exacerbating existing asthma by activating
33 allergen-specific memory T-cells. The current study confirms these findings and extends
34 them by suggesting a potential mechanism whereby O₃-activated dendritic cells could
35 stimulate naïve T-cells to promote the development of asthma ([Alexis et al., 2010](#)). A
36 companion study by these same investigators (described in detail in Section [5.4.2.1](#))
37 provides evidence of dendritic cell activation, measured as increased expression of HLA-
38 DR, in a subset of the human subjects (GSTM1 null) exposed to 400 ppb O₃ for 2 hours
39 while exercising at a light to moderate level ([Alexis et al., 2009](#)). Since dendritic cells are

1 a link between innate and adaptive immunity, these studies provide evidence for an
2 O₃-mediated interaction between the innate and adaptive immune systems.

3 Another recent study linked O₃-mediated activation of the innate immune system to the
4 development of non-specific AHR in a mouse model ([Pichavant et al., 2008](#)). Repeated
5 exposure to 1 ppm O₃ for 3 hours (3 days over a 5 day period) induced non-specific AHR
6 measured 24 hours following the last exposure ([Pichavant et al., 2008](#)). This response
7 was found to require NKT-cells, which are effector lymphocytes of innate immunity, as
8 well as IL-17 and airways neutrophilia ([Pichavant et al., 2008](#)). Since glycolipids such as
9 galactosyl ceramide are ligands for the invariant CD1 receptor on NKT-cells and serve as
10 endogenous activators of NKT-cells, a role for O₃-oxidized lipids in activating NKT-cells
11 was proposed ([Pichavant et al., 2008](#)). The authors contrasted this innate immunity
12 pathway with that of allergen-provoked specific AHR which involves adaptive immunity,
13 the cytokines IL-4, IL -13, IL-17, and airways eosinophilia ([Pichavant et al., 2008](#)).
14 Interestingly, NKT-cells were required for both the specific AHR provoked by allergen
15 and the non-specific AHR provoked by O₃ ([Pichavant et al., 2008](#)). Different cytokine
16 profiles of the NKT-cells from allergen and O₃-exposed mice were proposed to account
17 for the different pathways ([Pichavant et al., 2008](#)). More recently, NKT-cells have been
18 found to function in both innate and adaptive immunity ([Vivier et al., 2011](#)).

19 An interaction between allergen and O₃ in the induction of nonspecific AHR was shown
20 in another animal study ([Larsen et al., 2010](#)). Mice were sensitized with the aerosolized
21 allergen OVA on 10 consecutive days followed by exposure to O₃ (0.1-0.5 ppm for
22 3 hours) ([Larsen et al., 2010](#)). While allergen sensitization alone did not alter airways
23 responsiveness to a nonspecific challenge, O₃ exposure of sensitized mice resulted in
24 nonspecific AHR at 6- and 24-hours postexposure ([Larsen et al., 2010](#)). The effects of O₃
25 on AHR were independent of airways eosinophilia and neutrophilia ([Larsen et al., 2010](#)).
26 However, OVA pretreatment led to goblet cell metaplasia which was enhanced by O₃
27 exposure ([Larsen et al., 2010](#)). It should be noted that OVA sensitization using only
28 aerosolized antigen in this study is less common than the usual procedure for OVA
29 sensitization achieved by one or more initial systemic injections of OVA and adjuvant
30 followed by repeated inhalation exposure to OVA. This study also points to an interaction
31 between innate and adaptive immune systems in the development of the AHR response.

32 Furthermore, O₃ was found to act as an adjuvant for allergic sensitization ([Hollingsworth
33 et al., 2010](#)). Oropharyngeal aspiration of OVA on day 0 and day 6 failed to lead to
34 allergic sensitization unless mice were first exposed to 1 ppm O₃ for 2 hours
35 ([Hollingsworth et al., 2010](#)). The O₃-mediated response involved Th2 (IL-4, IL-5 and
36 IL-9) and Th17 cytokines (IL-17) and was dependent on a functioning TLR4
37 ([Hollingsworth et al., 2010](#)). Ozone exposure also activated OVA-bearing dendritic cells

1 in the thoracic lymph nodes, as measured by the presence of the CD86 surface marker,
2 which suggests naïve T-cell stimulation and the involvement of Th2 pathways
3 ([Hollingsworth et al., 2010](#)). Thus the adjuvant effects of O₃ may be due to activation of
4 both innate and adaptive immunity.

5 Priming of the innate immune system by O₃ was reported by [Hollingsworth et al. \(2007\)](#).
6 In this study, exposure of mice to 2 ppm O₃ for 3 hours led to nonspecific AHR at 24-
7 and 48-hours postexposure, an effect which subsided by 72 hours ([Hollingsworth et al.,](#)
8 [2007](#)). However, in mice treated with aerosolized endotoxin immediately following O₃
9 exposure, AHR was greatly enhanced at 48-and 72-hours postexposure ([Hollingsworth et](#)
10 [al., 2007](#)). In addition, O₃ pre-exposure was found to reduce the number of inflammatory
11 cells in the BALF, to increase cytokine production and total protein in the BALF and to
12 increase systemic IL-6 following exposure to endotoxin ([Hollingsworth et al., 2007](#)).
13 Furthermore, O₃ stimulated the apoptosis of alveolar macrophages 24-hours
14 postexposure, an effect which was greatly enhanced by endotoxin treatment. Apoptosis of
15 circulating blood monocytes was also observed in response to the combined exposures
16 ([Hollingsworth et al., 2007](#)). Ozone pre-exposure enhanced the response of lung
17 macrophages to endotoxin ([Hollingsworth et al., 2007](#)). Taken together, these findings
18 demonstrated that O₃ exposure increased innate immune responsiveness to endotoxin.
19 The authors attributed these effects to the increased surface expression of TLR4 and
20 increased signaling in macrophages observed in the study ([Hollingsworth et al., 2007](#)). It
21 was proposed that the resulting decrease in airway inflammatory cells could account for
22 O₃-mediated decreased clearance of bacterial pathogens observed in numerous animal
23 models ([Hollingsworth et al., 2007](#)).

24 More recently, these authors demonstrated that hyaluronan contributed to the O₃-primed
25 response to endotoxin ([Li et al., 2010](#)). In this study, exposure of mice to 1 ppm O₃ for
26 3 hours resulted in enhanced responses to endotoxin, which was mimicked by
27 intratracheal instillation of hyaluronan fragments ([Li et al., 2010](#)). Hyaluronan, like O₃,
28 was also found to induce TLR4 receptor peripheralization in the macrophage membrane
29 ([Li et al., 2010](#); [Hollingsworth et al., 2007](#)), an effect which is associated with enhanced
30 responses to endotoxin. This study and previous ones by the same investigators showed
31 elevation of BALF hyaluronan in response to O₃ exposure ([Garantziotis et al., 2010](#); [Li et](#)
32 [al., 2010](#); [Garantziotis et al., 2009](#)), providing evidence that the effects of O₃ on innate
33 immunity are at least in part mediated by hyaluronan fragments. The authors note that
34 excessive TLR4 signaling can lead to lung injury and suggest that O₃ may be responsible
35 for an exaggerated innate immune response which may underlie lung injury and
36 decreased host defense ([Li et al., 2010](#)).

1 Activation or upregulation of the immune system has not been reported in all studies.
2 Impaired antigen-specific immunity was demonstrated following subacute O₃ exposure
3 (0.6 ppm, 10 h/day for 15 days) in mice ([Feng et al., 2006](#)). Specifically, O₃ exposure
4 altered the lymphocyte subset and cytokine profile and impacted thymocyte early
5 development leading to immune dysfunction. Further, recent studies demonstrated SP-A
6 oxidation in mice exposed for 3-6 hours to 2 ppm O₃. SP-A is an important innate
7 immune protein which plays a number of roles in host defense including acting as
8 opsonin for the recognition of some pathogens ([Haque et al., 2009](#)). These investigations
9 found that O₃-mediated carbonylation of purified SP-A was associated with impaired
10 macrophage phagocytosis in vitro ([Mikeroev et al., 2008c](#)). In addition, O₃ exposure
11 (2 ppm for 3 hours) in mice was found to increase susceptibility to pneumonia infection
12 in mice through an impairment of SP-A dependent phagocytosis ([Mikeroev et al., 2008b](#);
13 [Mikeroev et al., 2008a](#)). Furthermore, early life exposure to O₃ in infant monkeys followed
14 by a recovery period led to hyporesponsiveness to endotoxin ([Maniar-Hew et al., 2011](#)),
15 as discussed below and in Section [5.4.2.4](#) and Section [7.2.3.1](#).

16 Taken together, results of recent studies provide evidence that O₃ alters host
17 immunologic response and leads to immune system dysfunction through its effects on
18 innate and adaptive immunity.

5.3.7 Airways Remodeling

19 The nasal airways, conducting airways and distal airways (i.e., respiratory bronchioles or
20 CAR depending on the species) have all been identified as sites of O₃-mediated injury
21 and inflammation ([Mudway and Kelly, 2000](#)). At all levels of the RT, loss of sensitive
22 epithelial cells, degranulation of secretory cells, proliferation of resistant epithelial cells
23 and neutrophilic influx have been observed as a result of O₃ exposure ([Mudway and
24 Kelly, 2000](#); [Cho et al., 1999](#)). An important study ([Plopper et al., 1998](#)) conducted in
25 adult rhesus monkeys (0.4 and 1.0 ppm O₃ for 2 hours at rest) found that 1 ppm O₃
26 resulted in the greatest epithelial injury in the respiratory bronchioles immediately
27 postexposure although injury was observed at all of the RT sites studied except for the
28 lung parenchyma. Exposure to 0.4 ppm O₃ resulted in epithelial injury only in the
29 respiratory bronchioles. Initial cellular injury correlated with site-specific O₃ dose since
30 the respiratory bronchioles received the greatest O₃ dose (¹⁸O mass/lung weight) and
31 sustained the greatest initial cellular injury. The respiratory bronchioles were also the site
32 of statistically significant GSH reduction. In addition, a study in isolated perfused rat
33 lungs found greater injury in conducting airways downstream of bifurcations where local
34 doses of O₃ were higher ([Postlethwait et al., 2000](#)).

1 In addition to the degree of initial injury, the degree of airways inflammation due to O₃
2 may have important long-term consequences since airways inflammation may lead to
3 tissue injury ([Balmes et al., 1996](#)). Persistent inflammation and injury, observed in animal
4 models of chronic and intermittent exposure to O₃, are associated with airways
5 remodeling, including mucous cell metaplasia of nasal transitional epithelium ([Harkema
6 et al., 1999](#); [Hotchkiss et al., 1991](#)) and bronchiolar metaplasia of alveolar ducts
7 ([Mudway and Kelly, 2000](#)). Fibrotic changes such as deposition of collagen in the
8 airways and sustained lung function decrements especially in small airways have also
9 been demonstrated as a response to chronic O₃ exposure ([Mudway and Kelly, 2000](#);
10 [Chang et al., 1992](#)). These effects, described in detail in Section [7.2.3.1](#), have been
11 demonstrated in rats exposed to levels of O₃ as low as 0.25 ppm. Mechanisms responsible
12 for the resolution of inflammation and the repair of injury remain to be clarified and there
13 is only a limited understanding of the biological processes underlying long-term
14 morphological changes. However, a recent study in mice demonstrated a key role for the
15 TGF-β signaling pathway in the deposition of collagen in the airways wall following
16 chronic intermittent exposure to 0.5 ppm O₃ ([Katre et al., 2011](#)). Studies in infant
17 monkeys have also documented effects of chronic intermittent exposure to 0.5 ppm O₃ on
18 the developing lung and immune system. Extensive discussion of this topic is found in
19 Section [5.4.2.4](#) (Lifestage) and in Section [7.2.3.1](#).

20 It should be noted that repeated exposure to O₃ results in attenuation of some O₃-induced
21 responses, including those associated with the activation of neural reflexes
22 (e.g., decrements in pulmonary function), as discussed in Section [5.3.2](#). However,
23 numerous studies demonstrate that some markers of injury and inflammation remain
24 increased during multi-day exposures to O₃. Mechanisms responsible for attenuation, or
25 the lack thereof, are incompletely understood.

5.3.8 Systemic Inflammation and Oxidative/Nitrosative Stress

26 Extrapulmonary effects of O₃ have been noted for decades ([U.S. EPA, 2006b](#)). It has
27 been proposed that lipid oxidation products resulting from reaction of O₃ with lipids in
28 the ELF are responsible for systemic effects, however it is not known whether they gain
29 access to the vascular space ([Chuang et al., 2009](#)). Alternatively, extrapulmonary release
30 of diffusible mediators may initiate or propagate inflammatory responses in the vascular
31 or systemic compartments ([Cole and Freeman, 2009](#)). A role for O₃ in modulating
32 endothelin, a potent vasoconstrictor, has also been proposed. Studies in rats found that
33 exposure to 0.4 and 0.8 ppm O₃ induced endothelin system genes in the lung and
34 increased circulating levels of endothelin ([Thomson et al., 2006](#); [Thomson et al., 2005](#)).
35 Systemic oxidative stress may be suggested by studies in humans which reported

1 associations between O₃ exposure and levels of plasma 8-isoprostanes and the presence
2 of peripheral blood lymphocyte micronuclei ([Chen et al., 2007a](#); [Chen et al., 2006a](#)).
3 However, plasma isoprostanes are not a direct measure of systemic oxidative stress since
4 they are stable and can be generated in any compartment before diffusion into the
5 vascular space. Evidence of O₃-mediated systemic oxidative stress is better provided by
6 new animal studies described below.

7 Ozone-induced perturbations of the cardiovascular system were recently investigated in
8 young mice and monkeys ([Chuang et al., 2009](#)) and in rats ([Kodavanti et al., 2011](#);
9 [Perepu et al., 2010](#)) (see Section [6.3.3](#) and Section [7.3.1.2](#)). These are the first studies to
10 suggest that systemic oxidative stress and inflammation play a mechanistic role in
11 O₃-induced effects on the systemic vascular and heart. Exposure to 0.5 ppm O₃ for 5 days
12 resulted in oxidative/nitrosative stress, vascular dysfunction and mitochondrial DNA
13 damage in the aorta ([Chuang et al., 2009](#)). Chronic exposure to 0.8 ppm O₃ resulted in an
14 enhancement of inflammation and lipid peroxidation in the heart following an ischemia-
15 reperfusion challenge ([Perepu et al., 2010](#)). In addition, chronic intermittent exposure to
16 0.4 ppm O₃ increased aortic levels of mRNA for biomarkers of oxidative stress,
17 thrombosis, vasoconstriction and proteolysis and aortic lectin-like oxidized-low density
18 lipoprotein receptor-1(LOX-1) mRNA and protein levels ([Kodavanti et al., 2011](#)). The
19 latter study suggests a role for circulating oxidized lipids in mediating the effects of O₃.

20 Systemic inflammation and oxidative/nitrosative stress may similarly affect other organ
21 systems as well as the plasma compartment. Circulating cytokines have the potential to
22 enter the brain through diffusion and active transport and to contribute to
23 neuroinflammation, neurotoxicity, cerebrovascular damage and a break-down of the
24 blood brain barrier ([Block and Calderón-Garcidueñas, 2009](#)) (see Section [6.4](#) and
25 Section [7.5](#)). They can also activate neuronal afferents ([Block and Calderón-Garcidueñas,](#)
26 [2009](#)). Vagal afferent pathways originating in the RT may also be responsible for
27 O₃-mediated activation of nucleus tractus solitarius neurons which resulted in neuronal
28 activation in stress-responsive regions of the CNS in rats (0.5 or 2 ppm O₃ for
29 1.5-120 hours) ([Gackière et al., 2011](#)). Recent studies have demonstrated O₃-induced
30 brain lipid peroxidation, cytokine production in the brain and upregulated expression of
31 VEGF in rats (0.5 ppm O₃, 3 hours or 0.25-0.5 ppm O₃, 4 h/day, 15-60 days) ([Guevara-](#)
32 [Guzmán et al., 2009](#); [Araneda et al., 2008](#); [Pereyra-Muñoz et al., 2006](#)). Further,
33 O₃-induced oxidative stress resulted in increased plasma lipid peroxides (0.25 ppm,
34 4h/day, 15-60 days) ([Santiago-López et al., 2010](#)), which was correlated with damage to
35 specific brain regions ([Pereyra-Muñoz et al., 2006](#)).

36 Oxidative stress is one mechanism by which testicular and sperm function may be
37 disrupted (see Section [7.4.1](#)). Studies in Leydig cells in vitro have demonstrated that

1 steroidogenesis is blocked by oxidative stress ([Diemer et al., 2003](#)). It has been proposed
2 that lipid peroxidation of sperm plasma membrane may lead to impaired sperm mobility
3 and decreased sperm quality ([Agarwal et al., 2003](#)). Further, it has been proposed that
4 oxidative stress may damage DNA in the sperm nucleus and lead to apoptosis and a
5 decline in sperm counts ([Agarwal et al., 2003](#)). One study reported an association
6 between O₃ exposure and semen quality and suggested oxidative stress as an underlying
7 mechanism ([Sokol et al., 2006](#)). Additional evidence is required to substantiate this link.

8 A role for plasma antioxidants in modulating O₃-induced respiratory effects was
9 suggested by a recent study ([Aibo et al., 2010](#)). In this study, pretreatment of rats with a
10 high dose of acetaminophen resulted in increased levels of plasma cytokines and the
11 influx of inflammatory cells into the lung following O₃ exposure (0.25-0.5 ppm, 6 hours)
12 ([Aibo et al., 2010](#)). These effects were not observed in response to O₃ alone.
13 Furthermore, acetaminophen-induced liver injury was exacerbated by O₃ exposure. A
14 greater increase in hepatic neutrophil accumulation and greater alteration in gene
15 expression profiles was observed in mice exposed to O₃ and acetaminophen compared
16 with either exposure alone ([Aibo et al., 2010](#)). Although not measured in this study,
17 glutathione depletion in the liver is known to occur in acetaminophen toxicity. Since liver
18 glutathione is the source of plasma glutathione, acetaminophen treatment may have
19 lowered plasma glutathione levels and altered the redox balance in the vascular
20 compartment. These findings indicate interdependence between RT, plasma and liver
21 responses to O₃, possibly related to glutathione status.

5.3.9 Impaired Alveolar-Arterial Oxygen Transfer

22 O₃ may impair alveolar-arterial oxygen transfer and reduce the supply of arterial oxygen
23 to the myocardium. This may have a greater impact in individuals with compromised
24 cardiopulmonary systems. [Gong et al. \(1998\)](#) provided evidence of a small decrease in
25 arterial oxygen saturation in human subjects exposed for 3 hours to 300 ppb O₃ while
26 exercising at a light to moderate level. In addition, [Delaunois et al. \(1998\)](#) demonstrated
27 pulmonary vasoconstriction in O₃-exposed rabbits (0.4 ppm, 4 hours). Although of
28 interest, the contribution of this pathway to O₃-induced cardiovascular effects remains
29 uncertain.

5.3.10 Summary

30 This section summarizes the modes of action and toxicity pathways resulting from O₃
31 inhalation ([Figure 5-8](#)). These pathways provide a mechanistic basis for the health effects

1 which are described in detail in Chapters 6 and 7. Three distinct short-term responses
 2 have been well-characterized in humans challenged with O₃: decreased pulmonary
 3 function, airways inflammation, and increased bronchial reactivity. In addition, O₃
 4 exposure exacerbates, and possibly also causes, asthma and allergic airways disease in
 5 humans. Animal studies have demonstrated airways remodeling and fibrotic changes in
 6 response to chronic and intermittent O₃ exposures and a wide range of other responses.
 7 While the RT is the primary target tissue, cardiovascular and other organ effects occur
 8 following short- and long-term exposures of animals to O₃.

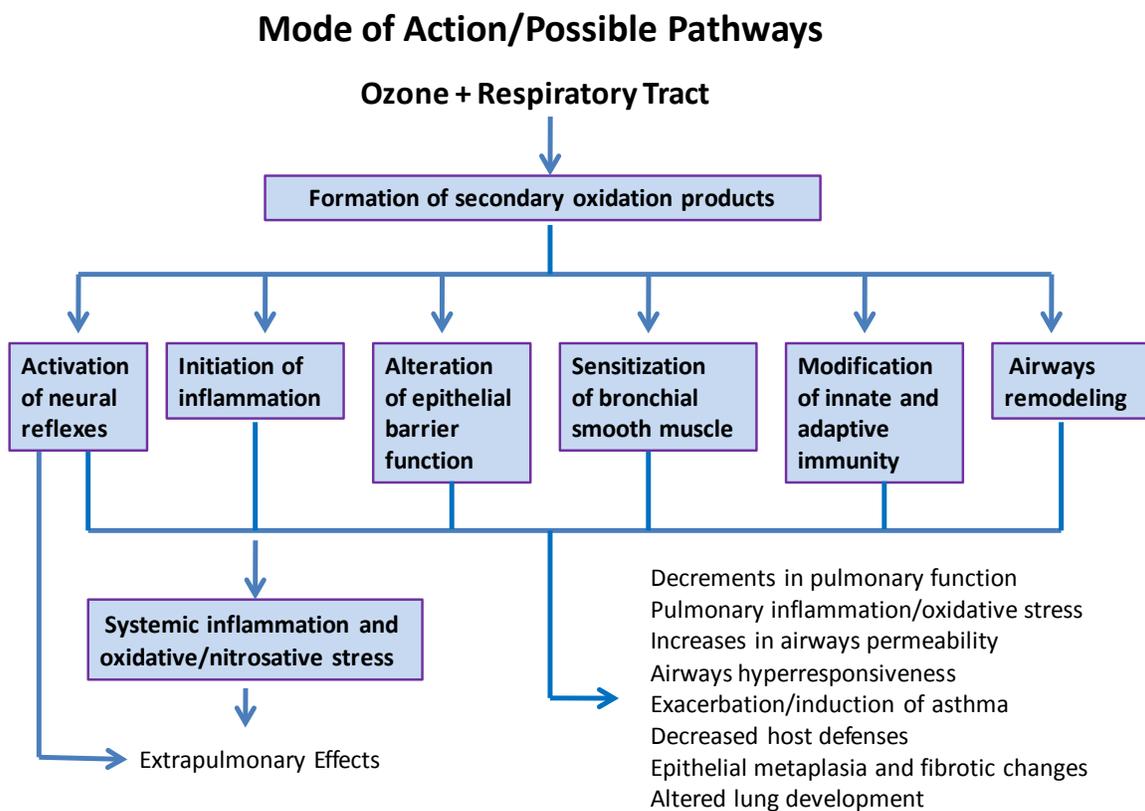


Figure 5-8 The modes of action/possible pathways underlying the health effects resulting from inhalation exposure to ozone.

9 The initial key event in the toxicity pathway of O₃ is the formation of secondary oxidation
 10 products in the RT. This mainly involves direct reactions with components of the ELF.
 11 The resulting secondary oxidation products transmit signals to the epithelium,
 12 nociceptive sensory nerve fibers and, if present, dendritic cells, mast cells and
 13 eosinophils. Thus, the effects of O₃ are mediated by components of ELF and by the

1 multiple cell types found in the RT. Further, oxidative stress is an implicit part of this
2 initial key event.

3 Another key event in the toxicity pathway of O₃ is the activation of neural reflexes which
4 lead to decrements in pulmonary function (see Section [6.2.1](#)). Evidence is accumulating
5 that secondary oxidation products are responsible for this effect. Eicosanoids have been
6 implicated in humans, while both eicosanoids and aldehydes are effective in animal
7 models. Different receptors on bronchial C-fibers have been shown to mediate separate
8 effects of O₃ on pulmonary function. Nociceptive sensory nerves are involved in the
9 involuntary truncation of inspiration which results in decreases in FVC, FEV₁, tidal
10 volume and pain upon deep inspiration. Opioids block these responses while atropine has
11 only a minimal effect. New evidence in an animal model suggests that TRPA1 receptors
12 on bronchial C-fibers mediate this pathway. Ozone exposure also results in activation of
13 vagal sensory nerves and a mild increase in airway obstruction measured as increased
14 sRaw. Atropine and β-adrenergic agonists greatly inhibit this response in humans
15 indicating that the airways obstruction is due to bronchoconstriction. Other studies in
16 humans implicated SP release from bronchial C-fibers resulting in airway narrowing due
17 to either neurogenic edema or bronchoconstriction. New evidence in an animal model
18 suggests that the SP-NK receptor pathway caused bronchoconstriction following O₃
19 exposure. Activation of neural reflexes also results in extrapulmonary effects such as
20 bradycardia.

21 Initiation of inflammation is also a key event in the toxicity pathway of O₃. Secondary
22 oxidation products, as well as chemokines and cytokines elaborated by airway epithelial
23 cells and macrophages, have been implicated in the initiation of inflammation. Vascular
24 endothelial adhesion molecules may also play a role. Work from several laboratories
25 using human subjects and animal models suggest that O₃ triggers the release of
26 tachykinins such as SP from airway sensory nerves which could contribute to
27 downstream effects including inflammation (see Section [6.2.3](#) and Section [7.2.4](#)).
28 Airways neutrophilia has been demonstrated in BALF, mucosal biopsy and induced
29 sputum samples. Influx of mast cells, monocytes and macrophages also occur.
30 Inflammation further contributes to O₃-mediated oxidative stress. Recent investigations
31 show that O₃ exposure leads to the generation of hyaluronan fragments from high
32 molecular weight polymers of hyaluronan normally found in the ELF in mice.
33 Hyaluronan activates TLR4 and CD44-dependent signaling pathways in macrophages,
34 and results in an increased number of macrophages in the BALF. Activation of these
35 pathways occurs later than the acute neutrophilic response suggesting that they may
36 contribute to longer-term effects of O₃. The mechanisms involved in clearing
37 O₃-provoked inflammation remain to be clarified. It should be noted that inflammation,

1 as measured by airways neutrophilia, is not correlated with decrements in pulmonary
2 function as measured by spirometry.

3 A fourth key event in the toxicity pathway of O₃ is alteration of epithelial barrier
4 function. Increased permeability occurs as a result of damage to tight junctions between
5 epithelial cells subsequent to O₃-induced injury and inflammation. It may play a role in
6 allergic sensitization and in AHR (see Section [6.2.2](#), Section [6.2.6](#), and Section [7.2.5](#)).
7 Tachykinins mediate this response while antioxidants may confer protection. Genetic
8 susceptibility has been associated with a functioning *Tlr4* and *Nos2* genes.

9 A fifth key event in the toxicity pathway of O₃ is the sensitization of bronchial smooth
10 muscle. Increased bronchial reactivity can be both a rapidly occurring and a persistent
11 response. The mechanisms responsible for early and later AHR are not well-understood
12 (see Section [6.2.2](#)). One proposed mechanism of sensitization, O₃-induced increases in
13 epithelial permeability, would improve access of agonist to smooth muscle receptors. The
14 evidence for this mechanism is not consistent. Another proposed mechanism, for which
15 there is greater evidence, is neurally-mediated sensitization. In humans exposed to O₃,
16 atropine blocked the early AHR response indicating the involvement of cholinergic
17 postganglionic pathways. Animal studies demonstrated that O₃-induced AHR involved
18 vagally-mediated responses and local axon reflex responses through bronchopulmonary
19 C-fiber-mediated release of SP. Later phases of increased bronchial reactivity may
20 involve the induction of IL-1 β which in turn upregulates SP production. In guinea pigs,
21 eosinophil-derived major basic protein contributed to the stimulation of cholinergic
22 postganglionic pathways. A novel role for hyaluronan in mediating the later phase effects
23 O₃-induced AHR has recently been demonstrated. Hyaluronan fragments stimulated AHR
24 in a TLR4- and CD44 receptor-dependent manner. Tachykinins and secondary oxidation
25 products of O₃ have been proposed as mediators of the early response and inflammation-
26 derived products have been proposed as mediators of the later response. Inhibition of
27 arachidonic acid metabolism was ineffective in blocking O₃-induced AHR in humans
28 while in animal models mixed results were found. Other cytokines and chemokines have
29 been implicated in the AHR response to O₃ in animal models.

30 A sixth key event in the toxicity pathway of O₃ is the modification of innate/adaptive
31 immunity. While the majority of evidence for this key event comes from animal studies,
32 there are several studies suggesting that this pathway may also be relevant in humans.
33 Ozone exposure of human subjects resulted in recruitment of activated innate immune
34 cells to the airways. This included macrophages and monocytes with increased
35 expression of cell surface markers characteristic of innate immunity and antigen
36 presentation, the latter of which could contribute to exaggerated T-cell responses and the
37 promotion of an allergic phenotype. Evidence of dendritic cell activation was observed in

1 GSTM1 null human subjects exposed to O₃, suggesting O₃-mediated interaction between
2 the innate and adaptive immune systems. Animal studies further linked O₃-mediated
3 activation of the innate immune system to the development of nonspecific AHR,
4 demonstrated an interaction between allergen and O₃ in the induction of nonspecific
5 AHR, and found that O₃ acted as an adjuvant for allergic sensitization through the
6 activation of both innate and adaptive immunity. Priming of the innate immune system by
7 O₃ was reported in mice. This resulted in an exaggerated response to endotoxin which
8 included enhanced TLR4 signaling in macrophages. Ozone-mediated impairment of the
9 function of SP-A, an innate immune protein, has also been demonstrated. Taken together
10 these studies provide evidence that O₃ can alter host immunologic response and lead to
11 immune system dysfunction. These mechanisms may underlie the exacerbation and
12 induction of asthma (see Section [6.2.6](#) and Section [7.2.1](#)), as well as decreases in host
13 defense (see Section [6.2.5](#) and Section [7.2.6](#)).

14 Another key event in the toxicity pathway of O₃ is airways remodeling. Persistent
15 inflammation and injury, which are observed in animal models of chronic and
16 intermittent exposure to O₃, are associated with morphologic changes such as mucous
17 cell metaplasia of nasal epithelium, bronchiolar metaplasia of alveolar ducts and fibrotic
18 changes in small airways (see Section [7.2.3](#)). Mechanisms responsible for these responses
19 are not well-understood. However a recent study in mice demonstrated a key role for the
20 TGF-β signaling pathway in the deposition of collagen in the airway wall following
21 chronic intermittent exposure to O₃. Chronic intermittent exposure to O₃ has also been
22 shown to result in effects on the developing lung and immune system.

23 Systemic inflammation and vascular oxidative/nitrosative stress are also key events in the
24 toxicity pathway of O₃. Extrapulmonary effects of O₃ occur in numerous organ systems,
25 including the cardiovascular, central nervous, reproductive and hepatic systems (see
26 Section [6.3](#) to Section [6.5](#) and Section [7.3](#) to Section [7.5](#)). It has been proposed that lipid
27 oxidation products resulting from reaction of O₃ with lipids and/or cellular membranes in
28 the ELF are responsible for systemic responses, however it is not known whether they
29 gain access to the vascular space. Alternatively, release of diffusible mediators from the
30 lung into the circulation may initiate or propagate inflammatory responses in the vascular
31 or in systemic compartments.

5.4 Interindividual Variability in Response

32 Responses to O₃ exposure are variable within the population ([Mudway and Kelly, 2000](#)).
33 Some studies have shown a large range of pulmonary function responses to O₃ among
34 healthy young adults (i.e., 4 hours to 200 ppb O₃ or for 1.5 hours to 420 ppb O₃ while

1 exercising at a moderate level) ([Hazucha et al., 2003](#); [Balmes et al., 1996](#)). Since
2 individual responses were relatively consistent across time in these studies, it was thought
3 that responsiveness reflected an intrinsic characteristic of the subject ([Mudway and Kelly,
4 2000](#)). Other studies have shown that age and body mass index may influence
5 responsiveness to O₃. In human subjects exercising moderately and exposed to 420 ppb
6 O₃ for 1.5 hours, older adults were generally not responsive to O₃ ([Hazucha et al., 2003](#)),
7 while obese young women appeared to be more responsive than lean young women
8 ([Bennett et al., 2007](#)). In another study, the observed lack of spirometric responsiveness
9 in one group of human subjects was not attributable to the presence of endogenous
10 endorphins, which could vary between individuals and which could potentially block C-
11 fiber stimulation by O₃ (420 ppb, 2 hours, moderate exercise ([Passannante et al., 1998](#))).
12 Other responses to O₃ have also been characterized by a large degree of interindividual
13 variability. For example, interindividual variability in the neutrophilic response has been
14 noted in human subjects ([Holz et al., 1999](#); [Devlin et al., 1991](#); [Schelegle et al., 1991](#)).
15 One study demonstrated a 3-fold difference in airways neutrophilia, measured as percent
16 of total cells in proximal BALF, among human subjects exposed to 300 ppb O₃ for 1 hour
17 while exercising at a heavy level ([Schelegle et al., 1991](#)). Another study reported a
18 20-fold difference in BAL neutrophils following exposure to 80-100 ppb O₃ for 6.6 hours
19 in human subjects exercising at a moderate level ([Devlin et al., 1991](#)). In contrast,
20 reproducibility of intraindividual responses to 1-hour exposure to 250 ppb O₃ in human
21 subjects exercising at a light level, measured as sputum neutrophilia, was demonstrated
22 by [Holz et al. \(1999\)](#). While the basis for the observed interindividual variability in
23 responsiveness to O₃ is not clear, both dosimetric and mechanistic factors are likely to
24 contribute and will be discussed below.

5.4.1 Dosimetric Considerations

25 Two studies have investigated the correlation of O₃ uptake with the pulmonary function
26 responses to O₃ exposure ([Reeser et al., 2005](#); [Gerrity et al., 1994](#)). These studies found
27 that the large subject-to-subject variability in % Δ FEV₁ response to O₃ does not appear to
28 have a dosimetric explanation. [Reeser et al. \(2005\)](#) found no significant relationship
29 between % Δ FEV₁ and fractional absorption of O₃ using the bolus method. Contrary to
30 previous findings, the percent change in dead space volume of the respiratory tract
31 (% Δ V_D) did not correlate with O₃ uptake, possibly due to the contraction of dead space
32 caused by airway closure. [Gerrity et al. \(1994\)](#) found that intersubject variability in FEV₁
33 and airway resistance was not related to differences in the O₃ dose delivered to the lower
34 airways, whereas minute ventilation was predictive of FEV₁ decrement. No study has yet
35 demonstrated that subjects show a consistent pattern of O₃ retention when re-exposed

1 over weeks of time, as has been shown to be the case for the FEV₁ response, or that
2 within-subject variation in FEV₁ response is related to fluctuations in O₃ uptake.
3 However, these studies did not control for the differences in conducting airway volume
4 between individuals. By controlling for conducting airway volume, it may be possible to
5 estimate how much of the intersubject variation in FEV₁ response at a given O₃ exposure
6 is due to actual inter-individual variability in dose.

5.4.2 Mechanistic Considerations

7 This section considers mechanistic factors that may contribute to variability in responses
8 between individuals. It has been proposed that some of the variability may be genetically
9 determined ([Yang et al., 2005a](#)). Besides gene-environment interactions, other factors
10 such as pre-existing diseases and conditions, nutritional status, lifestage, attenuation, and
11 co-exposures may also contribute to inter-individual variability in responses to O₃ and are
12 discussed below.

5.4.2.1 Gene-environment Interactions

13 The pronounced interindividual variation in responses to O₃ infers that genetic
14 background may play an important role in responsiveness to O₃ ([Cho and Kleeberger,
15 2007](#); [Kleeberger et al., 1997](#)) (see also Section [8.4](#)). Strains of mice which are prone or
16 resistant to O₃-induced effects have been used to systematically identify candidate
17 susceptibility genes. Using these recombinant inbred strains of mice and exposures to
18 0.3 ppm O₃ for up to 72 hours, genome wide linkage analyses (also known as positional
19 cloning) demonstrated quantitative trait loci for O₃-induced lung inflammation and
20 hyperpermeability on chromosome 17 ([Kleeberger et al., 1997](#)) and chromosome 4
21 ([Kleeberger et al., 2000](#)), respectively. More specifically, these studies found that *Tnf*,
22 whose protein product is the inflammatory cytokine TNF- α , and *Tlr4*, whose protein
23 product is TLR4, were candidate susceptibility genes ([Kleeberger et al., 2000](#); [Kleeberger
24 et al., 1997](#)). Other studies, which used targeted deletion, identified genes encoding iNOS
25 and heat shock proteins as TLR4 effector genes ([Bauer et al., 2011](#); [Kleeberger et al.,
26 2001](#)) and found that IL-10 protects against O₃-induced pulmonary inflammation ([Backus
27 et al., 2010](#)). Investigations in inbred mouse strains found that differences in expression
28 of certain proteins, such as CCSP (1.8 ppm O₃ for 3 hours) ([Broeckaert et al., 2003](#)) and
29 MARCO (0.3 ppm O₃ for up to 48 hours) ([Dahl et al., 2007](#)), were responsible for
30 phenotypic characteristics, such as epithelial permeability and scavenging of oxidized
31 lipids, respectively, which confer sensitivity to O₃.

1 Genetic polymorphisms have received increasing attention as modulators of O₃-mediated
2 effects. Functionally relevant polymorphisms in candidate susceptibility genes have been
3 studied at the individual and population level in humans, and also in animal models.
4 Genes whose protein products are involved in antioxidant defense/oxidative stress and
5 xenobiotic metabolism, such as glutathione-S-transferase M1 (GSTM1) and
6 NADPH:quinone oxidoreductase 1 (NQO1), have also been a major focuses of these
7 efforts. This is because oxidative stress resulting from O₃ exposure is thought to
8 contribute to the pathogenesis of asthma, and because xenobiotic metabolism detoxifies
9 secondary oxidation products formed by O₃ which contribute to oxidative stress ([Islam et
10 al., 2008](#)). TNF- α is of interest since it is linked to a candidate O₃ susceptibility gene and
11 since it plays a key role in initiating airways inflammation ([Li et al., 2006d](#)).
12 Polymorphisms of genes coding for GSTM1, NQO1 and TNF- α have been associated
13 with altered risk of O₃-mediated effects ([Li et al., 2006d](#); [Yang et al., 2005a](#); [Romieu et
14 al., 2004b](#); [Corradi et al., 2002](#); [Bergamaschi et al., 2001](#)). Additional studies have
15 focused on functional variants in other genes involved in antioxidant defense such as
16 catalase (CAT), myeloperoxidase, heme oxygenase (*HMOX-1*) and manganese
17 superoxide dismutase (*MnSOD*) ([Wenten et al., 2009](#); [Islam et al., 2008](#)). These studies
18 are discussed below.

19 GSTM1 is a phase II antioxidant enzyme which is transcriptionally regulated by
20 NF-e2-related factor 2-antioxidant response element (Nrf2-ARE) pathway. A large
21 proportion (40-50%) of the general public (across ethnic populations) has the
22 GSTM1-null genotype, which has been linked to an increased risk of health effects due to
23 exposure to air pollutants ([London, 2007](#)). A role for GSTs in metabolizing electrophiles
24 such as 4-hydroxynonenal, which is a secondary oxidation product resulting from O₃
25 exposure, has been demonstrated ([Awasthi et al., 2004](#)). A recent study found that the
26 GSTM1 genotype modulated the time course of the neutrophilic inflammatory response
27 following acute O₃ exposure (400 ppb for 2 hours with light to moderate exercise) in
28 healthy adults ([Alexis et al., 2009](#)). In GSTM1-null and -sufficient subjects, O₃-induced
29 sputum neutrophilia was similar at 4 hours. However, neutrophilia resolved by 24 hours
30 in sufficient subjects but not in GSTM1-null subjects. In contrast, no differences in
31 24 hour sputum neutrophilia were observed between GSTM1-null and -sufficient human
32 subjects exposed to 60 ppb O₃ for 2 hours with moderate exercise ([Kim et al., 2011](#)). It is
33 not known whether the effect seen at the higher exposure level ([Alexis et al., 2009](#)) was
34 due to the persistence of pro-inflammatory stimuli, impaired production of
35 downregulators or impaired neutrophil apoptosis and clearance. However, a subsequent
36 in vitro study by these same investigators found that GSTM1 deficiency in airway
37 epithelial cells enhanced IL-8 production in response to 0.4 ppm O₃ for 4 hours ([Wu et
38 al., 2011](#)). Furthermore, NF- κ B activation was required for O₃-induced IL-8 production
39 ([Wu et al., 2011](#)). Since IL-8 is a potent neutrophil activator and chemotaxin, this study

1 provides additional evidence for the role of GSTM1 as a modulator of inflammatory
2 responses due to O₃ exposure.

3 In addition, O₃ exposure increased the expression of the surface marker CD14 in airway
4 neutrophils of GSTM1-null subjects to a greater extent than in sufficient subjects ([Alexis
5 et al., 2009](#)). Furthermore, differences in airway macrophages were noted between the
6 GSTM1-sufficient and -null subjects. Numbers of airway macrophages were decreased at
7 4 and 24 hours following O₃ exposure in GSTM1-sufficient subjects ([Alexis et al., 2009](#)).
8 Airway macrophages in GSTM1-null subjects were greater in number and found to have
9 greater oxidative burst and phagocytic capability than those of sufficient subjects. Airway
10 macrophages and dendritic cells from GSTM1-null subjects exposed to O₃ expressed
11 higher levels of the surface marker HLA-DR, suggesting activation of the innate immune
12 system ([Alexis et al., 2009](#)). These differences in inflammatory responses between the
13 GSTM1-null and -sufficient subjects may provide biological plausibility for the
14 differences in O₃-mediated effects reported in controlled human exposure studies
15 ([Corradi et al., 2002](#); [Bergamaschi et al., 2001](#)). It should also be noted that GSTM1
16 genotype did not affect the acute pulmonary function (i.e., spirometric) response to O₃
17 which provides additional evidence for separate mechanisms underlying the effects of O₃
18 on pulmonary function and inflammation in adults ([Alexis et al., 2009](#)). However,
19 GSTM1-null asthmatic children were previously found to be more at risk of O₃-induced
20 effects on pulmonary function than GSTM1-sufficient asthmatic children ([Romieu et al.,
21 2004b](#)).

22 Another enzyme involved in the metabolism of secondary oxidation products is NQO1.
23 NQO1 catalyzes the 2-electron reduction by NADPH of quinones to hydroquinones.
24 Depending on the substrate, it is capable of both protective detoxification reactions and
25 redox cycling reactions resulting in the generation of reactive oxygen species. A recent
26 study using NQO1-null mice demonstrated that NQO1 contributes to O₃-induced
27 oxidative stress, AHR and inflammation following a 3-hour exposure to 1 ppm O₃
28 ([Voynow et al., 2009](#)). These experimental results may provide biological plausibility for
29 the increased biomarkers of oxidative stress and increased pulmonary function
30 decrements observed in O₃-exposed individuals bearing both the wild-type NQO1 gene
31 and the null GSTM1 gene ([Corradi et al., 2002](#); [Bergamaschi et al., 2001](#)).

32 Besides enzymatic metabolism, other mechanisms participate in the removal of
33 secondary oxidation products formed as a result of O₃ inhalation. One involves
34 scavenging of oxidized lipids via the macrophage receptor with collagenous structure
35 (MARCO) expressed on the cell surface of alveolar macrophages. A recent study
36 demonstrated increased gene expression of MARCO in the lungs of an O₃-resistant C3H
37 mouse strain (HeJ) but not in an O₃-sensitive, genetically similar strain (OuJ) ([Dahl et al.,](#)

1 [2007](#)). Upregulation of MARCO occurred in mice exposed to 0.3 ppm O₃ for
2 24-48 hours; inhalation exposure for 6 hours at this concentration was insufficient for this
3 response. Animals lacking the MARCO receptor exhibited greater inflammation and
4 injury, as measured by BAL neutrophils, protein and isoprostanes, following exposure to
5 0.3 ppm O₃ ([Dahl et al., 2007](#)). MARCO also protected against the inflammatory effects
6 of oxidized surfactant lipids ([Dahl et al., 2007](#)). Scavenging of oxidized lipids may limit
7 O₃-induced injury since ozonized cholesterol species formed in the ELF (mice, 0.5-3 ppm
8 O₃, 3 hours) ([Pulfer et al., 2005](#); [Pulfer and Murphy, 2004](#)) stimulated apoptosis and
9 cytotoxicity in vitro ([Gao et al., 2009b](#); [Sathishkumar et al., 2009](#); [Sathishkumar et al.,](#)
10 [2007b](#); [Sathishkumar et al., 2007a](#)).

11 Two studies reported relationships between *TNF* promoter variants and O₃-induced
12 effects in humans. In one study, O₃-induced change in lung function was significantly
13 lower in adult subjects with *TNF* promoter variants -308A/A and -308G/A compared with
14 adult subjects with the variant -308G/G ([Yang et al., 2005a](#)). This response was
15 modulated by a specific polymorphism of *LTA* ([Yang et al., 2005a](#)), a previously
16 identified candidate susceptibility gene whose protein product is lymphotoxin- α
17 ([Kleeberger et al., 1997](#)). In the second study, an association between the *TNF* promoter
18 variant -308G/G and decreased risk of asthma and lifetime wheezing in children was
19 found ([Li et al., 2006d](#)). The protective effect on wheezing was modulated by ambient O₃
20 levels and by *GSTM1* and *GSTP1* polymorphisms. The authors suggested that the
21 *TNF*-308 G/G genotype may have a protective role in the development of childhood
22 asthma ([Li et al., 2006d](#)).

23 Similarly, a promoter variant of the gene *HMOX-1*, consisting of a smaller number of
24 (GT)_n repeats, was associated with a reduced risk for new-onset asthma in non-Hispanic
25 white children ([Islam et al., 2008](#)). The number of (GT)_n repeats in this promoter has
26 been shown to be inversely related to the inducibility of *HMOX-1*. A modulatory effect of
27 O₃ was demonstrated since the beneficial effects of this polymorphism were seen only in
28 children living in low O₃ communities ([Islam et al., 2008](#)). This study also identified an
29 association between a polymorphism of the *CAT* gene and increased risk of new-onset
30 asthma in Hispanic children; however no modulation by O₃ was seen ([Islam et al., 2008](#)).
31 No association was observed in this study between a *MnSOD* polymorphism and asthma
32 ([Islam et al., 2008](#)).

33 Studies to date indicate that some variability in individual responsiveness to O₃ may be
34 accounted for by functional genetic polymorphisms. Further, the effects of
35 gene-environment interactions may be different in children and adults.

5.4.2.2 Pre-existing Diseases and Conditions

1 Pre-existing diseases and conditions can alter the response to O₃ exposure. For example,
2 responsiveness to O₃, as measured by spirometry, is decreased in smokers and individuals
3 with COPD ([U.S. EPA, 2006b](#)). Asthma and allergic diseases are of major importance in
4 this discussion. In individuals with asthma, there is increased responsiveness to
5 bronchoconstrictor challenge. This results from a combination of structural and
6 physiological factors including increased airway inner-wall thickness, smooth muscle
7 responsiveness and mucus secretion. Although inflammation is likely to contribute, its
8 relationship to AHR is not clear ([U.S. EPA, 2006b](#)). However, some asthmatics have
9 higher baseline levels of neutrophils, lymphocytes, eosinophils and mast cells in
10 bronchial washes and bronchial biopsy tissue ([Stenfors et al., 2002](#)). It has been proposed
11 that enhanced sensitivity to O₃ is conferred by the presence of greater numbers of resident
12 airway inflammatory cells in disease states such as asthma ([Mudway and Kelly, 2000](#)).

13 In order to determine whether asthmatics exhibit greater responses to O₃, several earlier
14 studies compared pulmonary function in asthmatic and non-asthmatic subjects following
15 O₃ exposure. Some also probed mechanisms which could account for enhanced
16 sensitivity. While the majority focused on measurements of FEV₁ and FVC and found no
17 differences between the two groups following exposures of 2-4 hours to 125-250 ppb O₃
18 or to a 30-minute exposure to 120-180 ppb O₃ by mouthpiece in human subjects
19 exercising at a light to moderate level ([Stenfors et al., 2002](#); [Mudway et al., 2001](#); [Holz et](#)
20 [al., 1999](#); [Scannell et al., 1996](#); [Koenig et al., 1987](#); [Linn et al., 1978](#)), there were notable
21 exceptions. In one study, greater airways obstruction in asthmatics compared with non-
22 asthmatic subjects was observed immediately following a 2-hour exposure to 400 ppb O₃
23 while exercising at a heavy level ([Kreit et al., 1989](#)). These changes were measured as
24 statistically significant greater decreases in FEV₁ and in FEF₂₅₋₇₅ (but not in FVC) in the
25 absence of a bronchoconstrictor challenge ([Kreit et al., 1989](#)). These results suggest that
26 this group of asthmatics responded to O₃-exposure with a greater degree of vagally-
27 mediated bronchoconstriction compared with the non-asthmatics. A second study
28 demonstrated a statistically significant greater decrease in FEV₁ and in FEV₁/FVC (but
29 not in FVC) in asthmatics compared with non-asthmatics exposed to 160 ppb O₃ for
30 7.6 hours with light exercise ([Horstman et al., 1995](#)). These responses were accompanied
31 by wheezing and inhaler use in the asthmatics ([Horstman et al., 1995](#)). Aerosol bolus
32 dispersion measurements demonstrated a statistically significant greater change in
33 asthmatics compared with non-asthmatics, which was suggestive of O₃-induced small
34 airway dysfunction ([Horstman et al., 1995](#)). Furthermore, a statistically significant
35 correlation was observed between the degree of baseline airway status and the FEV₁
36 response to O₃ in the asthmatic subjects ([Horstman et al., 1995](#)). A third study found
37 similar decreases in FVC and FEV₁ in both asthmatics and non-asthmatics exposed to

1 400 ppb O₃ for 2 hours with light exercise ([Alexis et al., 2000](#)). However, a statistically
2 significant decrease in FEF₇₅, a measure of small airway function, was observed in
3 asthmatics but not in non-asthmatics ([Alexis et al., 2000](#)). Taken together, these latter
4 studies indicate that while the magnitude of restrictive type spirometric decline was
5 similar in asthmatics and non-asthmatics, that obstructive type changes
6 (i.e., bronchoconstriction) were greater in asthmatics. Further, asthmatics exhibited
7 greater sensitivity to O₃ in terms of small airways function.

8 Since asthma exacerbations occur in response to allergens and/or other triggers, some
9 studies have focused on O₃-induced changes in AHR following a bronchoconstrictor
10 challenge. No difference in sensitivity to methacholine bronchoprovocation was observed
11 between asthmatics and non-asthmatics exposed to 400 ppb O₃ for 2 hours while
12 exercising at a heavy level ([Kreit et al., 1989](#)). However, increased bronchial reactivity to
13 inhaled allergens was demonstrated in mild allergic asthmatics exposed to 160 ppb for
14 7.6 hours, 250 ppb for 3 hours and 120 ppb for 1 hour while exercising at a light level or
15 at rest ([Kehrl et al., 1999](#); [Jorres et al., 1996](#); [Molfino et al., 1991](#)) and in allergen-
16 sensitized guinea pigs following O₃ exposure (1 ppm, 1 hour) ([Sun et al., 1997](#)). Similar,
17 but modest, responses were reported for individuals with allergic rhinitis ([Jorres et al.,](#)
18 [1996](#)). Further, the contractile response of isolated airways from human donor lung
19 tissue, which were sensitized and challenged with allergen, was increased by
20 pre-exposure to 1 ppm O₃ for 20 ([Roux et al., 1999](#)). These studies provide support for
21 O₃-mediated enhancement of responses to allergens in allergic subjects.

22 In terms of airways neutrophilia, larger responses were observed in asthmatics compared
23 to non-asthmatics subjects, who were exercising at a light to moderate level and exposed
24 to O₃, in some ([Balmes et al., 1997](#); [Scannell et al., 1996](#); [Basha et al., 1994](#)) but not all
25 ([Mudway et al., 2001](#)) of the earlier studies. While each of these studies involved
26 exposure of exercising human subjects to 200 ppb O₃, the duration of exposure was
27 longer (i.e., 4-6 hours) in the former studies than in the latter study (2 hours). Further,
28 statistically significant increases in myeloperoxidase levels (an indicator of neutrophil
29 activation) in bronchial washes was observed in mild asthmatics compared with non-
30 asthmatics, despite no difference in O₃-stimulated neutrophil influx between the 2 groups
31 following exposure to 200 ppb O₃ for 2 hours with moderate exercise ([Stenfors et al.,](#)
32 [2002](#)). A more recent study found that atopic asthmatic subjects exhibited an enhanced
33 inflammatory response to O₃ (400 ppb, 4 hours, with light to moderate exercise)
34 ([Hernandez et al., 2010](#)). This response was characterized by greater numbers of
35 neutrophils, higher levels of IL-6, IL-8 and IL-1 β and greater macrophage cell-surface
36 expression of TLR4 and IgE receptors in induced sputum compared with healthy
37 subjects. This study also reported a greater increase in hyaluronan in atopic subjects and
38 atopic asthmatics compared with healthy subjects following O₃ exposure. Animal studies

1 have previously reported that hyaluronic acid activates TLR4 signaling and results in
2 AHR (see Section [5.3.5](#)). Furthermore, levels of IL-10, a potent anti-inflammatory
3 cytokine, were greatly reduced in atopic asthmatics compared to healthy subjects. These
4 results provide evidence that innate immune and adaptive responses are different in
5 asthmatics and healthy subjects exposed to O₃.

6 Eosinophils may be an important modulator of responses to O₃ in asthma and allergic
7 airways disease. Eosinophils and associated proteins are thought to affect muscarinic
8 cholinergic receptors which are involved in vagally-mediated bronchoconstriction
9 ([Mudway and Kelly, 2000](#)). Studies described in Section [5.3.5](#) which demonstrated a key
10 role of eosinophils in O₃-mediated AHR may be relevant to human allergic airways
11 disease which is characterized by airways eosinophilia ([Yost et al., 2005](#)). Furthermore,
12 O₃ exposure sometimes results in airways eosinophilia in allergic subjects or animal
13 models. For example, eosinophilia of the nasal and other airways was observed in
14 individuals with pre-existing allergic disease following O₃ inhalation (160 ppb, 7.6 hours
15 with light exercise and 270 ppb, 2 hours with moderate exercise) ([Vagaggini et al., 2002](#);
16 [Peden et al., 1997](#)). Further, O₃ exposure (0.5 ppm, 8 hours/day for 1-3 days) increased
17 allergic responses, such as eosinophilia and augmented intraepithelial mucosubstances, in
18 the nasal airways of ovalbumin (OVA)-sensitized rats ([Wagner et al., 2002](#)). In contrast,
19 [Stenfors et al. \(2002\)](#) found no stimulation of eosinophil influx measured in bronchial
20 washes and BALF of mild asthmatics following exposure to a lower concentration
21 (200 ppb, 2 hours, with moderate exercise) of O₃.

22 The role of mast cells in O₃-mediated asthma exacerbations has been investigated. Mast
23 cells are thought to play a key role in O₃-induced airways inflammation, since airways
24 neutrophilia was decreased in mast cell-deficient mice exposed to O₃ ([Kleeberger et al.,
25 1993](#)). However, another study found that mast cells were not involved in the
26 development of increased bronchial reactivity in O₃-exposed mice ([Noviski et al., 1999](#)).
27 Nonetheless, mast cells release a wide variety of important inflammatory mediators
28 which may lead to asthma exacerbations ([Stenfors et al., 2002](#)). A large increase in mast
29 cell number in bronchial submucosa was observed in non-asthmatics and a significant
30 decrease in mast cell number in bronchial epithelium was observed in mild asthmatics
31 6 hours following exposure to 200 ppb O₃ for 2 hours during mild exercise ([Stenfors et
32 al., 2002](#)). While these results point to an O₃-mediated flux in bronchial mast cell
33 populations which differed between the non-asthmatics and mild asthmatics,
34 interpretation of these findings is difficult. Furthermore, mast cell number did not change
35 in airway lavages in either group in response to O₃ ([Stenfors et al., 2002](#))

36 Cytokine profiles in the airways have been investigated as an indicator of O₃ sensitivity.
37 Differences in epithelial cytokine expression were observed in bronchial biopsy samples

1 in non-asthmatic and asthmatic subjects both at baseline and 6-hours postexposure to
2 200 ppb O₃ for 2 hours with moderate exercise ([Bosson et al., 2003](#)). The asthmatic
3 subjects had a higher baseline expression of IL-4 and IL-5 compared to non-asthmatics.
4 In addition, expression of IL-5, IL-8, GM-CSF, and ENA-78 in asthmatics was increased
5 significantly following O₃ exposure compared to non-asthmatics ([Bosson et al., 2003](#)).
6 Some of these (IL-4, IL-5 and GM-CSF) are Th2-related cytokines or neutrophil
7 chemoattractants, and play a role in IgE production, airways eosinophilia and suppression
8 of Th1-cytokine production ([Bosson et al., 2003](#)). These findings suggest a link between
9 adaptive immunity and enhanced responses of asthmatics to O₃.

10 A further consideration is the compromised status of ELF antioxidants in disease states
11 such as asthma ([Mudway and Kelly, 2000](#)). This could possibly be due to ongoing
12 inflammation which causes antioxidant depletion or to abnormal antioxidant transport or
13 synthesis ([Mudway and Kelly, 2000](#)). For example, basal levels of AH2 were
14 significantly lower and basal levels of oxidized GSH and UA were significantly higher in
15 bronchial wash fluid and BALF of mild asthmatics compared with healthy control
16 subjects ([Mudway et al., 2001](#)). Differences in ELF antioxidant content have also been
17 noted between species. These observations have led to the suggestion that the amount and
18 composition of ELF antioxidants, the capacity to replenish antioxidants in the ELF or the
19 balance between beneficial and injurious interactions between antioxidants and O₃ may
20 contribute to O₃ sensitivity, which varies between individuals and species ([Mudway et](#)
21 [al., 2006](#); [Mudway and Kelly, 2000](#); [Mudway et al., 1999a](#)). The complexity of these
22 interactions was demonstrated by a study in which a 2-hour exposure to 200 ppb O₃,
23 while exercising at a moderate level, resulted in similar increases in airway neutrophils
24 and decreases in pulmonary function in both mild asthmatics and healthy controls,
25 despite differences in ELF antioxidant concentrations prior to O₃ exposure ([Mudway et](#)
26 [al., 2001](#)). Further, the O₃-induced increase in oxidized GSH and decrease in AH2
27 observed in ELF of healthy controls was not observed in mild asthmatics ([Mudway et al.,](#)
28 [2001](#)). While the authors concluded that basal AH2 and oxidized GSH concentrations
29 were not predictive of responsiveness to O₃, they also suggested that the increased basal
30 UA concentrations in the mild asthmatics may have played a protective role ([Mudway et](#)
31 [al., 2001](#)). Thus compensatory mechanisms resulting in enhanced total antioxidant
32 capacity may play a role in modulating responses to O₃.

33 Collectively these older and more recent studies provide insight into mechanisms which
34 may contribute to enhanced responses of asthmatic and atopic individuals following O₃
35 exposure. Greater airways inflammation and/or greater bronchial reactivity have been
36 demonstrated in asthmatics compared to non-asthmatics. This pre-existing inflammation
37 and altered baseline bronchial reactivity may contribute to the enhanced
38 bronchoconstriction seen in asthmatics exposed to O₃. Furthermore, O₃-induced

1 inflammation may contribute to O₃-mediated AHR. An enhanced neutrophilic response to
2 O₃ has been demonstrated in some asthmatics. A recent study in humans provided
3 evidence for differences in innate immune responses related to TLR4 signaling between
4 asthmatics and healthy subjects. Animal studies have demonstrated a role for eosinophil-
5 derived proteins in mediating the effects of O₃. Since airways eosinophilia occurs in both
6 allergic humans and allergic animal models, this pathway may underlie the exacerbation
7 of allergic asthma by O₃. In addition, differences have been noted in epithelial cytokine
8 expression in bronchial biopsy samples of healthy and asthmatic subjects. A Th2
9 phenotype, indicative of adaptive immune system activation and enhanced allergic
10 responses, was observed before O₃ exposure and was increased by O₃ exposure in
11 asthmatics. These findings support links between innate and adaptive immunity and
12 sensitivity to O₃-mediated effects in asthmatics and allergic airways disease.

13 In addition to asthma and allergic diseases, obesity may alter responses to O₃. While O₃ is
14 a trigger for asthma, obesity is a known risk factor for asthma ([Shore, 2007](#)). The
15 relationship between obesity and asthma is not well understood but recent investigations
16 have focused on alterations in endocrine function of adipose tissue in obesity. It is
17 thought that the increases in serum levels of factors produced by adipocytes
18 (i.e., adipokines), such as cytokines, chemokines, soluble cytokine receptors and energy
19 regulating hormones, may contribute to the relationship between obesity and asthma.
20 Some of these same mechanisms may be relevant to insulin resistant states such as
21 metabolic syndrome.

22 In a re analysis of the data of [Hazucha et al. \(2003\)](#), increasing body mass index in
23 young women was associated with increased O₃ responsiveness, as measured by
24 spirometry following a 1.5-hour exposure to 420 ppb O₃ while exercising at a moderate
25 level ([Bennett et al., 2007](#)). In several mouse models of obesity, airways were found to be
26 innately more hyperresponsive and responded more vigorously to acute O₃ exposure than
27 lean controls ([Shore, 2007](#)). Pulmonary inflammatory and injury in response to O₃ were
28 also enhanced ([Shore, 2007](#)). It was postulated that oxidative stress resulting from
29 obesity-related hyperglycemia could account for these effects ([Shore, 2007](#)). However,
30 responses to O₃ in the different mouse models are somewhat variable and depend on
31 whether exposures are acute or subacute. For example, diet-induced obesity augmented
32 inflammation and injury, as measured by BALF markers, and enhanced AHR in mice
33 exposed acutely to O₃ (2 ppm, 3 hours) ([Johnston et al., 2008](#)). In contrast, the
34 inflammatory response following sub-acute exposure to O₃ was dampened by obesity in a
35 different mouse model (0.3 ppm, 72 hours) ([Shore et al., 2009](#)). It is not known whether
36 differences in responsiveness to O₃ are due to differences in lung development in
37 genetically-modified animals which result in smaller lungs and thus to differences in
38 inhaled dose because of the altered body mass to lung size ratio.

5.4.2.3 Nutritional Status

1 A further consideration is the compromised status of ELF antioxidants in nutritional
2 deficiencies. Thus, many investigations have focused on antioxidant deficiency and
3 supplementation as modulators of O₃-mediated effects. One study in mice found that
4 vitamin A deficiency enhanced lung injury induced by exposure to 0.3 ppm O₃ for
5 72 hours ([Paquette et al., 1996](#)). Ascorbate deficiency was shown to increase the effects
6 of acute (0.5-1 ppm for 4 hours), but not subacute (0.2-0.8 ppm for 7 days), O₃ exposure
7 in guinea pigs ([Kodavanti et al., 1995](#); [Slade et al., 1989](#)). Supplementation with AH2
8 and α-TOH was protective in healthy adults who were on an AH2-deficient diet and
9 exposed to 400 ppb O₃ for 2 hours while exercising at a moderate level ([Samet et al.,
10 2001](#)). In this study, the protective effect consisted of a smaller reduction in FEV₁
11 following O₃ exposure ([Samet et al., 2001](#)). However the inflammatory response (influx
12 of neutrophils and levels of IL-6) measured in BALF 1 hour after O₃ exposure was not
13 different between supplemented and non-supplemented subjects ([Samet et al., 2001](#)).
14 Other investigators found that AH2 and α-TOH supplementation failed to ameliorate the
15 pulmonary function decrements or airways neutrophilia observed in humans exposed to
16 200 ppb O₃ for 2 hours while exercising at a moderate level ([Mudway et al., 2006](#)). It was
17 suggested that supplementation may be ineffective in the absence of antioxidant
18 deficiency ([Mudway et al., 2006](#)).

19 In asthmatic adults, these same dietary antioxidants reduced O₃-induced bronchial
20 hyperresponsiveness (120 ppb, 45 min, light exercise) ([Trenga et al., 2001](#)). Furthermore,
21 supplementation with AH2 and α-tocopherol protected against pulmonary function
22 decrements and nasal inflammatory responses which were associated with high levels of
23 ambient O₃ in asthmatic children living in Mexico City ([Sienra-Monge et al., 2004](#);
24 [Romieu et al., 2002](#)). Similarly, supplementation with ascorbate, α-tocopherol and
25 β-carotene improved pulmonary function in Mexico City street workers ([Romieu et al.,
26 1998b](#)).

27 Protective effects of supplementation with α-tocopherol alone have not been observed in
28 humans experimentally exposed to O₃ ([Mudway and Kelly, 2000](#)). Alpha-TOH
29 supplementation also failed to protect against O₃-induced effects in animal models of
30 allergic rhinosinusitis and lower airways allergic inflammation (rats, 1 ppm O₃ for
31 2 days) ([Wagner et al., 2007](#)). However, protection in these same animal models was
32 reported using γ-TOH supplementation ([Wagner et al., 2009](#); [Wagner et al., 2007](#)).
33 Whether or not this effect was due to enhanced antioxidant status or to activated signaling
34 pathways is not known. Other investigators found that α-TOH deficiency led to an
35 increase in liver lipid peroxidation (rats, 0.3 ppm 3 hours/day for 7 months) ([Sato et al.,
36 1980](#)) and a drop in liver α-TOH levels following O₃ exposure (mice, 0.5 ppm,

1 6 hours/day for 3 days) ([Vasu et al., 2010](#)). A recent study used α -TOH transfer protein
2 null mice as a model of α -TOH deficiency and demonstrated an altered adaptive response
3 of the lung genome to O₃ exposure ([Vasu et al., 2010](#)). Taken together, these studies
4 provide evidence that the tocopherol system modulates O₃-induced responses.

5.4.2.4 Lifestage

5 Responses to O₃ are modulated by factors associated with lifestage. On one end of the
6 lifestage spectrum is aging. The spirometric response to O₃ appears to be lost in humans
7 as they age, as was demonstrated in two studies involving exposures of human subjects
8 exercising at levels ranging from light to heavy to 420-450 ppb O₃ for 1.5-2 hours
9 ([Hazucha et al., 2003](#); [Drechsler-Parks, 1995](#)). In mice, physiological responses to O₃
10 (600 ppb, 2 hours) were diminished with age ([Hamade et al., 2010](#)). Mechanisms
11 accounting for this effect have not been well-studied but could include altered number
12 and sensitivity of receptors, altered signaling pathways involved in neural reflexes or
13 compromised status of ELF antioxidants.

14 On the other side of the lifestage spectrum is pre/postnatal development. Critical
15 windows of development during the pre/postnatal period are associated with an enhanced
16 sensitivity to environmental toxicants. Adverse birth outcomes and developmental
17 disorders may occur as a result (Section [7.4](#)).

18 Adverse birth outcomes may result from stressors which impact transplacental oxygen
19 and nutrient transport by a variety of mechanisms including oxidative stress, placental
20 inflammation and placental vascular dysfunction ([Kannan et al., 2006](#)). These
21 mechanisms may be linked since oxidative/nitrosative stress is reported to cause vascular
22 dysfunction in the placenta ([Myatt et al., 2000](#)). As described earlier in this chapter and in
23 Section [7.4](#), systemic inflammation and oxidative/nitrosative stress and modification of
24 innate and adaptive immunity are key events underlying the health effects of O₃ and as
25 such they may contribute to adverse birth outcomes. An animal toxicology study showing
26 that exposure to 2 ppm O₃ led to anorexia ([Kavlock et al., 1979](#)) (see Section [7.4.2](#)) in
27 exposed rat dams provide an additional mechanism by which O₃ exposure could lead to
28 diminished transplacental nutrient transport. Disturbances of the pituitary-adrenocortico-
29 placental system ([Ritz et al., 2000](#)) may also impact normal intrauterine growth and
30 development. Further, restricted fetal growth may result from pro-inflammatory
31 cytokines which limit trophoblast invasion during the early stages of pregnancy ([Hansen
32 et al., 2008](#)). Direct effects on maternal health, such as risk of infection, and on fetal
33 health, such as DNA damage, have also been proposed as mechanisms underlying
34 adverse birth outcomes ([Ritz et al., 2000](#)). In addition to restricted fetal growth, preterm

1 birth may contribute to adverse birth outcomes. Preterm birth may result from the
2 development of premature contractions and/or premature rupture of membranes as well
3 as from disrupted implantation and placentation which results in suboptimal placental
4 function ([Darrow et al., 2009](#); [Ritz et al., 2000](#)). Genetic mutations are thought to be an
5 important cause of placental abnormalities in the first trimester, while vascular alterations
6 may be the main cause of placental abnormalities in later trimesters ([Jalaludin et al.,
7 2007](#)). Ozone-mediated systemic inflammation and oxidative stress/nitrosative stress may
8 possibly be related to these effects although there is no firm evidence.

9 Enhanced sensitivity to environmental toxicants during critical windows of development
10 may also result in developmental disorders. For example, normal migration and
11 differentiation of neural crest cells are important for heart development and are
12 particularly sensitive to toxic insults ([Ritz et al., 2002](#)). Further, immune dysregulation
13 and related pathologies are known to be associated with pre/postnatal environmental
14 exposures ([Dietert et al., 2010](#)). Ozone exposure is associated with developmental effects
15 in several organ systems. These include the lung and immune system (see below) and
16 neurobehavioral changes which could reflect the effect of O₃ on CNS plasticity or the
17 hypothalamic-pituitary axis ([Auten and Foster, 2011](#)) (see Section [7.4.9](#)).

18 The majority of developmental effects due to O₃ have been described for the respiratory
19 system (see Section [7.2.3](#) and [7.4.8](#)). Since its growth and development take place during
20 both the prenatal and early postnatal periods, both prenatal and postnatal exposures to O₃
21 have been studied. Maternal exposure to 0.4-1.2 ppm O₃ during gestation resulted in
22 developmental health effects in the RT of mice ([Sharkhuu et al., 2011](#)). Recent studies
23 involving postnatal exposure to O₃ have focused on differences between developing and
24 adult animals in antioxidant defenses, respiratory physiology and sensitivity to cellular
25 injury, and on mechanisms, such as lung structural changes, antigen sensitization,
26 interaction with nitric oxide signaling, altered airway afferent innervation and loss of
27 alveolar repair capacity, by which early O₃ exposure could lead to asthma pathogenesis or
28 exacerbations in later life ([Auten and Foster, 2011](#)).

29 An interesting set of studies conducted over the last 10 years in the infant rhesus monkey
30 has identified numerous O₃-mediated perturbations in the developing lung and immune
31 system ([Plopper et al., 2007](#)). These investigations were prompted by the dramatic rise in
32 the incidence of childhood asthma and focused on the possible interaction of O₃ and
33 allergens in promoting remodeling of the epithelial-mesenchymal trophic unit during
34 postnatal development of the tracheobronchial airway wall. In humans, airways growth
35 during the 8-12 year period of postnatal development is not well understood. Rhesus
36 monkeys were used in these studies because the branching pattern and distribution of
37 airways in this model are more similar to humans than those of rodents are to humans. In

1 addition, a model of allergic airways disease, which exhibits the main features of human
2 asthma, had already been established in the adult rhesus monkey. Studies in infant
3 monkeys were designed to determine whether repeated exposure to O₃ altered postnatal
4 growth and development, and if so, whether such effects were reversible. In addition,
5 exposure to O₃ was evaluated for its potential to increase the development of allergic
6 airways disease. Exposures were to cyclic episodic O₃ over 5 months which involved 5
7 biweekly cycles of alternating filtered air and O₃ - 9 consecutive days of filtered air and 5
8 consecutive days of 0.5 ppm O₃, 8 h/day – and to house dust mite allergen (HDMA) for
9 2 hours per day for 3 days on the last 3 days of O₃ exposure followed by 11 days of
10 filtered air.

11 Key findings were numerous. First, baseline airway resistance and AHR in the infant
12 monkeys were dramatically increased by combined exposure to both HDMA and O₃
13 ([Joad et al., 2006](#); [Schelegle et al., 2003](#)). Secondly, O₃ exposure led to a large increase in
14 BAL eosinophils ([Schelegle et al., 2003](#)) while HDMA exposure led to a large increase of
15 eosinophils in airways tissue ([Joad et al., 2006](#); [Schelegle et al., 2003](#)). Thirdly, the
16 growth pattern of distal airways was changed to a large extent by exposure to O₃ alone
17 and in combination with HDMA. More specifically, longer and narrower airways resulted
18 and the number of conducting airway generations between the trachea and the gas
19 exchange area was decreased ([Fanucchi et al., 2006](#)). This latter effect was not
20 ameliorated by a recovery period of 6 months. Fourthly, exposure to both HDMA and O₃
21 altered the abundance and distribution of CD25+ lymphocytes in the airways ([Miller et](#)
22 [al., 2009](#)). Lastly, several effects were seen at the level of the epithelial mesenchymal
23 trophic unit in response to O₃. These include altered organization of the airways
24 epithelium ([Schelegle et al., 2003](#)), increased abundance of mucous goblet cells
25 ([Schelegle et al., 2003](#)), disruption of the basement membrane zone ([Evans et al., 2003](#)),
26 reduced innervation ([Larson et al., 2004](#)), increased neuroendocrine-like cells ([Joad et al.,](#)
27 [2006](#)), and altered orientation and abundance of smooth muscle bundles ([Plopper et al.,](#)
28 [2007](#); [Tran et al., 2004](#)). Six months of recovery in filtered air led to reversal of some but
29 not all of these effects ([Kajekar et al., 2007](#); [Plopper et al., 2007](#); [Evans et al., 2004](#)). The
30 authors concluded that cyclic challenge of infant rhesus monkeys to allergen and O₃
31 during the postnatal period compromised airway growth and development and resulted in
32 changes which favor allergic airways responses and persistent effects on the immune
33 system ([Plopper et al., 2007](#)). A more recent study in this same model reported that early
34 life exposure to O₃ resulted in decreased total peripheral blood leukocyte numbers and
35 increased blood eosinophils as well as persistent effects on pulmonary and systemic
36 innate immunity in the infant rhesus monkey model ([Maniar-Hew et al., 2011](#)).

37 Furthermore, the effect of cyclic episodic O₃ exposure on nasal airways was studied in
38 the infant rhesus monkey model. The three-dimensional detail of the nasal passages was

1 analyzed for developing predictive dosimetry models and exposure-dose-response
2 relationships ([Carey et al., 2007](#)). The authors reported that the relative amounts of the
3 five epithelial cell types in the nasal airways of monkeys remained consistent between
4 infancy and adulthood [comparing to ([Gross, 1987](#); [Gross, 1982](#))]. Cyclic episodic O₃
5 exposure (as described in the previous paragraphs) resulted in 50-80% decreases in
6 epithelial thickness and epithelial cell volume of the ciliated respiratory and transitional
7 epithelium, confirming that these cell types in the nasal cavity were the most sensitive to
8 O₃ exposure. The character and location of nasal lesions resulting from O₃ exposure were
9 similar in the infant monkeys and adult monkeys similarly exposed. However, the nasal
10 epithelium of infant monkeys did not undergo nasal airway epithelial remodeling or
11 adaptation which occurs in adult animals following O₃-mediated injury and which may
12 protect against subsequent O₃ challenge. The authors suggested that infant monkeys may
13 be prone to developing persistent necrotizing rhinitis following episodic longer-term
14 exposures.

5.4.2.5 Attenuation of Responses

15 Repeated daily exposure to O₃ often results in a reduction in the degree of a response,
16 i.e., an attenuation of response. This phenomenon may reflect compensatory mechanisms
17 and is not necessarily beneficial. Furthermore, there is variability among the different
18 O₃-related endpoints in terms of response attenuation, as will be described below. As a
19 result, attenuation of some responses occurs concomitantly with the exacerbation of
20 others.

21 In responsive individuals, a striking degree of attenuation of the FEV₁ response occurred
22 following repeated daily exposures to O₃. Generally, the young O₃ responder was no
23 longer responsive on the fourth or fifth day of consecutive daily O₃ exposure
24 (200-500 ppb O₃ for 2-4 hours with light to heavy levels of exercise) and required days to
25 weeks of non-exposure in order for the subject to regain O₃ responsiveness ([Christian et
26 al., 1998](#); [Devlin et al., 1997](#); [Linn et al., 1982b](#); [Horvath et al., 1981](#); [Hackney et al.,
27 1977b](#)). This phenomena has been reported for both lung function and symptoms such as
28 upper airway irritation, nonproductive cough, substernal discomfort and pain upon deep
29 inspiration ([Linn et al., 1982b](#); [Horvath et al., 1981](#); [Hackney et al., 1977b](#)). Repeated
30 daily exposures also led to an attenuation of the sRaw response in moderately exercising
31 human subjects exposed for 4 hours to 200 ppb O₃ ([Christian et al., 1998](#)) and to a
32 dampened AHR response compared with a single day exposure in light exercising human
33 subjects exposed for 2 hours to 400 ppb O₃ ([Dimeo et al., 1981](#)). However, one group
34 reported persistent small airway dysfunction despite attenuation of the FEV₁ response on

1 the third day of consecutive O₃ exposure (250 ppb, 2 hours, with moderate exercise)
2 ([Frank et al., 2001](#)).

3 Studies in rodents also indicated an attenuation of the physiologic response measured by
4 breathing patterns and tidal volume following five consecutive days of exposure to
5 0.35-1 ppm O₃ for 2.25 hours ([Tepper et al., 1989](#)). Attenuation of O₃-induced
6 bradycardic responses, which also result from activation of neural reflexes, has been
7 reported in rodents (0.5-0.6 ppm O₃, 2-6 h/day, 3-5 days ([Hamade and Tankersley, 2009](#);
8 [Watkinson et al., 2001](#)).

9 Multi-day exposure to O₃ has been found to decrease some markers of inflammation
10 compared with a single day exposure ([Christian et al., 1998](#); [Devlin et al., 1997](#)). For
11 example, in human subjects exposed for 4 hours to 200 ppb O₃ during moderate exercise,
12 decreased numbers of BAL neutrophils and decreased levels of BALF fibronectin and
13 IL-6 were observed after 4 days of consecutive exposure compared with responses after
14 1 day ([Christian et al., 1998](#)). Results indicated an attenuation of the inflammatory
15 response in both proximal airways and distal lung. However markers of injury, such as
16 lactate dehydrogenase (LDH) and protein in the BALF, were not attenuated in this study
17 ([Christian et al., 1998](#)). Other investigators found that repeated O₃ exposure (200 ppb O₃
18 for 4 hours on 4 consecutive days with light exercise) resulted in increased numbers of
19 neutrophils in bronchial mucosal biopsies despite decreased BAL neutrophilia ([Jorres et
20 al., 2000](#)). Other markers of inflammation, including BALF protein and IL-6 remained
21 elevated following the multi-day exposure ([Jorres et al., 2000](#)).

22 In rats, the increases in BALF levels of proteins, fibronectin, IL-6 and inflammatory cells
23 observed after one day of exposure to 0.4 ppm O₃ for 12 hours were no longer observed
24 after 5 consecutive days of exposure ([Van Bree et al., 2002](#)). A separate study in rats
25 exposed to 0.35-1 ppm O₃ for 2.25 hours for 5 consecutive days demonstrated a lack of
26 attenuation of the increase in BALF protein, persistence of macrophages in the
27 centriacinar region and histological evidence of progressive tissue injury ([Tepper et al.,
28 1989](#)). Findings that injury, measured by BALF markers or by histopathology, persist in
29 the absence of BAL neutrophilia or pulmonary function decrements suggested that
30 repeated exposure to O₃ may have serious long-term consequences such as airway
31 remodeling. In particular, the small airways were identified as a site where cumulative
32 injury may occur ([Frank et al., 2001](#)).

33 Some studies examined the recovery of responses which were attenuated by repeated O₃
34 exposure. In a study of humans undergoing heavy exercise who were exposed for 2 hours
35 to 400 ppb O₃ for five consecutive days ([Devlin et al., 1997](#)), recovery of the
36 inflammatory responses which were diminished by repeated exposure required
37 10-20 days following the exposure ([Devlin et al., 1997](#)). In an animal study conducted in

1 parallel ([Van Bree et al., 2002](#)), full susceptibility to O₃ challenge following exposure to
2 O₃ for five consecutive days required 15-20 days recovery.

3 Several mechanisms have been postulated to explain the attenuation of some responses
4 observed in human subjects and animal models following repeated exposure to O₃. First,
5 the upregulation of antioxidant defenses (or conversely, a decrease in critical O₃-reactive
6 substrates) may protect against O₃-mediated effects. Increases in antioxidant content of
7 the BALF have been demonstrated in rats exposed to 0.25 and 0.5 ppm O₃ for
8 several hours on consecutive days ([Devlin et al., 1997](#); [Wiester et al., 1996b](#); [Tepper et
9 al., 1989](#)). Second, IL-6 was demonstrated to be an important mediator of attenuation in
10 rats exposed to 0.5 ppm for 4 hours on two consecutive days ([Mckinney et al., 1998](#)).
11 Third, a protective role for increases in mucus producing cells and mucus concentrations
12 in the airways has been proposed ([Devlin et al., 1997](#)). Fourth, epithelial hyperplasia or
13 metaplasia may decrease further effects due to subsequent O₃ challenge ([Carey et al.,
14 2007](#); [Harkema et al., 1987a](#); [Harkema et al., 1987b](#)). These morphologic changes have
15 been observed in nasal and lower airways in monkeys exposed chronically to
16 0.15-0.5 ppm O₃ and reflect a persistent change in epithelial architecture which may lead
17 to other long-term sequelae. Although there is some evidence to support these
18 possibilities, there is no consensus on mechanisms underlying response attenuation.
19 Recent studies demonstrating that O₃ activates TRP receptors suggest that modulation of
20 TRP receptor number or sensitivity by repeated O₃ exposures may also contribute to the
21 attenuation of responses.

22 In summary, the attenuation of pulmonary function responses by repeated exposure to O₃
23 has been linked to exacerbation of O₃-mediated injury. Enhanced exposure to O₃ due to a
24 dampening of the O₃-mediated truncation of inspiration may be one factor which
25 contributes to this relationship.

5.4.2.6 Co-exposures with Particulate Matter

26 Numerous studies have investigated the effects of co-exposure to O₃ and PM because of
27 the prevalence of these pollutants in ambient air. Results are highly variable and depend
28 on whether exposures are simultaneous or sequential, the type of PM employed and the
29 endpoint examined. Additive and interactive effects have been demonstrated. For
30 example, simultaneous exposure to O₃ (120 ppb for 2 hours at rest) and concentrated
31 ambient particles (CAPs) in human subjects resulted in a diminished systemic IL-6
32 response compared with exposure to CAPs alone ([Urch et al., 2010](#)). However, exposure
33 to O₃ alone did not alter blood IL-6 levels ([Urch et al., 2010](#)). The authors provided
34 evidence that O₃ mediated a switch to shallow breathing which may have accounted for

1 the observed antagonism ([Urch et al., 2010](#)). Further, simultaneous exposure to O₃
2 (114 ppb for 2 hours at rest) and CAPs but not exposure to either alone, resulted in
3 increased diastolic blood pressure in human subjects ([Fakhri et al., 2009](#)). Mechanisms
4 underlying this potentiation of response were not explored. In some strains of mice,
5 pre-exposure to O₃ (0.5 ppm for 2 hours) modulated the effects of carbon black PM on
6 heart rate, HRV and breathing patterns ([Hamade and Tankersley, 2009](#)). Another recent
7 study in mice demonstrated that treatment with carbon nanotubes followed 12 hours later
8 by O₃ exposure (0.5 ppm for 3 hours) resulted in a dampening of some of the pulmonary
9 effects of carbon nanotubes measured as markers of inflammation and injury in the
10 BALF ([Han et al., 2008](#)). Further, [Harkema and Wagner \(2005\)](#) found that epithelial and
11 inflammatory responses in the airways of rats were enhanced by co-exposure to O₃
12 (0.5 ppm for 3 days) and LPS (used as a model of biogenic PM) or to O₃ (1 ppm for
13 2 days) and OVA (used as a model of an aeroallergen). Lastly, a recent study
14 demonstrated that maternal exposure to particulate matter (PM) resulted in augmented
15 lung inflammation, airway epithelial mucous metaplasia and AHR in young mice
16 exposed chronically and intermittently to 1 ppm O₃ ([Auten et al., 2009](#)).

17 In summary, many of the demonstrated responses to co-exposure were more than
18 additive. These findings are hard to interpret but demonstrate the complexity of responses
19 following combined exposure to PM and O₃.

5.4.2.7 Summary

20 Collectively, these earlier and more recent studies provide some evidence for
21 mechanisms that may underlie the variability in responsiveness seen among individuals
22 ([Figure 5-9](#)). Certain functional genetic polymorphisms, pre-existing conditions and
23 diseases, nutritional status, lifestage and co-exposures contribute to altered risk of
24 O₃-induced effects. Attenuation of responses may also be important, but it is
25 incompletely understood, both in terms of the pathways involved and the resulting
26 consequences.

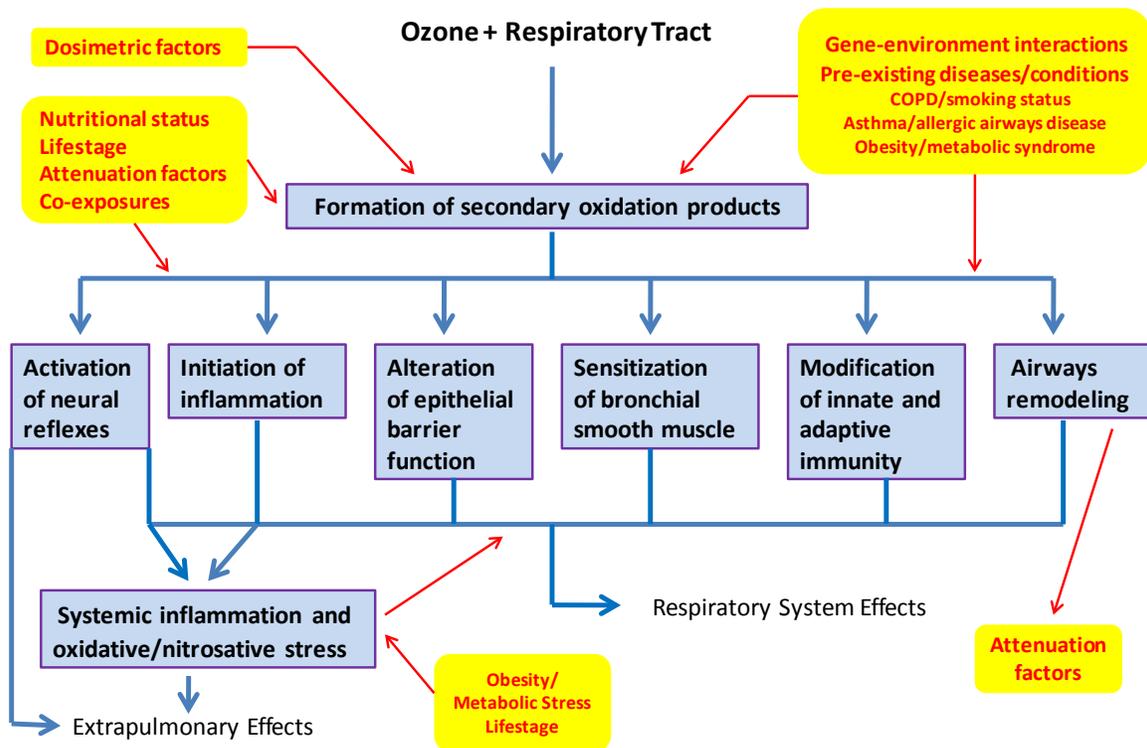


Figure 5-9 Some factors, illustrated in yellow, that likely contribute to the interindividual variability in responses resulting from inhalation of ozone.

5.5 Species Homology and Interspecies Sensitivity

1 The previous O₃ AQCDs discussed the suitability of animal models for comparison with
 2 human O₃ exposure and concluded that the acute and chronic functional responses of
 3 laboratory animals to O₃ appear qualitatively homologous to human responses. Thus,
 4 animal studies can provide important data in determining cause-effect relationships
 5 between exposure and health outcome that would be impossible to collect in human
 6 studies. Furthermore, animal studies add to a better understanding of the full range of
 7 potential O₃-mediated effects.

8 Still, care must be taken when comparing quantitative dose-response relationships in
 9 animal models to humans due to obvious interspecies differences. This section will
 10 qualitatively describe basic concepts in species homology concerning both dose and
 11 response to O₃ exposure. Overall, there have been few new publications examining
 12 interspecies differences in dosimetry and response to O₃ since the last AQCD. These
 13 studies do not overtly change the conclusions discussed in the previous document.

5.5.1 Interspecies Dosimetry

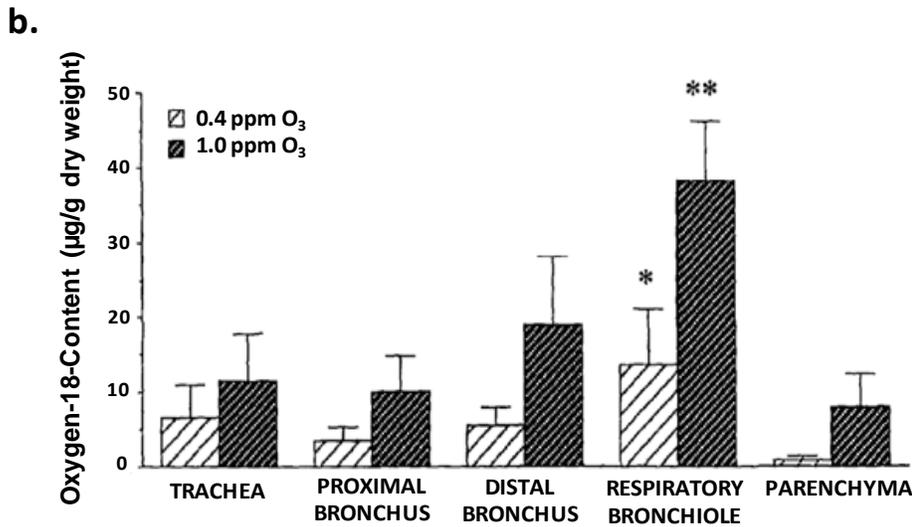
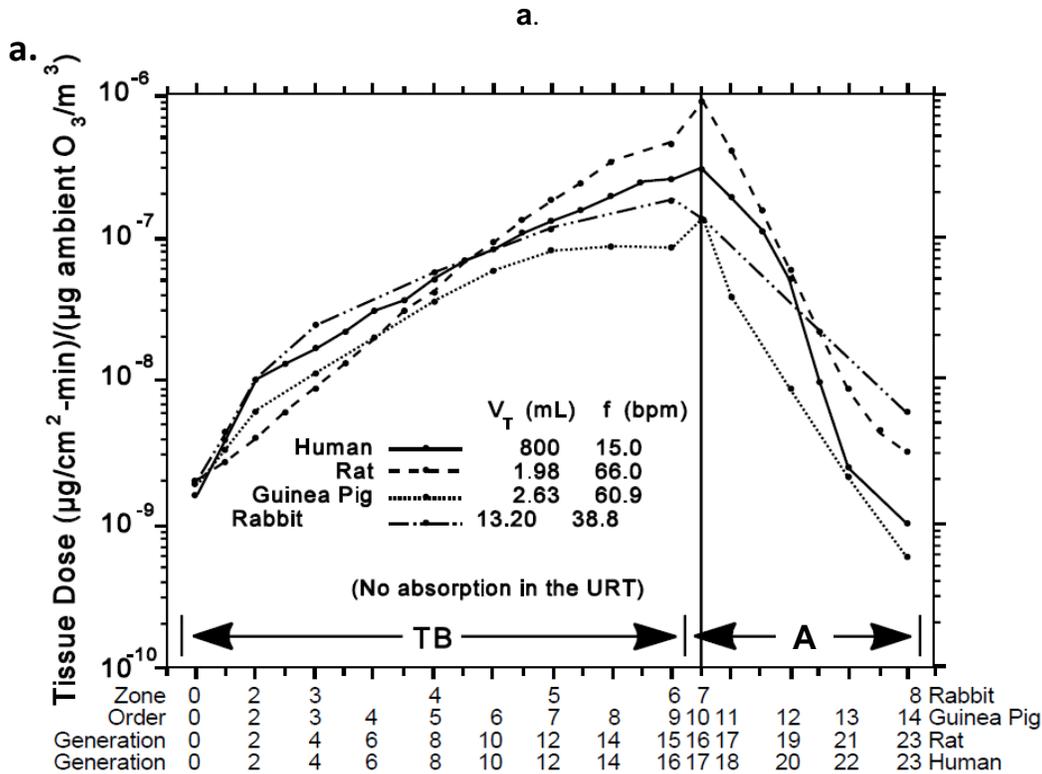
1 As discussed in Section [5.2.1](#), O₃ uptake depends on complex interactions between RT
2 morphology, breathing route, rate, and depth, physicochemical properties of the gas,
3 physical processes of gas transport, as well as the physical and chemical properties of the
4 ELF and tissue layers. Understanding differences in these variables between humans and
5 experimental animals is important to interpreting delivered doses in animal and human
6 toxicology studies.

7 Physiological and anatomical differences exist between experimental species. The
8 structure of the URT is vastly different between rodents and humans but scales according
9 to body mass. The difference in the cross-sectional shape and size of the nasal passages
10 affects bulk airflow patterns, particularly the shape of major airflow streams. The nasal
11 epithelium is lined by squamous, respiratory, or olfactory cells, depending on location.
12 The differences in airflow patterns in the URT mean that not all nasal surfaces and cell
13 types receive the same exposure to inhaled O₃ leading to differences in local absorption
14 and potential for site-specific tissue damage. The morphology of the LRT also varies
15 within and among species. Rats and mice do not possess respiratory bronchioles;
16 however, these structures are present in humans, dogs, ferrets, cats, and monkeys.
17 Respiratory bronchioles are abbreviated in hamsters, guinea pigs, sheep, and pigs. The
18 branching structure of the ciliated bronchi and bronchioles also differs between species
19 from being a rather symmetric and dichotomous branching network of airways in humans
20 and primates to a more monopodial branching network in other mammals. In addition,
21 rodents have fewer terminal bronchioles due to a smaller lung size compared to humans
22 or canines ([McBride, 1992](#)). The cellular composition in the pulmonary region is similar
23 across mammalian species; at least 95% of the alveolar epithelial tissue is composed of
24 Type I cells. However, considerable differences exist between species in the number and
25 type of cells in the TB airways. Differences also exist in breathing route and rate.
26 Primates are oronasal breathers, while rodents are obligate nasal breathers. Past studies of
27 the effect of body size on resting oxygen consumption also suggest that rodents inhale
28 more volume of air per lung mass than primates. These distinctions as well as differences
29 in nasal structure between primates and rodents affect the amount of O₃ uptake.

30 As O₃ absorption and reactivity relies on ELF antioxidant substances (see Section [5.2.3](#)),
31 variability in antioxidant concentrations and metabolism between species may affect dose
32 and O₃-induced health outcomes. The thickness of the ELF in the TB airways varies
33 among species. [Mercer et al. \(1992\)](#) found that the human ELF thickness in bronchi and
34 bronchioles was 6.9 and 1.8 μm, respectively, compared to 2.6 and 1.9 μm for the same
35 locations in the rat. Guinea pigs and mice have a lower basal activity of GSH transferase
36 and GSH peroxidase, and lower α-TOH levels in the lung compared to rats ([Ichinose et](#)

1 [al., 1988](#); [Sagai et al., 1987](#)). Nasal lavage fluid analysis shows that humans have a higher
2 proportion of their nasal antioxidants as UA and low levels of AH₂ whereas mice, rats, or
3 guinea pigs have high levels of AH₂ and undetectable levels of UA. GSH is not detected
4 in the nasal lavage of most of these species, but is present in monkey nasal lavage.
5 Guinea pigs and rats have a higher antioxidant to protein ratio in nasal lavage and BALF
6 than humans ([Hatch, 1992](#)). The BALF profile differs from the nasal lavage. Humans
7 have a higher proportion of GSH and less AH₂ making up their BALF content compared
8 to the guinea pigs and rats ([Slade et al., 1993](#); [Hatch, 1992](#)). Similar to the nose, rats have
9 the highest antioxidant to protein mass ratio found in BALF ([Slade et al., 1993](#)).
10 Antioxidant defenses also vary with age ([Servais et al., 2005](#)) and exposure history ([Duan](#)
11 [et al., 1996](#)). [Duan et al. \(1996\)](#); [Duan et al. \(1993\)](#) reported that differences in
12 antioxidant levels between species and lung regions did not appear to be the primary
13 factor in O₃ induced tissue injury. However, a close correlation between site-specific O₃
14 dose, the degree of epithelial injury, and reduced glutathione depletion was observed in
15 monkeys ([Plopper et al., 1998](#)).

16 Even with these differences humans and animals are similar in the pattern of regional O₃
17 dose distribution. As discussed for humans in Section [5.2.2](#), O₃ flux to the air-liquid
18 interface of the ELF slowly decreases distally in the TB region and then rapidly decreases
19 distally in the alveolar region ([Miller et al., 1985](#)). Modeled tissue dose in the human RT,
20 representing O₃ flux to the liquid-tissue interface, is very low in the trachea, increases to
21 a maximum in the CAR, and then rapidly decreases distally in the alveolar region
22 ([Figure 5-10](#)). Similar patterns of O₃ tissue dose profiles normalized to inhaled O₃
23 concentration were predicted for rat, guinea pig, and rabbit ([Miller et al., 1988](#); [Overton](#)
24 [et al., 1987](#)) ([Figure 5-10a](#)). [Overton et al. \(1987\)](#) modeled rat and guinea pig O₃ dose
25 distribution and found that after comparing two different morphometrically based
26 anatomical models for each species, considerable difference in predicted percent RT and
27 alveolar region uptakes were observed. This was due to the variability between the two
28 anatomical models in airway path distance to the first alveolated duct. As a result, the
29 overall dose profile was similar between species however the O₃ uptake efficiency varied
30 due to RT size and path length (Section [5.2.2](#)). A similar pattern of O₃ dose distribution
31 was measured in monkeys exposed to 0.4 and 1.0 ppm ¹⁸O₃ ([Plopper et al., 1998](#))
32 ([Figure 5-10b](#)). Less ¹⁸O was measured in the trachea, proximal bronchus, and distal
33 bronchus than was observed in the respiratory bronchioles. Again indicating the highest
34 concentration of O₃ tissue dose is localized to the CAR, which are the respiratory
35 bronchioles in nonhuman primates. In addition, the lowest ¹⁸O detected in the RT was in
36 the parenchyma (i.e., alveolar region), mimicking the rapid decrease in tissue O₃ dose
37 predicted by models for the alveolar regions of humans and other animals.

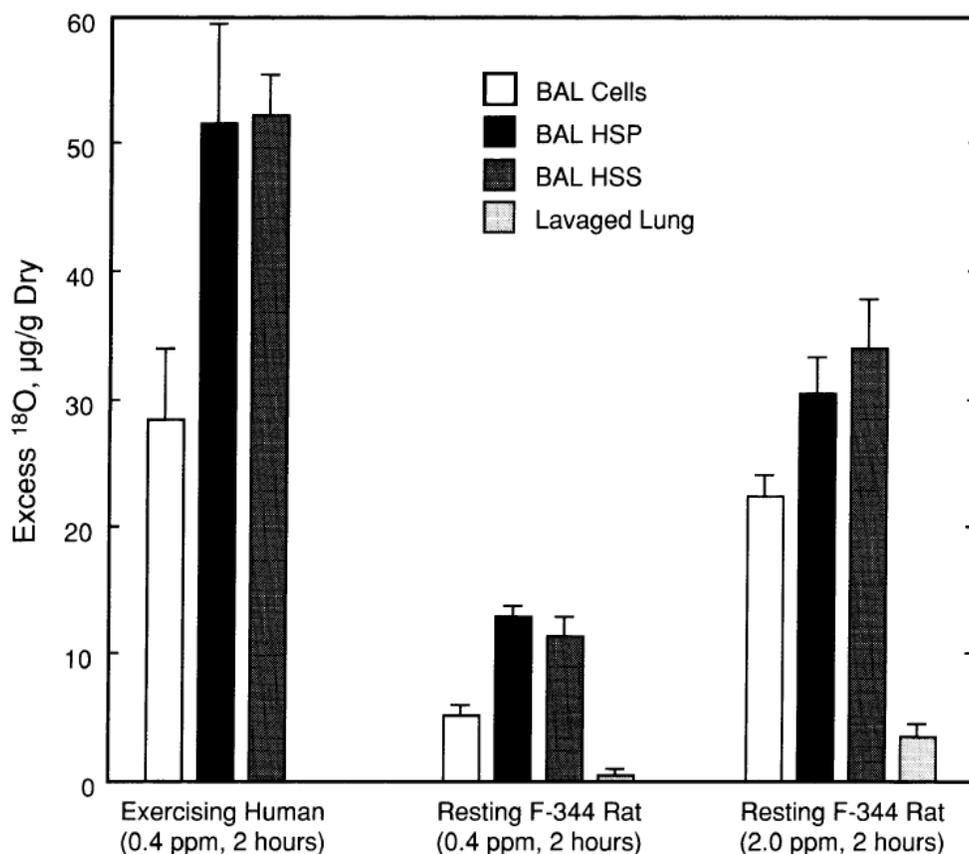


Note: Panel (a) presents the predicted tissue dose of O_3 (as μg of O_3 per cm^2 of segment surface area per min, standardized to a tracheal O_3 value of $1 \mu\text{g}/\text{m}^3$) for various regions of the rabbit, guinea pig, rat, and human RT. TB = tracheobronchial region, A = alveolar region. Panel (b) presents a comparison of excess ^{18}O in the five regions of the TB airways of rhesus monkeys exposed to O_3 for 2h. *p < 0.05 comparing the same O_3 concentration across regions. **p < 0.05 comparing different O_3 concentrations in the same region.

Source: Panel (a) [U.S. EPA \(1996a\)](#) (b) [Plopper et al. \(1998\)](#)

Figure 5-10 Humans and animals are similar in the regional pattern of ozone tissue dose distribution.

1 Humans and animal models are similar in the pattern of regional O₃ dose, but absolute
2 values differ. [Hatch et al. \(1994\)](#) reported that exercising humans exposed to oxygen-18
3 labeled O₃ (400 ppb) accumulated 4-5 times higher concentrations of O₃ reaction product
4 in BAL cells, surfactant and protein fractions compared to resting rats similarly exposed
5 (400 ppb) ([Figure 5-11](#)). The use of ¹⁸O was specifically employed in an attempt to
6 accurately measure O₃ dose to BALF fractions and lung tissue and was normalized to the
7 dried mass of lavaged constituents. It was necessary to expose resting rats to 2 ppm O₃ to
8 achieve the same BALF accumulation of ¹⁸O reaction product that was observed in
9 humans exposed to 400 ppb with intermittent heavy exercise ($\dot{V}_E \sim 60$ L/min). The
10 concentration of ¹⁸O reaction product in BALF paralleled the accumulation of BALF
11 protein and cellular effects of the O₃ exposure observed such that these responses to
12 2.0 ppm O₃ were similar to those of the 400 ppb O₃ in exercising humans. This suggests
13 that animal data obtained in resting conditions would underestimate the reaction of O₃
14 with cells in the RT and presumably the resultant risk of effect for humans. However
15 these results should be interpreted with caution given an important limitation in the ¹⁸O
16 labeling technique when used for interspecies comparisons. The reaction between O₃ and
17 some reactants such as ascorbate produce ¹⁸O-labeled products that are lost during sample
18 processing. When levels of ascorbate or other such reactants vary between species, this
19 lost portion of the total ¹⁸O-reaction products will also vary, leading to uncertainty in
20 interspecies comparisons.



Note: The excess ^{18}O in each fraction is expressed relative to the dry weight of that fraction. Fractions assayed include cells, high speed pellet (HSP), high speed supernatant (HSS), and lavaged lung homogenates.

Source: [Hatch et al. \(1994\)](#)

Figure 5-11 Oxygen-18 incorporation into different fractions of BALF from humans and rats exposed to 0.4 and 2.0 ppm $^{18}\text{O}_3$.

1 Recently, a quantitative comparison of O_3 transport in the airways of rats, dogs, and
 2 humans was conducted using a three-compartment airways model, based on upper and
 3 lower airway casts and mathematical calculation for alveolar parameters ([Tsujino et al.,
 4 2005](#)). This one-dimensional gas transport model examined how interspecies anatomical
 5 and physiological differences affect intra-airway O_3 concentrations and the amount of gas
 6 absorbed. The morphological model consisted of cylindrical tubes with constant volume
 7 and no airway branching patterns. Peak, real-time, and mean O_3 concentrations were
 8 higher in the upper and lower airways of humans compared to rats and dogs, but lowest
 9 in the alveoli of humans. The amount of O_3 absorbed was lowest in humans when
 10 normalized by body weight. The intra-airway concentration decreased distally in all
 11 species. Sensitivity analysis demonstrated that V_T , f_B , and upper and lower airways

1 surface area had a statistically significant impact on model results. The model is limited
2 in that it did not account for chemical reactions in the ELF or consider gas diffusion as a
3 driving force for O₃ transport. Also, the model was run at a respiratory rate of 16/min
4 simulating a resting individual, however exercise may cause a further deviation from
5 animal models as was seen in [Hatch et al. \(1994\)](#).

6 Overall, animal models exhibit qualitatively similar patterns of O₃ net and tissue dose
7 distribution with the largest tissue dose delivered to the CAR. However, due to
8 anatomical and biochemical RT differences the absolute values of O₃ dose delivered
9 differs. Past results suggest that animal data obtained in resting conditions would
10 underestimate the O₃ reactions with cells in the BALF and presumably the resultant risk
11 of effect for humans, especially for humans during exercise.

5.5.2 Interspecies Homology of Response

12 Biological response to O₃ exposure broadly shows commonalities in many species.
13 Among rodents, non-human primates, and humans, for example, ample data suggest that
14 O₃ induces oxidative stress, cell injury, upregulation of cytokines/chemokines,
15 inflammation, alterations in lung function, and disruption of normal lung growth and
16 development (See Chapters 6 and 7).

17 The effects related to early life exposures can differ appreciably across species due to the
18 maturation stage of the lung and immune systems at birth. Evidence from non-human
19 primate studies shows that early life O₃ exposure disrupts lung development producing
20 physiologic perturbations that are similar to those observed in children exposed to urban
21 air pollution ([Fanucchi et al., 2006](#); [Joad et al., 2006](#)). Studies of O₃ effects on lung
22 surface chemistry also show some degree of homology. Lipid oxidation products specific
23 to O₃ reactions with unsaturated fatty acids have been reported, for example, in lavage
24 fluids from both rodents and humans ([Frampton et al., 1999](#); [Pryor et al., 1996](#)). In
25 humans, the extent to which systemic effects occur is less well studied; plasma indices of
26 lipid oxidation such as isoprostanes unfortunately do not pinpoint the compartment(s)
27 where oxidative stress has transpired. That oxidative stress occurs systemically in both
28 rodents and non-human primates ([Chuang et al., 2009](#)), nevertheless, suggests that it
29 likely also occurs in humans.

30 Despite the overall similarities in responses to O₃ among species, studies have reported
31 variability in the responsiveness to O₃ between and within species, as well as between
32 endpoints. Rodents appear to have a slightly higher tachypneic response to O₃ and are
33 less sensitive to changes in pulmonary function responses than humans ([U.S. EPA,](#)
34 [1996a](#)). However, rats experience attenuation of pulmonary function and tachypneic

1 ventilatory responses, similar to humans ([Wiester et al., 1996b](#)). [Hatch et al. \(1986\)](#)
2 reported that guinea pigs were the most responsive to O₃-induced inflammatory cell and
3 protein influx. Rabbits were the least responsive and rats, hamsters, and mice were
4 intermediate responders. Further analysis of this study by [Miller et al. \(1988\)](#) found that
5 the protein levels in BALF from guinea pigs increased more rapidly with predicted
6 pulmonary tissue dose than in rats and rabbits. Alveolar macrophages isolated from
7 guinea pigs and humans mounted similar qualitative and quantitative cytokine responses
8 to in vitro O₃ (0.1-1.0 ppm for 60 minutes) exposure ([Arsalane et al., 1995](#)).

9 Also, because of their higher body surface to volume ratio, rodents can rapidly lower
10 body temperature during exposure leading to lowered O₃ dose and toxicity ([Watkinson et](#)
11 [al., 2003](#); [Iwasaki et al., 1998](#); [Slade et al., 1997](#)). In addition to lowering the O₃ dose to
12 the lungs, this hypothermic response may cause: (1) lower metabolic rate, (2) altered
13 enzyme kinetics, and (3) altered membrane function. The thermoregulatory mechanisms
14 also may affect disruption of heart rate that may lead to: (1) decreased cardiac output, (2)
15 lowered blood pressure, and (3) decreased tissue perfusion ([Watkinson et al., 2003](#)).
16 These responses have not been observed in humans except at very high exposures, thus
17 further complicating extrapolation of effects from animals to humans.

18 The degree to which O₃ induces injury and inflammation responses appears to be variable
19 between species. However, the majority of those studies did not normalize the response
20 to the dose received to account for species differences in O₃ absorption. For example,
21 [Dormans et al. \(1999\)](#) found that rats, mice, and guinea pigs all exhibited O₃-induced (0.2
22 - 0.4 ppm for 3-56 days) inflammation; however, guinea pigs were the most responsive
23 with respect to alveolar macrophage elicitation and pulmonary cell density in the
24 centriacinar region. Mice were the most responsive in terms of bronchiolar epithelial
25 hypertrophy and biochemical changes (e.g., LDH, glutathione reductase, glucose-
26 6-phosphate dehydrogenase activity), and had the slowest recovery from O₃ exposure. All
27 species displayed increased collagen in the ductal septa and large lamellar bodies in Type
28 II pneumocytes at the longest exposure and highest concentration; whereas this response
29 occurred in the rat and guinea pig at lower O₃ levels (0.2 ppm) as well. Overall, the
30 authors rated mice as most responsive, followed by guinea pigs, then rats ([Dormans et al.,](#)
31 [1999](#)). Rats were also less responsive in terms of epithelial necrosis and inflammatory
32 responses as a result of O₃ exposure (1.0 ppm for 8 hours) compared with monkeys and
33 ferrets, which manifested a similar response ([Sterner-Kock et al., 2000](#)). Results of this
34 study should be interpreted with caution since no dose metric was used to normalize the
35 total inhaled dose or local organ dose between species.

36 To further understand the genetic basis for age-dependent differential response to O₃,
37 adult (15 week old) and neonatal (15-16 day old) mice from 8 genetically diverse strains

1 were examined for O₃-induced (0.8 ppm for 5 hours) pulmonary injury and lung
2 inflammation ([Vancza et al., 2009](#)). Ozone exposure increased polymorphonuclear
3 leukocytes (PMN) influx in all strains of neonatal mice tested, but significantly greater
4 PMNs occurred in neonatal compared to adult mice for only some sensitive strains,
5 suggesting a genetic background effect. This strain difference was not due to differences
6 in delivered dose of O₃ to the lung, evidenced by ¹⁸O lung enrichment. The sensitivity of
7 strains for O₃-induced increases in BALF protein and PMNs was different for different
8 strains of mice suggesting that genetic factors contributed to heightened responses.
9 Interestingly, adult mice accumulated more than twice the levels of ¹⁸O reaction product
10 of O₃ than corresponding strain neonates. Thus, it appeared that the infant mice showed a
11 2-fold- to 3-fold higher response than the adults when expressed relative to the
12 accumulated O₃ reaction product in their lungs. The apparent decrease in delivered O₃
13 dose in neonates could be a result of a more rapid loss of body temperature in infant
14 rodents incident to maternal separation and chamber air flow.

15 In animal studies, inhaled O₃ concentration and exposure history rarely reflect actual
16 human environmental exposures. Generally, very high exposure concentrations are used
17 to induce murine AHR, which in some human subjects is observed at far more relevant
18 concentrations. This calls into question whether the differences in airway reactivity are
19 simply a function of differential nasopharyngeal scrubbing or whether the complexities
20 encompassing a variety of contributory biological pathways show species divergence.
21 Furthermore, in non-human primates exposed during early life, eosinophil trafficking
22 occurs, which has not been observed in rodents (unless sensitized) ([Maniar-Hew et al.,
23 2011](#)). This response has been shown to be persistent when O₃ challenges are
24 administered after a recovery period of ≥9 months during which no exposure transpired.

25 Quantitative extrapolation is challenging due to a number of uncertainties. Unfortunately,
26 many input parameters needed to conduct quantitative extrapolations across species have
27 not been obtained or currently remain undefined. It is not clear whether characterization
28 of the ELF provides the information needed to compute a profile of reaction products or
29 whether environmentally relevant exposure has altered the physicochemical interactions
30 that occur within the RT surface compartment (e.g., O₃ diffusion through regions where
31 the ELF is thin). That systemic effects have been documented in both rodents and non-
32 human primates leads to the question of whether reaction products,
33 cytokines/chemokines, or both enter the nasopharyngeal or bronchial circulation, both of
34 which show species-dependent differences ([Chuang et al., 2009](#); [Cole and Freeman,
35 2009](#)).

36 In addition, the response to O₃ insult across species and more recent health effects such as
37 immune system development are uncertain. Non-human primate studies have shown

1 hypo-responsiveness to endotoxin challenge as a consequence of exposure; whether this
2 occurs in rodents and humans is largely unknown ([Maniar-Hew et al., 2011](#)). In addition,
3 structural changes (e.g., airways remodeling, fibrogenesis) might differ appreciably
4 across species. Moreover, whether the upper airways differentially contribute to either
5 distal lung or systemic impacts has not been explored.

6 Some outcomes (e.g., inflammation) support the conclusion of homologous responses
7 across species. However, factors such as age, exposure history, diet, endogenous
8 substrate generation and homeostatic regulation, the cellular machinery that regulates
9 inflammatory cell trafficking, responses to other environmental challenges, and the
10 precise chemical species (whether ELF or cell membrane-derived) that account for
11 exposure-related initiation of pathophysiologic sequelae might differ across species, but
12 the extent of species-specific contributing factors remains unknown. Consequently, some
13 level of uncertainty cannot be dismissed. Nonetheless, if experimental animals show
14 pathophysiological consequences of exposure, assuming that qualitatively similar human
15 health impacts could occur is not unreasonable.

5.5.3 Summary

16 In summary, biological response to O₃ exposure broadly shows commonalities in many
17 species and thus supports the use of animal studies in determining mechanistic and cause-
18 effect relationships and as supporting evidence that similar effects could occur in humans
19 if O₃ exposure is sufficient. However, there is uncertainty regarding the similarity of
20 response to ozone across species for some recently described endpoints. Differences exist
21 between species in a number of factors that influence O₃ dosimetry and responses, such
22 as RT anatomy, breathing patterns, and ELF antioxidant concentrations and chemical
23 species. While humans and animals are similar in the pattern of regional O₃ dose
24 distribution, these differences will likely result in differences in the absolute values of
25 O₃ dose delivered throughout the RT. These considerations limit quantitative comparison
26 between species.

5.6 Chapter Summary

27 Ozone is a highly reactive gas and a powerful oxidant with a short half-life. Both O₃
28 uptake and responses are dependent upon the formation of secondary reaction products in
29 the ELF; however more complex interactions occur. Uptake in humans at rest is 80-95%
30 efficient and it is influenced by a number of factors including RT morphology, breathing
31 route, frequency, and volume, physicochemical properties of the gas, physical processes

1 of gas transport, as well as the physical and chemical properties of the ELF and tissue
2 layers. In fact, even though the average LRT dose may be at a level where health effects
3 would not be predicted, local regions of the RT may receive considerably higher than
4 average doses due to RT inhomogeneity and differences in the pathlengths, and therefore
5 be at greater risk of effects. The primary uptake site of O₃ delivery to the lung epithelium
6 is believed to be the CAR, however changes in a number of factors (e.g., physical
7 activity) can alter the distribution of O₃ uptake in the RT. Ozone uptake is chemical
8 reaction-dependent and the substances present in the ELF appear in most cases to limit
9 interaction of O₃ with underlying tissues and to prevent penetration of O₃ distally into the
10 RT. Still, reactions of O₃ with soluble ELF components or possibly plasma membranes
11 result in distinct products, some of which are highly reactive and can injure and/or
12 transmit signals to RT-cells.

13 Thus, in addition to contributing to the driving force for O₃ uptake, formation of
14 secondary oxidation products initiates pathways that provide the mechanistic basis for
15 health effects that are described in detail in Chapters 6 and 7 and that involve the RT as
16 well as extrapulmonary systems. These pathways include activation of neural reflexes,
17 initiation of inflammation, alteration of epithelial barrier function, sensitization of
18 bronchial smooth muscle, modification of innate and adaptive immunity, airways
19 remodeling, and systemic inflammation and oxidative/nitrosative stress. With the
20 exception of airways remodeling, these pathways have been demonstrated in both
21 animals and human subjects in response to the inhalation of O₃.

22 Both dosimetric and mechanistic factors contribute to the understanding of
23 interindividual variability in responses to O₃. This variability is influenced by differences
24 in RT volume and surface area, certain genetic polymorphisms, pre-existing conditions
25 and disease, nutritional status, lifestages, attenuation, and co-exposures. Some of these
26 factors also underlie differences in species homology and sensitivity. Qualitatively,
27 animal models exhibit similar patterns of O₃ net and tissue dose distribution with the
28 largest tissue dose of O₃ delivered to the CAR. However, due to anatomical and
29 biochemical RT differences, the absolute value of delivered O₃ dose differs, with animal
30 data obtained in resting conditions underestimating the dose to the RT and presumably
31 the resultant risk of effect for humans, especially humans during exercise. Even though
32 interspecies differences limit quantitative comparison between species, many short-term
33 responses of laboratory animals to O₃ appear qualitatively homologous to those of the
34 human. Furthermore, animal studies add to a better understanding of the full range of
35 potential O₃-mediated effects. Given the commonalities in many responses across
36 species, animal studies that observe O₃-induced effects may be used as supporting
37 evidence that similar effects could occur in humans or in determining mechanistic and
38 cause-effect relationships if O₃ exposure is sufficient.

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6 INTEGRATED HEALTH EFFECTS OF SHORT-TERM OZONE EXPOSURE

6.1 Introduction

1 This chapter reviews, summarizes, and integrates the evidence for various health
2 outcomes associated with short-term (i.e., hours, days, or weeks) exposures to O₃.
3 Numerous controlled human exposure, epidemiologic, and toxicological studies have
4 permitted evaluation of the relationships between short-term O₃ exposure and a range of
5 endpoints related to respiratory effects (Section [6.2](#)), cardiovascular effects (Section [6.3](#)),
6 and mortality (Section [6.2](#), Section [6.3](#), and Section [6.6](#)). A smaller number of studies
7 were available to assess the effects of O₃ exposure on other physiological systems such as
8 the central nervous system (Section [6.4](#)), liver and metabolism (Section [6.5.1](#)), and
9 cutaneous and ocular tissues (Section [6.5.2](#)). This chapter evaluates the majority of recent
10 (i.e., published since the completion of the 2006 O₃ AQCD) short-term exposure studies;
11 however, those for birth outcomes and infant mortality are evaluated in Chapter [7](#)
12 (Section [7.4](#)), because they compare associations among overlapping short- and long-
13 term exposure windows that are difficult to distinguish.

14 Within each individual section of this chapter, a brief summary of conclusions from the
15 2006 O₃ AQCD is included along with an evaluation of recent evidence that is intended
16 to build upon the body of evidence from previous reviews. The studies evaluated are
17 organized by health endpoint (e.g., lung function, pulmonary inflammation) then by
18 scientific discipline (e.g., controlled human exposure, epidemiology, and toxicology).
19 Each major section (e.g., respiratory, cardiovascular, mortality) concludes with an
20 integrated summary of the findings and a conclusion regarding causality based upon the
21 framework described in the Preamble to this ISA. The causal determinations are
22 presented for a broad health effect category, such as respiratory effects, with coherence
23 and plausibility based on the total evidence available across disciplines and across the
24 suite of related health endpoints, including cause-specific mortality.

6.2 Respiratory Effects

25 Based on evidence integrated across controlled human exposure, epidemiologic, and
26 toxicological studies, the 2006 O₃ AQCD concluded “that acute O₃ exposure is causally
27 associated with respiratory system effects” ([U.S. EPA, 2006b](#)). Contributing to this
28 conclusion were the consistency and coherence across scientific disciplines for the effects

1 of short-term O₃ exposure on a variety of respiratory outcomes including “pulmonary
2 function decrements, respiratory symptoms, lung inflammation, and increased lung
3 permeability, airway hyperresponsiveness.” Collectively, these findings provided
4 biological plausibility for associations in epidemiologic studies observed between short-
5 term increases in ambient O₃ concentration and increases in respiratory symptoms and
6 respiratory-related hospitalizations and emergency department (ED) visits.

7 Controlled human exposure studies have provided strong and quantifiable exposure-
8 response data on the human health effects of O₃. The most salient observations from
9 studies reviewed in the 1996 and 2006 O₃ AQCDs ([U.S. EPA, 2006b](#), [1996a](#)) included:
10 (1) young healthy adults exposed to O₃ concentrations ≥ 80 ppb develop significant
11 reversible, transient decrements in pulmonary function and symptoms of breathing
12 discomfort if minute ventilation (\dot{V}_E) or duration of exposure is increased sufficiently;
13 (2) relative to young adults, children experience similar spirometric responses but lower
14 incidence of symptoms from O₃ exposure; (3) relative to young adults, O₃-induced
15 spirometric responses are decreased in older individuals; (4) there is a large degree of
16 intersubject variability in physiologic and symptomatic responses to O₃, but responses
17 tend to be reproducible within a given individual over a period of several months; (5)
18 subjects exposed repeatedly to O₃ for several days experience an attenuation of
19 spirometric and symptomatic responses on successive exposures, which is lost after about
20 a week without exposure; and (6) acute O₃ exposure initiates an inflammatory response
21 that may persist for at least 18 to 24 hours postexposure.

22 Substantial evidence for biologically plausible O₃-induced respiratory morbidity has been
23 derived from the coherence between toxicological and controlled human exposure study
24 findings for parallel endpoints. For example, O₃-induced lung function decrements and
25 increased airway hyperresponsiveness have been observed in both animals and humans.
26 Airway hyperresponsiveness could be an important consequence of exposure to ambient
27 O₃ because the airways are then predisposed to narrowing upon inhalation of a variety of
28 ambient stimuli. Additional airway hyperresponsiveness tends to resolve more slowly and
29 appears less subject to attenuation with repeated exposures than lung function
30 decrements. Increased permeability and inflammation have been observed in the airways
31 of humans and animals alike after O₃ exposure, although these processes are not
32 necessarily associated with immediate changes in lung function or hyperresponsiveness.
33 Furthermore, the potential relationship between repetitive bouts of acute inflammation
34 and the development of chronic respiratory disease is unknown. Another feature of
35 O₃-related respiratory morbidity is impaired host defense and reduced resistance to lung
36 infection, which has been strongly supported by toxicological evidence and, to a limited
37 extent, by evidence from controlled human exposure studies. Recurrent respiratory
38 infection in early life is associated with increased incidence of asthma in humans.

1 In concordance with experimental studies, epidemiologic studies have provided clear
2 evidence for decrements in lung function related to short-term ambient O₃ exposure.
3 These effects were demonstrated in healthy children attending camps, adults exercising or
4 working outdoors, and children with and without asthma ([U.S. EPA, 2006b](#), [1996a](#)). In
5 addition to lung function decrements, short-term increases in ambient O₃ concentration
6 were associated with increases in respiratory symptoms (e.g., cough, wheeze, shortness of
7 breath), notably in large U.S. panel studies of children with asthma ([Gent et al., 2003](#);
8 [Mortimer et al., 2000](#)). The evidence across disciplines for O₃ effects on a range of
9 respiratory endpoints collectively provides support for epidemiologic studies that have
10 demonstrated consistent associations between short-term increases in ambient O₃
11 concentration and increases in respiratory hospital admissions and ED visits, specifically
12 during the summer or warm months. In contrast with other respiratory health endpoints,
13 epidemiologic evidence did not clearly support a relationship between short-term O₃
14 exposure and respiratory mortality. Although O₃ was consistently associated with
15 nonaccidental and cardiopulmonary mortality, the contribution of respiratory causes to
16 these findings was uncertain as the few studies that examined mortality specifically from
17 respiratory causes reported inconsistent associations with ambient O₃ concentrations.

18 As will be discussed throughout this section, consistent with the strong body of evidence
19 presented in the 2006 O₃ AQCD, recent studies continue to support associations between
20 short-term O₃ exposure and respiratory effects, in particular, lung function decrements in
21 controlled human exposure studies, airway inflammatory responses in toxicological
22 studies, and respiratory-related hospitalizations and ED visits. Recent epidemiologic
23 studies contribute new evidence for potentially at-risk populations and associations
24 linking ambient O₃ concentrations with biological markers of airway inflammation and
25 oxidative stress, which is consistent with the extensive evidence from controlled human
26 exposure and toxicological studies. Furthermore, extending the potential range of
27 well-established O₃-associated respiratory effects, recent multicity studies and a
28 multicontinent study demonstrate associations between short-term increases in ambient
29 O₃ concentration and respiratory-related mortality.

6.2.1 Lung Function

6.2.1.1 Controlled Human Exposure

30 This section focuses on studies examining O₃ effects on lung function and respiratory
31 symptoms in volunteers exposed, for periods of up to 8 hours, to O₃ concentrations
32 ranging from 40 to 500 ppb, while at rest or during exercise of varying intensity.

1 Responses to acute O₃ exposures in the range of ambient concentrations include
2 decreased inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing
3 patterns during exercise; and symptoms of cough and pain on deep inspiration (PDI).
4 Reflex inhibition of inspiration results in a decrease in forced vital capacity (FVC) and
5 total lung capacity (TLC) and, in combination with mild bronchoconstriction, contributes
6 to a decrease in the forced expiratory volume in 1 second (FEV₁).

7 In studies that have exposed subjects during exercise, the majority of shorter duration
8 (≤ 4-hour exposures) studies utilized an intermittent exercise protocol in which subjects
9 rotated between 15-minute periods of exercise and rest. A limited number of 1- to 2-hour
10 studies, mainly focusing on exercise performance, have utilized a continuous exercise
11 regime. A quasi continuous exercise protocol is common to prolonged exposure studies
12 where subjects complete 50-minute periods of exercise followed by 10-minute rest
13 periods.

14 The majority of controlled human exposure studies have been conducted within exposure
15 chambers, although a smaller number of studies used a facemask to expose subjects to
16 O₃. Little effort has been made herein to differentiate between facemask and chamber
17 exposures since FEV₁ and respiratory symptom responses appear minimally affected by
18 these exposure modalities. Similar responses between facemask and chamber exposures
19 have been reported for exposures to 80 and 120 ppb O₃ (6.6-hour, moderate quasi
20 continuous exercise, 40 L/min) and 300 ppb O₃ (2 h, heavy intermittent exercise, 70
21 L/min) ([Adams, 2003a, b, 2002](#)).

22 The majority of controlled human exposure studies investigating the effects O₃ are of a
23 randomized, controlled, crossover design in which subjects were exposed, without
24 knowledge of the exposure condition and in random order to clean filtered air (FA; the
25 control) and, depending on the study, to one or more O₃ concentrations. The FA control
26 exposure provides an unbiased estimate of the effects of the experimental procedures on
27 the outcome(s) of interest. Comparison of responses following this FA exposure to those
28 following an O₃ exposure allows for estimation of the effects of O₃ itself on an outcome
29 measurement while controlling for independent effects of the experimental procedures.
30 As individuals may experience small changes in various health endpoints from exercise,
31 diurnal variation, or other effects in addition to those of O₃ during the course of an
32 exposure, the term “O₃-induced” is used herein to designate effects that have been
33 corrected or adjusted for such extraneous responses as measured during FA exposures.

34 Spirometry, viz., FEV₁, is a common health endpoint used to assess effects of O₃ on
35 respiratory health in controlled human exposure studies. In considering 6.6-hour
36 exposures to FA, group mean FEV₁ changes have ranged from -0.7% ([McDonnell et al.,
37 1991](#)) to 2.7% ([Adams, 2006a](#)). On average, across ten 6.6-hour exposure studies, there

1 has been a 1.0% (n = 279) increase in FEV₁ ([Kim et al., 2011](#); [Schelegle et al., 2009](#);
2 [Adams, 2006a, 2003a, 2002](#); [Adams and Ollison, 1997](#); [Folinsbee et al., 1994](#);
3 [McDonnell et al., 1991](#); [Horstman et al., 1990](#); [Folinsbee et al., 1988](#)). Regardless of the
4 reason for small changes in FEV₁ over the course of FA exposures, whether biologically
5 based or a systematic effect of the experimental procedures, the use of FA responses as a
6 control for the assessment of responses following O₃ exposure in randomized exposure
7 studies serves to eliminate alternative explanations other than those of O₃ itself in causing
8 the measured responses.

9 Considering FEV₁ responses in young healthy adults, an O₃-induced change in FEV₁ is
10 typically the difference between the decrement observed with O₃ exposure and the
11 improvement observed with FA exposure. Noting that some healthy individuals
12 experience small improvements while others have small decrements in FEV₁ following
13 FA exposure, investigators have used the randomized, crossover design with each subject
14 serving as their own control (exposure to FA) to discern relatively small effects with
15 certainty since alternative explanations for these effects are controlled for by the nature of
16 the experimental design. The utility of intraindividual FA control exposures becomes
17 more apparent when considering individuals with respiratory disease. The occurrence of
18 exercise-induced bronchospasm is well recognized in patients with asthma and COPD
19 and may be experienced during both FA and O₃ exposures. Absent correction for FA
20 responses, exercise-induced changes in FEV₁ could be mistaken for responses due to O₃.
21 This biological phenomenon serves as an example to emphasize the need for a proper
22 control exposure in assessing the effects of O₃ as well as the role of this control in
23 eliminating the influence of other factors on the outcomes of interest.

Pulmonary Function Effects of Ozone Exposure in Healthy Subjects

Acute Exposure of Healthy Subjects

24 The majority of controlled human exposure studies have investigated the effects of
25 exposure to O₃ in young healthy nonsmoking adults (18-35 years of age). These studies
26 typically use fixed concentrations of O₃ under carefully regulated environmental
27 conditions and subject activity levels. The magnitude of respiratory effects (decrements
28 in spirometry measurements and increases in symptomatic response) in these individuals
29 is a function of O₃ concentration (C), minute ventilation (\dot{V}_E), and exposure duration
30 (time). Any physical activity will increase minute ventilation and therefore the dose of
31 inhaled O₃. Dose of inhaled O₃ to the lower airways is also increased due to a shift from
32 nasal to oronasal breathing with a consequential decrease in O₃ scrubbing by the upper
33 airways. Thus, the intensity of physiological response following an acute exposure will
34 be strongly associated with minute ventilation.

1 The product of $C \times \dot{V}_E \times \text{time}$ is commonly used as a surrogate for O_3 dose to the
2 respiratory tract in controlled human exposure studies. A large body of data regarding the
3 interdependent effects of C , \dot{V}_E , and time on pulmonary responses was assessed in the
4 1986 and 1996 O_3 AQCDs ([U.S. EPA, 1996a, 1986](#)). Acute responses were modeled as a
5 function of total inhaled dose ($C \times \dot{V}_E \times \text{time}$) which was found to be a better predictor of
6 response to O_3 than C , \dot{V}_E , or time of exposure, alone, or as a combination of any two of
7 these factors. However, intake dose ($C \times \dot{V}_E \times \text{time}$) did not adequately capture the
8 temporal dynamics of pulmonary responses in a comparison between a constant (square-
9 wave) and a variable (triangular) O_3 exposure (average 120 ppb O_3 ; moderate exercise,
10 $\dot{V}_E = 40$ L/min; 8 hour duration) conducted by [Hazucha et al. \(1992\)](#). Recent nonlinear
11 statistical models clearly describe the temporal dynamics of FEV₁ responses as a function
12 of C , \dot{V}_E , time, and age of the exposed subject ([McDonnell et al., 2010, 2007](#)).

13 For healthy young adults exposed at rest for 2 hours, 500 ppb is the lowest O_3
14 concentration reported to produce a statistically significant O_3 -induced group mean FEV₁
15 decrement of 6.4% (n = 10) ([Folinsbee et al., 1978](#)) to 6.7% (n = 13) ([Horvath et al.,](#)
16 [1979](#)). Airway resistance was not clearly affected during at-rest exposure to these
17 O_3 concentrations. For exposures of 1-2 hours to ≥ 120 ppb O_3 , statistically significant
18 symptomatic responses and effects on FEV₁ are observed when \dot{V}_E is sufficiently
19 increased by exercise ([McDonnell et al., 1999b](#)). For instance, 5% of young healthy
20 adults exposed to 400 ppb O_3 for 2 hours during rest experienced pain on deep
21 inspiration. Respiratory symptoms were not observed at lower exposure concentrations
22 (120-300 ppb) or with only 1 hour of exposure even at 400 ppb. However, when exposed
23 to 120 ppb O_3 for 2 hours during light-to-moderate intermittent exercise (\dot{V}_E of 22 -
24 35 L/min), 9% of individuals experienced pain on deep inspiration, 5% experienced
25 cough, and 4% experienced shortness of breath. With very heavy continuous exercise
26 ($\dot{V}_E = 89$ L/min), an O_3 -induced group mean decrement of 9.7% in FEV₁ has been reported
27 for healthy young adults exposed for 1 hour to 120 ppb O_3 ([Gong et al., 1986](#)). Symptoms
28 are present and decrements in forced expiratory volumes and flows occur at 160-240 ppb
29 O_3 following 1 hour of continuous heavy exercise ($\dot{V}_E \approx 55$ to 90 L/min ([Gong et al.,](#)
30 [1986](#); [Avol et al., 1984](#); [Folinsbee et al., 1984](#); [Adams and Schelegle, 1983](#)) and
31 following 2 hours of intermittent heavy exercise ($\dot{V}_E \approx 65$ -68 L/min) ([Linn et al., 1986](#);
32 [Kulle et al., 1985](#); [McDonnell et al., 1983](#)). With heavy intermittent exercise (15-min
33 intervals of rest and exercise [$\dot{V}_E = 68$ L/min]), symptoms of breathing discomfort and a
34 group mean O_3 -induced decrement of 3.4% in FEV₁ occurred in young healthy adults
35 exposed for 2 hours to 120 ppb O_3 ([McDonnell et al., 1983](#)).¹ [Table 6-1](#) provides
36 examples of typical exercise protocols utilized in controlled human exposures to O_3 . The

¹ In total, subjects were exposed to O_3 for 2.5 hours. Intermittent exercise periods, however, were only conducted for the first 2 hours of exposure and FEV₁ was determined 5 minutes after the exercise was completed.

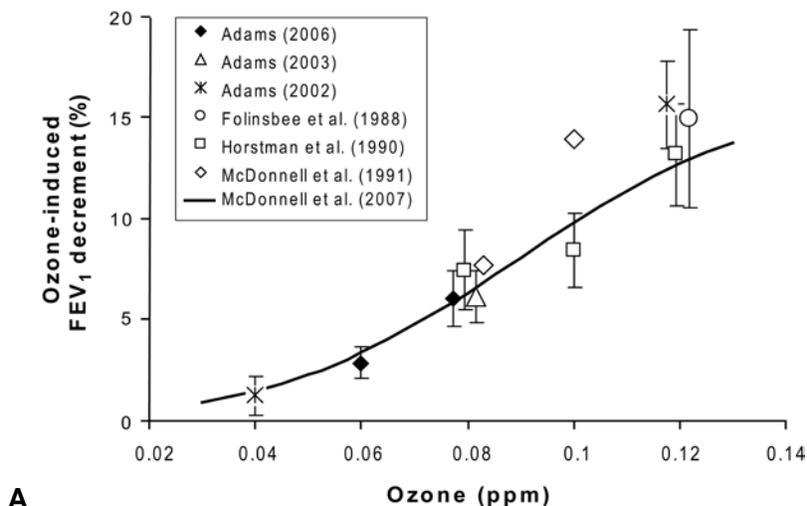
1 \dot{V}_E rates in this table are per body surface area (BSA) which is, on average, about 1.7 m²
 2 and 2.0 m² for young healthy adult females and males, respectively, who participated in
 3 controlled O₃ exposure studies.

Table 6-1 Activity levels used in controlled exposures of healthy young adults to ozone.

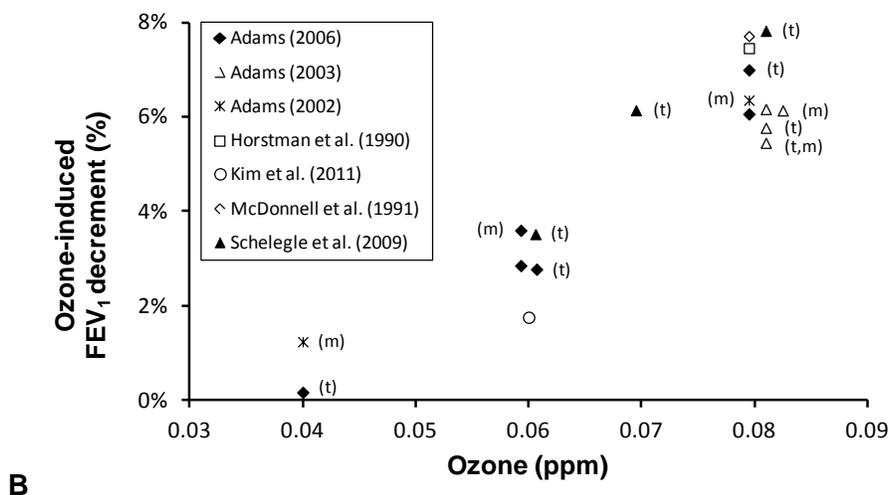
| Activity ^{a,b} | Study Duration (hours) | \dot{V}_E (L/min per m ² BSA) | Heart Rate (bpm) | Treadmill Speed (mph) | Treadmill Grade (%) | Cycle (watts) |
|------------------------------------|------------------------|--|------------------|-----------------------|---------------------|---------------|
| Rest | 2 | 4 | 70 | n.a. | n.a. | n.a. |
| Light quasi-continuous exercise | 6.6-7.6 | 15 | 110 | 3.5-4.4 | 0 | 42 |
| Moderate quasi-continuous exercise | 6.6 | 17-23 | 115-130 | 3.3-3.5 | 4-5 | 72 |
| Heavy intermittent exercise | 1-2 | 27-33 | 160 | 3.5-5 | 10 | 100 |
| Very heavy continuous exercise | 1 | 45 | 160 | n.a. | n.a. | 260 |

^aBased on group mean exercise specific data provided in the individual studies. On average, subjects were 23 years of age. For exercise protocols, the minute ventilation and heart rate are for the exercise periods. Quasi-continuous exercise consists of 50 minutes of exercise periods followed by 10 minutes of rest. Intermittent exercise consists of alternating periods of 15 minutes of exercise and 15 minutes of rest.

^bReferences: [Horvath et al. \(1979\)](#) for rest; [Adams \(2000\)](#) and [Horstman et al. \(1995\)](#) for light quasi-continuous exercise, [2006a](#)); ([2002, 2000](#)), [Folinsbee et al. \(1988\)](#), [Horstman et al. \(1990\)](#), and [McDonnell et al. \(1991\)](#) for moderate quasi-continuous exercise; [Kehrl et al. \(1987\)](#), [Kreit et al. \(1989\)](#), and [McDonnell et al. \(1983\)](#) for heavy intermittent exercise, and [Gong et al. \(1986\)](#) for very heavy continuous exercise.



Source: [Brown et al. \(2008\)](#).



Top, panel A: All studies exposed subjects to a constant (square-wave) concentration in a chamber, except [Adams \(2002\)](#) where a facemask was used. All responses at and above 0.06 ppm were statistically significant. The [McDonnell et al. \(2007\)](#) curve illustrates the predicted FEV₁ decrement at 6.6 hours as a function of O₃ concentration for a 23 year-old (the average age of subjects that participated in the illustrated studies). Note that this curve was not “fitted” to the plotted data. Error bars (where available) are the standard error of responses.

Bottom, panel B: All studies used constant (square-wave) exposures in a chamber unless designated as triangular (t) and/or facemask (m) exposures. All responses at and above 0.07 ppm were statistically significant. At 0.06 ppm, [Adams \(2006a\)](#) and [Kim et al. \(2011\)](#) responses to square-wave chamber exposures were statistically significant. During each hour of the exposures, subjects were engaged in moderate quasi continuous exercise (40 L/min) for 50 minutes and rest for 10 minutes. Following the third hour, subjects had an additional 35-minute rest period for lunch. The data at 0.06, 0.08 and 0.12 ppm have been offset for illustrative purposes.

Studies appearing in the figure legends: [Adams \(2006a\)](#); [\(2003a, 2002\)](#), [Folinsbee et al. \(1988\)](#), [Horstman et al. \(1990\)](#), [\(Kim et al., 2011, 2007\)](#); [\(1991\)](#), and [Schelegle et al. \(2009\)](#).

Figure 6-1 Cross-study comparison of mean ozone-induced FEV₁ decrements following 6.6 hours of exposure to ozone.

1 For prolonged (6.6 hours) exposures relative to shorter exposures, significant pulmonary
2 function responses and symptoms have been observed at lower O₃ concentrations and at a
3 moderate level of exercise ($\dot{V}_E = 40$ L/min). The 6.6-hour experimental protocol was
4 intended to simulate the performance of heavy physical labor for a full workday
5 ([Folinsbee et al., 1988](#)). The results from studies using 6.6 hours of constant or square-
6 wave exposures to between 40 and 120 ppb O₃ are illustrated in [Figure 6-1\(A\)](#).
7 [Figure 6-1\(B\)](#) focuses on the range from 40 to 80 ppb and includes triangular exposure
8 protocols as well as facemask exposures. Exposure to 40 ppb O₃ for 6.6 hours produces
9 small, statistically nonsignificant changes in FEV₁ that are relatively similar to responses
10 from FA exposure ([Adams, 2002](#)). Volunteers exposed to 60 ppb O₃ experience group
11 mean O₃-induced FEV₁ decrements of about 3% ([Kim et al., 2011](#); [Brown et al., 2008](#);
12 [Adams, 2006a](#))¹; those exposed to 80 ppb have group mean decrements that range from 6
13 to 8% ([Adams, 2006a, 2003a](#); [McDonnell et al., 1991](#); [Horstman et al., 1990](#)); at 100 ppb,
14 group mean decrements range from 8 to 14% ([McDonnell et al., 1991](#); [Horstman et al.,](#)
15 [1990](#)); and at 120 ppb, group mean decrements of 13 to 16% are observed ([Adams, 2002](#);
16 [Horstman et al., 1990](#); [Folinsbee et al., 1988](#)). As illustrated in [Figure 6-1](#), there is a
17 smooth intake dose-response curve without evidence of a threshold for exposures
18 between 40 and 120 ppb O₃. This is consistent with [Hazucha and Lefohn \(2007\)](#), who
19 suggested that a randomly selected group of healthy individuals of sufficient size would
20 include hypo-, normo-, and hyper-responsive individuals such that the average response
21 would show no threshold for any spirometric endpoint. Taken together, these data
22 indicate that mean FEV₁ is clearly decreased by 6.6-hour exposures to 60 ppb O₃ and
23 higher concentrations in subjects performing moderate exercise.

24 The time course of responses during prolonged (6.6 hours) square-wave O₃ exposures
25 with moderate exercise ($\dot{V}_E = 40$ L/min) depends on O₃ concentration. At 120 ppb O₃,
26 [Folinsbee et al. \(1988\)](#) observed that somewhat small FEV₁ decrements and symptoms of
27 breathing discomfort become apparent in healthy subjects following the second hour of
28 exposure with a more rapid change in responses between the 3rd and 5th hour of
29 exposure and a diminishing response or plateau in responses over the last hour of
30 exposure. Relative to FA, the change in FEV₁ at 120 ppb O₃ became statistically
31 significant after 4.6 hours. Following the same exposure protocol, [Horstman et al. \(1990\)](#)
32 observed a linear increase in FEV₁ responses with time following 2 hours of exposure to
33 120 ppb O₃ that was statistically different from FA responses after 3 h. At 100 ppb O₃,
34 FEV₁ responses diverged from FA after 3 hours and were statistically different at 4.6
35 hours ([Horstman et al., 1990](#)). At 80 ppb O₃, FEV₁ responses diverged from FA after 4.6

¹ [Adams \(2006b\)](#) did not find effects on FEV₁ at 60 ppb to be statistically significant. In an analysis of the [Adams \(2006b\)](#) data, even after removal of potential outliers, [Brown et al. \(2008\)](#) found the average effect on FEV₁ at 60 ppb to be small, but highly statistically significant ($p < 0.002$) using several common statistical tests.

1 hours and were statistically different from FA at 5.6 hours ([Horstman et al., 1990](#)).
2 Subsequently, [Adams \(2006a\)](#) observed FEV₁ decrements and total respiratory symptoms
3 at 80 ppb O₃ to diverge from FA responses after 3 h, but did not become statistically
4 different until 6.6 hours. At 60 ppb O₃, FEV₁ responses generally tracked responses in FA
5 for the first 4.6 hours of exposure and diverged after 5.6 hours ([Adams, 2006a](#)). FEV₁
6 responses, but not symptomatic responses, become statistically different between 60 ppb
7 O₃ and FA at 6.6 hours ([Kim et al., 2011](#); [Brown et al., 2008](#)). At 40 ppb, FEV₁ and
8 symptomatic responses track FA for 5.6 hours of exposure and may begin to diverge after
9 6.6 hours ([Adams, 2002](#)). In prolonged (6.6 hours) square-wave O₃ exposures between 40
10 and 120 ppb with moderate exercise ($\dot{V}_E = 40$ L/min), the time required for group mean
11 responses to differ between O₃ and FA exposures increases with decreasing O₃
12 concentration.

13 As opposed to constant (i.e., square-wave) concentration patterns used in the studies
14 described above, many studies conducted at the levels of 40-80 ppb have used variable
15 O₃ concentration patterns. It has been suggested that a triangular (variable concentration)
16 exposure profile can potentially lead to higher FEV₁ responses than square-wave profiles
17 despite having the same average O₃ concentration over the exposure period. [Hazucha et](#)
18 [al. \(1992\)](#) were the first to investigate the effects of variable versus constant
19 concentration exposures on responsiveness to O₃. In their study, volunteers were
20 randomly exposed to a triangular concentration profile (averaging 120 ppb over the
21 8-hour exposure) that increased linearly from 0-240 ppb for the first 4 hours of the 8-hour
22 exposure, then decreased linearly from 240 to 0 ppb over the next 4 hours of the 8-hour
23 exposure, and to an square-wave exposure of 120 ppb O₃ for 8 hours. While the total
24 inhaled O₃ doses at 4 hours and 8 hours for the square-wave and the triangular
25 concentration profile were almost identical, the FEV₁ responses were dissimilar. For the
26 square-wave exposure, FEV₁ declined ~5% by the fifth hour and then remained at that
27 level. With the triangular O₃ profile, there was minimal FEV₁ response over the first
28 3 hours followed by a rapid decrease in FEV₁ to a decrement of 10.3% over the next 3
29 hours. During the seventh and eighth hours, mean FEV₁ decrement improved to 6.3% as
30 the O₃ concentration decreased from 120 to 0 ppb (mean = 60 ppb). These findings
31 illustrate that the severity of symptoms and the magnitude of spirometric responses are
32 time-dependent functions of O₃ delivery rate with periods of both effect development and
33 recovery during the course of an exposure.

34 Subsequently, others have also demonstrated that variable concentration exposures can
35 elicit greater FEV₁ and symptomatic responses than do square-wave exposures ([Adams,](#)
36 [2006a, b, 2003a](#)). [Adams \(2006b\)](#) reproduced the findings of [Hazucha et al. \(1992\)](#) at
37 120 ppb. However, [Adams \(2006a\)](#); ([2003a](#)) found that responses from an 80 ppb O₃
38 (average) triangular exposure did not differ significantly from those observed in the

1 80 ppb O₃ square-wave exposure at 6.6 hours. Nevertheless, FEV₁ and symptoms were
2 significantly different from pre-exposure at 4.6 hours (when the O₃ concentration was
3 150 ppb) in the triangular exposure, but not until 6.6 hours in the square-wave exposure.
4 At the lower O₃ concentration of 60 ppb, no temporal pattern differences in FEV₁
5 responses between square-wave and triangular exposure profiles could be discerned
6 ([Adams, 2006a](#)). However, both total symptom scores and pain on deep inspiration
7 tended to be greater following the 60 ppb triangular than the 60 ppb square-wave
8 exposure. At 80 ppb, respiratory symptoms tended to increase more rapidly during the
9 triangular than square-wave exposure protocol, but then decreased during the last hour of
10 exposure to be less than that observed with the square-wave exposure at 6.6 hours. Both
11 total symptom scores and pain on deep inspiration were significantly increased following
12 exposures to 80 ppb relative to all other exposure protocols, i.e., FA, 40, and 60 ppb
13 exposures. Following the 6.6-hour exposures, respiratory symptoms at 80 ppb were
14 roughly 2-3 times greater than those observed at 60 ppb. At 40 ppb, triangular and
15 square-wave patterns produced spirometric and subjective symptom responses similar to
16 FA exposure ([Adams, 2006a, 2002](#)).

17 For O₃ exposures of 60 ppb and greater, studies ([Adams, 2006a, b, 2003a](#); [Hazucha et al.,](#)
18 [1992](#)) demonstrate that during triangular exposure protocols, volunteers exposed during
19 moderate exercise ($\dot{V}_E = 40$ L/min) may develop greater spirometric and/or symptomatic
20 responses during and following peak O₃ concentrations as compared to responses over
21 the same time interval of square-wave exposures. This observation is not unexpected
22 since the inhaled dose rate during peaks of the triangular protocols approached twice that
23 of the square-wave protocols, e.g., 150 ppb versus 80 ppb peak concentration. At time
24 intervals toward the end of an exposure, O₃ delivery rates for the triangular protocols
25 were less than those of square-wave. At these later time intervals, there is some recovery
26 of responses during triangular exposure protocols, whereas there is a continued
27 development of or a plateau of responses in the square-wave exposure protocols. Thus,
28 responses during triangular protocols relative to square-wave protocols may be expected
29 to diverge and be greater following peak exposures and then converge toward the end of
30 an exposure. Subsequent discussion will focus on exposures between 40 and 80 ppb
31 where FEV₁ pre-to-post responses are similar (although not identical) between triangular
32 and square-wave protocols having equivalent average exposure concentrations.

33 [Schelegle et al. \(2009\)](#) recently investigated the effects of 6.6-hour variable O₃ exposure
34 protocols at mean concentrations of 60, 70, 80, and 87 ppb on respiratory symptoms and
35 pulmonary function in young healthy adults (16 F, 15 M; 21.4 ± 0.6 years) exposed
36 during moderate quasi continuous exercise ($\dot{V}_E = 40$ L/min). The mean FEV₁ (± standard
37 error) decrements at 6.6 hours (end of exposure relative to pre-exposure) were -
38 0.80 ± 0.90%, 2.72 ± 1.48%, 5.34 ± 1.42%, 7.02 ± 1.60%, and 11.42 ± 2.20% for

1 exposure to FA, 60, 70, 80, and 87 ppb O₃, respectively. Statistically significant
2 decrements in FEV₁ and increases in total subjective symptom scores (p < 0.05) were
3 found following exposure to mean concentrations of 70, 80, and 87 ppb O₃ relative to FA.
4 Statistically significant effects were not found at 60 ppb. One of the expressed purposes
5 of the [Schelegle et al. \(2009\)](#) study was to determine the minimal mean O₃ concentration
6 that produces a statistically significant decrement in FEV₁ and respiratory symptoms in
7 healthy individuals completing 6.6-hour exposure protocols. At 70 ppb, [Schelegle et al.](#)
8 [\(2009\)](#) observed a statistically significant O₃-induced FEV₁ decrement of 6.1% at
9 6.6 hours and a significant increase in total subjective symptoms at 5.6 and 6.6 hours. A
10 re analysis found the FEV₁ responses at 70 ppb to be significantly different from FA
11 responses beginning at 4.6 hours of exposure ([Lefohn et al., 2010a](#)). At 60 ppb, an
12 O₃-induced 3.5% FEV₁ decrement was not found to be statistically significant. However,
13 this effect is similar in magnitude to the 2.9% FEV₁ decrement at 60 ppb observed by
14 [Adams \(2006a\)](#), which was found to be statistically significant by [Brown et al. \(2008\)](#).

15 More recently, [Kim et al. \(2011\)](#) investigated the effects of a 6.6-hour exposure to 60 ppb
16 O₃ during moderate quasi continuous exercise ($\dot{V}_E = 40$ L/min) on pulmonary function
17 and respiratory symptoms in young healthy adults (32 F, 27 M; 25.0 ± 0.5 year) who
18 were roughly half GSTM1-null and half GSTM1-positive. Sputum neutrophil levels were
19 also measured in a subset of the subjects (13 F, 11 M). The mean FEV₁ (± standard error)
20 decrements at 6.6 hours (end of exposure relative to pre-exposure) were significantly
21 different (p = 0.008) between the FA (0.002 ± 0.46%) and O₃ (1.76 ± 0.50%) exposures.
22 The inflammatory response following O₃ exposure was also significantly (p < 0.001)
23 increased relative to the FA exposure. Respiratory symptoms were not affected by O₃
24 exposure. There was also no significant effect of GSTM1 genotype on FEV₁ or
25 inflammatory responses to O₃.

26 Consideration of the minimal O₃ concentration producing statistically significant effects
27 on FEV₁ and respiratory symptoms (e.g., cough and pain on deep inspiration) following
28 6.6-hour exposures warrants additional discussion. As discussed above, numerous studies
29 have demonstrated statistically significant O₃-induced group mean FEV₁ decrements of
30 6-8% and an increase in respiratory symptoms at 80 ppb. [Schelegle et al. \(2009\)](#) have
31 now reported a statistically significant O₃-induced group mean FEV₁ decrement of 6%, as
32 well as increased respiratory symptoms, at 70 ppb. At 60 ppb, there is information
33 available from 4 separate studies ([Kim et al., 2011](#); [Schelegle et al., 2009](#); [Adams, 2006a](#),

1 [2002](#)).¹ The group mean O₃-induced FEV₁ decrements observed in these studies were
2 3.6% (facemask, square-wave) by [Adams \(2006a\)](#); [\(2002\)](#)², 2.8% (triangular exposure)
3 and 2.9% (square-wave exposure) by [Adams \(2006a\)](#), 3.5% (triangular exposure) by
4 [Schelegle et al. \(2009\)](#), and 1.8% (square-wave exposure) by [Kim et al. \(2011\)](#). Based on
5 data from these studies, at 60 ppb, the weighted-average group mean O₃-induced FEV₁
6 decrement (i.e., adjusted for FA responses) is 2.7% (n = 150). Although not consistently
7 statistically significant, these group mean changes in FEV₁ at 60 ppb are consistent
8 among studies, i.e., none observed an average improvement in lung function following a
9 6.6-hour exposure to 60 ppb O₃. Indeed, as was illustrated in [Figure 6-1](#), the group mean
10 FEV₁ responses at 60 ppb fall on a smooth intake dose-response curve for exposures
11 between 40 and 120 ppb O₃. Furthermore, in a re-analysis of the 60 ppb square-wave data
12 from [Adams \(2006a\)](#), [Brown et al. \(2008\)](#) found the mean effects on FEV₁ to be highly
13 statistically significant (p <0.002) using several common statistical tests even after
14 removal of 3 potential outliers. A statistically significant increase in total respiratory
15 symptoms at 60 ppb has only been reported by [Adams \(2006a\)](#) for a triangular exposure
16 protocol at 5.6 hours and 6.6 hours relative to baseline (not FA). Although not
17 statistically significant, there was a tendency for an increase in total symptoms and pain
18 on deep inspiration following the 60 ppb exposures (triangular and square-wave) relative
19 to those following both FA and 40 ppb exposures. The time-course and magnitude of
20 FEV₁ responses at 40 ppb resemble those occurring during FA exposures ([Adams, 2006a](#),
21 [2002](#)). In both of these studies, there was a tendency (not statistically significant) for a
22 small increase in total symptoms and pain on deep inspiration following the 40 ppb
23 exposures relative to those following FA. Taken together, the available evidence shows
24 that detectable effects of O₃ on group mean FEV₁ persist down to 60 ppb, but not 40 ppb
25 in young healthy adults exposed for 6.6 hours during moderate exercise. Although group
26 mean FEV₁ responses at 60 ppb are relatively small (2-3% mean FEV₁ decrement), it
27 should be emphasized that there is considerable intersubject variability, with some
28 responsive individuals consistently experiencing larger than average FEV₁ responses.

29 In addition to overt effects of O₃ exposure on the large airways indicated by spirometric
30 responses, O₃ exposure also affects the function of the small airways and parenchymal
31 lung. [Foster et al. \(1997\)](#); [\(1993\)](#) examined the effect of O₃ on ventilation distribution. In
32 healthy adult males (n = 6; 26.7 ± 7 years old) exposed to O₃ (330 ppb with light
33 intermittent exercise for 2 h), there was a significant reduction in ventilation to the lower

¹ [Adams \(2006a\)](#); [\(2002\)](#) both provide data for an additional group of 30 healthy subjects that were exposed via facemask to 60 ppb (square-wave) O₃ for 6.6 hours with moderate exercise ($\dot{V}_E = 23$ L/min per m² BSA). These subjects are described on page 133 of [Adams \(2006a\)](#) and pages 747 and 761 of [Adams \(2002\)](#). The FEV₁ decrement may be somewhat increased due to a target \dot{V}_E of 23 L/min per m² BSA relative to other studies with which it is listed having the target \dot{V}_E of 20 L/min per m² BSA. Based on [Adams \(2003a, b, 2002\)](#) the facemask exposure is not expect to affect the FEV₁ responses relative to a chamber exposure.

² This group average FEV₁ response is for a set of subjects exposed via facemask to 60 ppb O₃, see page 133 of [Adams \(2006a\)](#).

1 lung (31% of lung volume) and significant increases in ventilation to the upper- and
2 middle-lung regions ([Foster et al., 1993](#)). In a subsequent study of healthy males (n = 15;
3 25.4 ± 2 years old) exposed to O₃ (350 ppb with moderate intermittent exercise for 2.2 h),
4 O₃ exposure caused a delayed gas washout in addition to a 14% FEV₁ decrement ([Foster](#)
5 [et al., 1997](#)). The pronounced slow phase of gas washout following O₃ exposure
6 represented a 24% decrease in the washout rate. A day following O₃ exposure, 50% of
7 the subjects still had (or developed) a delayed washout relative to the pre-O₃ maneuver.
8 These studies suggest a prolonged O₃ effect on the small airways and ventilation
9 distribution in healthy young individuals.

10 There is a rapid recovery of O₃-induced spirometric responses and symptoms; 40 to 65%
11 recovery appears to occur within about 2 hours following exposure ([Folinsbee and](#)
12 [Hazucha, 1989](#)). For example, following a 2-hour exposure to 400 ppb O₃ with
13 intermittent exercise, [Nightingale et al. \(2000\)](#) observed a 13.5% mean decrement in
14 FEV₁. By 3 hours postexposure, however, only a 2.7% FEV₁ decrement persisted. Partial
15 recovery also occurs following cessation of exercise despite continued exposure to O₃
16 ([Folinsbee et al., 1977](#)) and at low O₃ concentrations during exposure ([Hazucha et al.,](#)
17 [1992](#)). A slower recovery phase, especially after exposure to higher O₃ concentrations,
18 may take at least 24 hours to complete ([Folinsbee and Hazucha, 2000](#); [Folinsbee et al.,](#)
19 [1993](#)). Repeated daily exposure studies at higher concentrations typically show that FEV₁
20 response to O₃ is enhanced on the second day of exposure. This enhanced response
21 suggests a residual effect of the previous exposure, about 22 hours earlier, even though
22 the pre-exposure spirometry may be the same as on the previous day. The absence of the
23 enhanced response with repeated exposure at lower O₃ concentrations may be the result
24 of a more complete recovery or less damage to pulmonary tissues ([Folinsbee et al., 1994](#)).

Predicted Responses in Healthy Subjects

25 Studies analyzing large data sets (hundreds of subjects) provide better predictive ability
26 of acute changes in FEV₁ at low levels of O₃ and \dot{V}_E than is possible via comparisons
27 between smaller studies. A few such studies described in the 2006 O₃ AQCD ([U.S. EPA,](#)
28 [2006b](#)) analyzed FEV₁ responses in healthy young adults (18-35 years of age) recruited
29 from the area around Chapel Hill, NC and exposed for 2 hours to O₃ concentrations of up
30 to 400 ppb at rest or with intermittent exercise ([McDonnell et al., 1997](#); [Seal et al., 1996](#);
31 [Seal et al., 1993](#)). [McDonnell et al. \(1999b\)](#) examined changes in respiratory symptoms
32 with O₃ exposure in a subset of the Chapel Hill data. In general, these studies showed that
33 FEV₁ and respiratory symptom responses increase with increasing O₃ concentration and
34 \dot{V}_E and decrease with increasing subject age. More recent studies expand upon these
35 analyses of FEV₁ responses to also include longer duration (up to 8 h) studies and periods
36 of recovery following exposure.

1 [McDonnell et al. \(2007\)](#) provided a nonlinear empirical model for predicting group
2 average FEV₁ responses as a function of O₃ concentration, exposure time, \dot{V}_E , and age of
3 the exposed individual. The model predicts temporal dynamics of FEV₁ change in
4 response to any set of O₃ exposure conditions that might reasonably be experienced in the
5 ambient environment. The model substantially differs from earlier statistical models in
6 that it effectively considers the concurrent processes of damage and repair, i.e., the model
7 allows effects on FEV₁ to accumulate during exposure at the same time they are reduced
8 due to the reversible nature of the effects. The model was based on response data of
9 healthy, nonsmoking, white males (n = 541), 18-35 years old, from 15 studies conducted
10 at the U.S. EPA Human Studies Facility in Chapel Hill, NC.

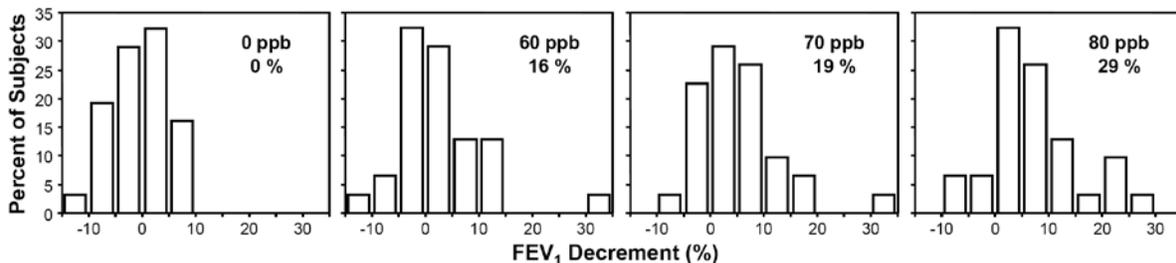
11 [McDonnell et al. \(2010\)](#) tested the predictive ability of the model ([McDonnell et al.,](#)
12 [2007](#)) against independent data (i.e., data that were not used to fit the model) of [Adams](#)
13 [\(2006a\)](#); [\(2006b, 2003a, 2002, 2000\)](#), [Hazucha et al. \(1992\)](#), and [Schelegle et al. \(2009\)](#).
14 The model generally captured the dynamics of group average FEV₁ responses within
15 about a one percentage point of the experimental data. Consistent with [Bennett et al.](#)
16 [\(2007\)](#), an increased body mass index (BMI) was found to be associated with enhanced
17 FEV₁ responses to O₃ by [McDonnell et al. \(2010\)](#). The BMI effect is of the same order of
18 magnitude but in the opposite direction of the age effect where by FEV₁ responses
19 diminish with increasing age. Although the effects of age and BMI are relatively strong,
20 these characteristics account for only a small amount of the observed variability in
21 individual responses.

22 Alternatively, [Lefohn et al. \(2010a\)](#) proposed that FEV₁ responses to O₃ exposure might
23 be described by a cumulative integrated exposure index with a sigmoidal weighting
24 function similar to the W126 used for predicting vegetation effects (see Section 9.5). The
25 integrated exposure index is the sum of the hourly average O₃ concentrations times their
26 respective weighting factors. Based on a limited number of studies, the authors assumed
27 weighting factors ranged from near zero at 50 ppb up to approximately 1.0 for
28 concentrations at ≥ 125 ppb. The concentrations of 60, 70 and 80 ppb correspond to the
29 weights of 0.14, 0.28, and 0.50, respectively. These weighting factors apply only to the
30 case of exposure during moderate exercise ($\dot{V}_E = 20$ L/min per m² BSA). [Lefohn et al.](#)
31 [\(2010a\)](#) calculated the cumulative exposure index for the protocols used by [Adams](#)
32 [\(2006a\)](#); [\(2003a\)](#) and [Schelegle et al. \(2009\)](#). They found statistically significant O₃
33 effects after 4 hours on FEV₁ at 105 ppb-hour based on [Schelegle et al. \(2009\)](#) and at
34 235 ppb-hour based on [Adams \(2006a\)](#); [\(2003a\)](#). Based on this analysis, the authors
35 recommended a 5-hour accumulation period to protect against O₃ effects on lung
36 function.

Intersubject Variability in Response of Healthy Subjects

1 Consideration of group mean changes is important in discerning if observed effects are
2 due to O₃ exposure rather than chance alone. Inter-individual variability in responses is,
3 however, considerable and pertinent to assessing the fraction of the population that might
4 actually be affected during an O₃ exposure. [Hackney et al. \(1975\)](#) first recognized a wide
5 range in the sensitivity of subjects to O₃. The range in the subjects' ages (29 to 49 years)
6 and smoking status (0 to 50 pack years) in the [Hackney et al. \(1975\)](#) study are now
7 understood to affect the spirometric and symptomatic responses to O₃. Subsequently,
8 [DeLucia and Adams \(1977\)](#) examined responses to O₃ in six healthy non-smokers and
9 found that two exhibited notably greater sensitivity to O₃. Since that time, numerous
10 studies have documented considerable variability in responsiveness to O₃ even in subjects
11 recruited to assure homogeneity in factors recognized or presumed to affect responses.

12 An individual's FEV₁ response to a 2 hour O₃ exposure is generally reproducible over
13 several months and presumably reflects the intrinsic responsiveness of the individual to
14 O₃ ([Hazucha et al., 2003](#); [McDonnell et al., 1985b](#)). The frequency distribution of
15 individual FEV₁ responses following these relatively short exposures becomes skewed as
16 the group mean response increases, with some individuals experiencing large reductions
17 in FEV₁ ([Weinmann et al., 1995a](#); [Kulle et al., 1985](#)). For 2-hour exposures with
18 intermittent exercise causing a predicted average FEV₁ decrement of 10%, individual
19 decrements ranged from approximately 0 to 40% in white males aged 18-36 years
20 ([McDonnell et al., 1997](#)). For an average FEV₁ decrement of 13%, [Ultman et al. \(2004\)](#)
21 reported FEV₁ responses ranging from a 4% improvement to a 56% decrement in young
22 healthy adults (32 M, 28 F) exposed for 1 hour to 250 ppb O₃. One-third of the subjects
23 had FEV₁ decrements of >15%, and 7% of the subjects had decrements of >40%. The
24 differences in FEV₁ responses did not appear to be explained by intersubject differences
25 in the fraction of inhaled O₃ retained in the lung ([Ultman et al., 2004](#)).



Note: During each hour of the exposures, subjects were engaged in moderate quasi continuous exercise (40 L/min) for 50 minutes and rest for 10 minutes. Following the third hour, subjects had an additional 35 minute rest period for lunch. Subjects were exposed to a triangular O₃ concentration profile having the average O₃ concentration provided in each panel. As average ozone concentration increased, the distribution of responses became asymmetric with a few individuals exhibiting large FEV₁ decrements. The percentage indicated in each panel is the portion of subjects having a FEV₁ decrement in excess of 10%.

Source: Adapted with permission of American Thoracic Society ([Schelegle et al., 2009](#)).

Figure 6-2 Frequency distributions of FEV₁ decrements observed by Schelegle et al. (2009) in young healthy adults (16 F, 15 M) following 6.6-hour exposures to ozone or filtered air.

1 Consistent with the 1- to 2-hour studies, the distribution of individual responses
 2 following 6.6-hour exposures becomes skewed with increasing exposure concentration
 3 and magnitude of the group mean FEV₁ response ([McDonnell, 1996](#)). [Figure 6-2](#)
 4 illustrates frequency distributions of individual FEV₁ responses observed in 31 young
 5 healthy adults following 6.6-hour exposures between 0 and 80 ppb. [Schelegle et al.](#)
 6 ([2009](#)) found >10% FEV₁ decrements in 16, 19, 29, and 42% of individuals exposed for
 7 6.6 hours to 60, 70, 80, and 87 ppb, respectively. Just as there are differences in mean
 8 decrements between studies having similar exposure scenarios ([Figure 6-1](#) at 80 and
 9 120 ppb), there are differences in the proportion of individuals affected with >10% FEV₁
 10 decrements. At 80 ppb, the proportion affected with >10% FEV₁ decrements was 17%
 11 (n = 30) by [Adams \(2006a\)](#)¹, 26% (n = 60) by [McDonnell \(1996\)](#), and 29% (n = 31) by
 12 [Schelegle et al. \(2009\)](#). At 60 ppb, the proportion with >10% FEV₁ decrements was 20%
 13 (n = 30) by [Adams \(2002\)](#)², 3% (n = 30) by [Adams \(2006a\)](#)¹, 16% (n = 31) by [Schelegle](#)
 14 [et al. \(2009\)](#), and 5% (n = 59) by [Kim et al. \(2011\)](#). Based on these studies, the weighted
 15 average proportion of individuals with >10% FEV₁ decrements is 10% following
 16 exposure to 60 ppb. Due to limited data within the published papers, these proportions
 17 were not corrected for responses to FA exposure where lung function typically improves
 18 in healthy adults. For example, uncorrected versus O₃-induced (i.e., adjusted for response

¹ Not assessed by [Adams \(2006a\)](#), the proportion was provided in Figure 8-1B of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)).

² This information is from page 761 of [Adams \(2002\)](#). [Adams \(2006a, 2002\)](#) both provide data for a group of 30 healthy subjects that were exposed via facemask to 60 ppb (square-wave) O₃ for 6.6 hours with moderate exercise ($\dot{V}_E = 23$ L/min per m² BSA). These subjects are described on page 133 of [Adams \(2006a\)](#) and pages 747 and 761 of [Adams \(2002\)](#). The FEV₁ decrement may be somewhat increased due to a target \dot{V}_E of 23 L/min per m² BSA relative to other studies with which it is listed having the target \dot{V}_E of 20 L/min per m² BSA. Based on [Adams \(2003a, b, 2002\)](#), similar FEV₁ responses are expected between facemask and chamber exposures.

1 during FA exposure) proportions of individuals having >10% FEV₁ decrements in the
2 [Adams \(2006a\)](#)¹ study were, respectively, 3% versus 7% at 60 ppb and 17% versus 23%
3 at 80 ppb. Thus, uncorrected proportions underestimate the actual fraction of healthy
4 individuals affected.

5 Given considerable inter-individual variability in responses, the interpretation of
6 biologically small group mean decrements requires careful consideration. Following
7 prolonged 6.6-hour exposures to an average level of 60 ppb O₃, data available from four
8 studies yield a weighted-average group mean O₃-induced FEV₁ decrement (i.e., adjusted
9 for FA responses) of 2.7% (n = 150) ([Kim et al., 2011](#); [Schelegle et al., 2009](#); [Adams,
10 2006a, 1998](#)). The data from these studies also yield a weighted-average proportion
11 (uncorrected for FA responses) of subjects with >10% FEV₁ decrements of 10%
12 (n = 150) ([Kim et al., 2011](#); [Schelegle et al., 2009](#); [Adams, 2006a, 1998](#)). In an individual
13 with relatively “normal” lung function, with recognition of the technical and biological
14 variability in measurements, confidence can be given that within-day changes in FEV₁ of
15 ≥ 5% are clinically meaningful ([Pellegrino et al., 2005](#); [ATS, 1991](#)). Here focus is given
16 to individuals with >10% decrements in FEV₁ since some individuals in the [Schelegle et
17 al. \(2009\)](#) study experienced 5-10% FEV₁ decrements following exposure to FA. A 10%
18 FEV₁ decrement is also generally accepted as an abnormal response and a reasonable
19 criterion for assessing exercise-induced bronchoconstriction ([Dryden et al., 2010](#); [ATS,
20 2000a](#)). The data are not available in the published papers to determine the O₃-induced
21 proportion for either the [Adams \(1998\)](#) or [Schelegle et al. \(2009\)](#) studies. As already
22 stated, however, this uncorrected proportion likely underestimates the actual proportion
23 of healthy individuals experiencing O₃-induced FEV₁ decrements in excess of 10%.
24 Therefore, by considering uncorrected responses and those individuals having >10%
25 decrements, 10% is an underestimate of the proportion of healthy individuals that are
26 likely to experience clinically meaningful changes in lung function following exposure
27 for 6.6 hours to 60 ppb O₃ during moderate exercise. Of the studies conducted at 60 ppb,
28 only [Kim et al. \(2011\)](#) reported FEV₁ decrements at 60 ppb to be statistically significant.
29 However, [Brown et al. \(2008\)](#) found those from [Adams \(2006a\)](#) to be highly statistically
30 significant. Though group mean decrements are biologically small and generally do not
31 attain statistical significance, a considerable fraction of exposed individuals experience
32 clinically meaningful decrements in lung function.

¹ Not assessed by [Adams \(2006a\)](#), uncorrected and O₃-induced proportions are from Figures 8-1B and 8-2, respectively, of the 2006 O₃ AQCD ([2006b](#)).

Factors Modifying Responsiveness to Ozone

1 Physical activity increases \dot{V}_E and therefore the dose of inhaled O₃. Consequently, the
2 intensity of physiological response during and following an acute O₃ exposure will be
3 strongly associated with minute ventilation. Apart from inhaled O₃ dose and related
4 environmental factors (e.g., repeated daily exposures), individual-level factors, such as
5 health status, age, gender, ethnicity, race, smoking habit, diet, and socioeconomic status
6 (SES) have been considered as potential modulators of a physiologic response to such
7 exposures.

Responses in Individuals with Pre-existing Disease

8 Individuals with respiratory disease are of primary concern in evaluating the health
9 effects of O₃ because a given change in function is likely to have more impact on a
10 person with preexisting function impairment and reduced reserve.

11 Possibly due to the age of subjects studied, patients with COPD performing light to
12 moderate exercise do not generally experience statistically significant pulmonary
13 function decrements following 1- and 2-hour exposures to ≤ 300 ppb O₃ ([Kehrl et al.,](#)
14 [1985](#); [Linn et al., 1983](#); [Linn et al., 1982a](#); [Solic et al., 1982](#)). Following a 4-hour
15 exposure to 240 ppb O₃ during exercise, [Gong et al. \(1997b\)](#) found an O₃-induced FEV₁
16 decrement of 8% in COPD patients which was not statistically different from the
17 decrement of 3% in healthy subjects. Demonstrating the need for control exposures and
18 presumably due to exercise, four of the patients in the [Gong et al. \(1997b\)](#) study had
19 FEV₁ decrements of $>14\%$ following both the FA and O₃ exposures. Although the
20 clinical significance is uncertain, small transient decreases in arterial blood oxygen
21 saturation have also been observed in some of these studies.

22 Based on studies reviewed in the 1996 and 2006 O₃ AQCDs, asthmatic subjects appear to
23 be at least as sensitive to acute effects of O₃ as healthy nonasthmatic subjects. [Horstman](#)
24 [et al. \(1995\)](#) found the O₃-induced FEV₁ decrement in 17 mild-to-moderate asthmatics to
25 be significantly larger than that in 13 healthy subjects (19% versus 10%, respectively)
26 exposed to 160 ppb O₃ during light exercise (\dot{V}_E of 15 L/min per m² BSA) for 7.6-hour
27 exposure. In asthmatics, a significant positive correlation between O₃-induced
28 spirometric responses and baseline lung function was observed, i.e., responses increased
29 with severity of disease. In the shorter duration study by [Kreit et al. \(1989\)](#), 9 asthmatics
30 also showed a considerable larger average O₃-induced FEV₁ decrement than 9 healthy
31 controls (25% vs. 16%, respectively) following exposure to 400 ppb O₃ for 2 hours with
32 moderate-heavy exercise ($\dot{V}_E = 54$ L/min). [Alexis et al. \(2000\)](#) [400 ppb; 2 h; exercise,
33 $\dot{V}_E = 30$ L/min] and [Jorres et al. \(1996\)](#) [250 ppb; 3 h; exercise, $\dot{V}_E = 30$ L/min] reported a
34 tendency for slightly greater FEV₁ decrements in asthmatics than healthy subjects.

1 Several studies reported similar responses between asthmatics and healthy individuals
2 ([Scannell et al., 1996](#); [Hiltermann et al., 1995](#); [Basha et al., 1994](#)). The lack of differences
3 in the [Hiltermann et al. \(1995\)](#) [400 ppb; 2 h; exercise, $\dot{V}_E = 20$ L/min] and [Basha et al.](#)
4 [\(1994\)](#) [200 ppb; 6 h; exercise, $\dot{V}_E = 25$ L/min] studies was not surprising, however, given
5 extremely small sample sizes (5-6 subjects per group) and corresponding lack of
6 statistical power. Power was not likely problematic for [Scannell et al. \(1996\)](#) [200 ppb;
7 4 h; exercise, $\dot{V}_E \approx 44$ L/min] with 18 mild asthmatics and 81 age-matched healthy
8 controls from companion studies ([Balmes et al., 1996](#); [Aris et al., 1995](#)). Of note,
9 [Mudway et al. \(2001\)](#) reported a tendency for asthmatics to have smaller O₃-induced
10 FEV₁ decrements than healthy subjects (3% versus 8%, respectively) when exposed to
11 200 ppb O₃ for 2 hours during exercise. However, the asthmatics in ([Mudway et al.,](#)
12 [2001](#)) also tended to be older than the healthy subjects, which could partially explain
13 their smaller response since FEV₁ responses to O₃ diminish with age.

14 In a study published since the 2006 O₃ AQCD, [Stenfors et al. \(2010\)](#) exposed persistent
15 asthmatics (n = 13; aged 33 years) receiving chronic inhaled corticosteroid therapy to
16 200 ppb O₃ for 2 hours with moderate exercise. An average O₃-induced FEV₁ decrement
17 of 8.4% was observed, whereas, only a 3.0% FEV₁ decrement is predicted for similarly
18 exposed age-matched healthy controls ([McDonnell et al., 2007](#)). [Vagaggini et al. \(2010\)](#)
19 exposed mild-to-moderate asthmatics (n = 23; 33 ± 11 years) to 300 ppb O₃ for 2 hours
20 with moderate exercise. Although the group mean O₃-induced FEV₁ decrement was only
21 4%, eight subjects were categorized as “responders” with >10% FEV₁ decrements.
22 Baseline lung function did not differ between the responders and nonresponders
23 suggesting that, in contrast to [Horstman et al. \(1995\)](#), O₃-induced FEV₁ responses were
24 not associated with disease severity.

Lifestage

25 Children, adolescents, and young adults (<18 years of age) appear, on average, to have
26 nearly equivalent spirometric responses to O₃, but have greater responses than middle-
27 aged and older adults when similarly exposed to O₃ ([U.S. EPA, 1996a](#)). Symptomatic
28 responses to O₃ exposure, however, appear to increase with age until early adulthood and
29 then gradually decrease with increasing age ([U.S. EPA, 1996a](#)). For example, healthy
30 children (aged 8-11 y) exposed to 120 ppb O₃ (2.5 h; heavy intermittent exercise)
31 experienced similar spirometric responses, but lesser symptoms than similarly exposed
32 young healthy adults ([McDonnell et al., 1985a](#)). For subjects aged 18-36 years,
33 [McDonnell et al. \(1999b\)](#) reported that symptom responses from O₃ exposure also
34 decrease with increasing age. Diminished symptomatic responses in children and the
35 elderly might put these groups at increased risk for continued O₃ exposure, i.e., a lack of
36 symptoms may result in their not avoiding or ceasing exposure. Once lung growth and

1 development reaches the peak (18-20 years of age in females and early twenties in
2 males), pulmonary function, which is at its maximum as well, begins to decline
3 progressively with age as does O₃ sensitivity.

4 In healthy individuals, the fastest rate of decline in O₃ responsiveness appears between
5 the ages of 18 and 35 years ([Passannante et al., 1998](#); [Seal et al., 1996](#)), more so for
6 females than males ([Hazucha et al., 2003](#)). During the middle age period (35-55 years),
7 O₃ sensitivity continues to decline, but at a much lower rate. Beyond this age (>55 years),
8 acute O₃ exposure elicits minimal spirometric changes. Whether the same age-dependent
9 pattern of O₃ sensitivity decline also holds for nonspirometric pulmonary function,
10 airway reactivity or inflammatory endpoints has not been determined. Although there is
11 considerable evidence that spirometric and symptomatic responses to O₃ exposure
12 decrease with age beyond young adulthood, this evidence comes from cross-sectional
13 analyses and has not been confirmed by longitudinal studies of the same individuals.

Sex

14 Several studies have suggested that physiological differences between sexes may
15 predispose females to greater O₃-induced health effects. In females, lower plasma and
16 nasal lavage fluid (NLF) levels of uric acid (the most prevalent antioxidant), the initial
17 defense mechanism of O₃ neutralization in airway surface liquid, may be a contributing
18 factor ([Housley et al., 1996](#)). Consequently, reduced absorption of O₃ in the upper
19 airways may promote its deeper penetration. Dosimetric measurements have shown that
20 the absorption distribution of O₃ is independent of sex when absorption is normalized to
21 anatomical dead space ([Bush et al., 1996](#)). Thus, a sex-related differential removal of O₃
22 by uric acid seems to be minimal. In general, the physiologic response of young healthy
23 females to O₃ exposure appears comparable to the response of young males ([Hazucha et
24 al., 2003](#)). Several studies have investigated the effects of the menstrual cycle on
25 responses to O₃ in healthy young women. In a study of 9 women exposed during exercise
26 to 300 ppb O₃ for an hour, [Fox et al. \(1993\)](#) found lung function responses to O₃
27 significantly enhanced during the follicular phase relative to the luteal phase. However,
28 [Weinmann et al. \(1995c\)](#) found no difference in responses between the follicular and
29 luteal phases as well as no significant differences between 12 males and 12 females
30 exposed during exercise to 350 ppb O₃ for 2.15 hours. [Seal et al. \(1996\)](#) also reported no
31 effect of menstrual cycle phase in their analysis of responses of 150 women (n = 25 per
32 exposure group; 0, 120, 240, 300, and 400 ppb O₃). [Seal et al. \(1996\)](#) conceded that the
33 methods used by [Fox et al. \(1993\)](#) more precisely defined menstrual cycle phase.

Ethnicity

1 Only two controlled human exposure studies have assessed differences in lung function
2 responses between races. [Seal et al. \(1993\)](#) compared lung function responses of whites
3 (93 M, 94 F) and blacks (undefined ancestry; 92 M, 93 F) exposed to a range of O₃
4 concentrations (0-400 ppb). The main effects of the sex-race group and O₃ concentration
5 were statistically significant (both at p < 0.001), although the interaction between sex-race
6 group and O₃ concentration was not significant (p = 0.13). These findings indicate some
7 overall difference between the sex-race groups that is independent of O₃ concentration,
8 i.e., the concentration-response (C-R) curves for the four sex-race groups are parallel. In
9 a multiple comparison procedure on data collapsed across all O₃ concentrations for each
10 sex-race group, both black men and black women had significantly larger decrements in
11 FEV₁ than did white men. The authors noted that the O₃ dose per unit of lung tissue
12 would be greater in blacks and females than whites and males, respectively. It cannot be
13 ruled out that this difference in tissue dose might have affected responses to O₃. The
14 college students recruited for the [Seal et al. \(1993\)](#) study were noted by the authors as
15 probably being from better educated and SES advantaged families, thus reducing the
16 potential influence of these variables on results. In a follow-up analysis, [Seal et al. \(1996\)](#)
17 reported that, of three SES categories, individuals in the middle SES category showed
18 greater concentration-dependent decline in percent-predicted FEV₁ (4-5% at 400 ppb O₃)
19 than low and high SES groups. The authors did not have an “immediately clear”
20 explanation for this finding.

21 More recently, [Que et al. \(2011\)](#) assessed pulmonary responses in blacks of African
22 American ancestry (22 M, 24 F) and Caucasians (55 M, 28 F) exposed to 220 ppb O₃ for
23 2.25 hours (alternating 15 min periods of rest and brisk treadmill walking). On average,
24 the black males experienced a 16.8% decrement in FEV₁ following O₃ exposure which
25 was significantly larger than mean FEV₁ decrements of 6.2, 7.9, and 8.3% in black
26 females and Caucasian males and Caucasian females, respectively. In the study by [Seal et
27 al. \(1993\)](#), there was potential that the increased FEV₁ decrements in blacks relative to
28 whites were due to increased O₃ tissue doses since exercise rates were normalized to
29 BSA. Differences in O₃ tissue doses between the races should not have occurred in the
30 [Que et al. \(2011\)](#) study because exercise rates were normalized to lung volume (viz.,
31 6-8 times FVC). Thus, the increased mean FEV₁ decrement in black males is not likely
32 attributable to systematically larger O₃ tissue doses in blacks relative to whites.

Smoking

33 Smokers are less responsive to O₃ for some (but not all) health endpoints than
34 nonsmokers. Spirometric and plethysmographic pulmonary function decline, respiratory
35 symptoms, and nonspecific airway hyperreactivity of smokers to O₃ were all weaker than

1 data reported for nonsmokers. However, the time course of development and recovery of
2 these effects as well their reproducibility in smokers was not different from nonsmokers
3 ([Frampton et al., 1997a](#)). Another similarity between smokers and nonsmokers is that, the
4 inflammatory response to O₃ does not appear to depend on smoking status nor the
5 responsiveness of individuals to changes in lung function ([Torres et al., 1997](#)). Chronic
6 airway inflammation with desensitization of bronchial nerve endings and an increased
7 production of mucus may plausibly explain the reduced responses to O₃ in smokers
8 relative to nonsmokers ([Frampton et al., 1997a](#); [Torres et al., 1997](#)).

Antioxidant supplementation

9 The first line of defense against oxidative stress is antioxidants-rich ELF which
10 scavenges free radicals and limits lipid peroxidation. Exposure to O₃ depletes the
11 antioxidant level in nasal ELF probably due to scrubbing of O₃ ([Mudway et al., 1999a](#)),
12 however, the concentration and the activity of antioxidant enzymes either in ELF or
13 plasma do not appear to be related to O₃ responsiveness ([Samet et al., 2001](#); [Avissar et
14 al., 2000](#); [Blomberg et al., 1999](#)). Carefully controlled studies of dietary antioxidant
15 supplementation have demonstrated some protective effects of α -tocopherol and
16 ascorbate on spirometric lung function from O₃ but not on the intensity of subjective
17 symptoms and inflammatory response including cell recruitment, activation and a release
18 of mediators ([Samet et al., 2001](#); [Trenga et al., 2001](#)). Dietary antioxidants have also been
19 reported to attenuate O₃-induced bronchial hyperresponsiveness in asthmatics ([Trenga et
20 al., 2001](#)).

Genetic polymorphisms

21 Some studies (e.g., [Corradi et al., 2002](#); [Bergamaschi et al., 2001](#)) reviewed in the 2006
22 O₃ AQCD reported that genetic polymorphisms of antioxidant enzymes may modulate
23 pulmonary function and inflammatory response to O₃ challenge. It was suggested that
24 healthy carriers of NAD(P)H:quinone oxidoreductase wild type (NQO1wt) in
25 combination with glutathione S-transferase μ -1 genetic deficiency (GSTM1null) were
26 more responsive to O₃. [Bergamaschi et al. \(2001\)](#) reported that subjects having NQO1wt
27 and GSTM1null genotypes had increased O₃ responsiveness (FEV₁ decrements and
28 epithelial permeability), whereas subjects with other combinations of these genotypes
29 were less affected. A subsequent study from the same laboratory reported a positive
30 association between O₃ responsiveness, as characterized by the level of oxidative stress
31 and inflammatory mediators (8-isoprostane, LTB₄ and TBARS) in exhaled breath
32 condensate and the NQO1wt and GSTM1null genotypes ([Corradi et al., 2002](#)). However,
33 none of the spirometric endpoints (e.g., FEV₁) were affected by O₃ exposure.

1 In a controlled exposure of mild-to-moderate asthmatics ($n = 23$; 33 ± 11 years) to
2 300 ppb O_3 for 2 hours with moderate exercise, [Vagaggini et al. \(2010\)](#) found that six of
3 the subjects had a $NQO1_{wt}$ and $GSTM1$ null, but this genotype was not associated with
4 the changes in lung function or inflammatory responses to O_3 . [Kim et al. \(2011\)](#) also
5 recently reported that $GSTM1$ genotype was not predictive of FEV_1 responses in young
6 healthy adults (32 F, 27 M; 25.0 ± 0.5 year) who were roughly half $GSTM1$ -null and half
7 $GSTM1$ -sufficient. Sputum neutrophil levels, measured in a subset of the subjects (13 F,
8 11 M), were also not significantly associated with $GSTM1$ genotype.

9 In a study of healthy volunteers with $GSTM1$ sufficient ($n = 19$; 24 ± 3) and $GSTM1$ null
10 ($n = 16$; 25 ± 5) genotypes exposed to 400 ppb O_3 for 2 hours with exercise, [Alexis et al.](#)
11 [\(2009\)](#) found that inflammatory responses but not lung function responses to O_3 were
12 dependent on genotype. At 4 hours post- O_3 exposure, both $GSTM1$ genotype groups had
13 significant increases in sputum neutrophils with a tendency for a greater increase in
14 $GSTM1$ sufficient than nulls. At 24 hours postexposure, sputum neutrophils had returned
15 to baseline levels in the $GSTM1$ sufficient individuals. In the $GSTM1$ null subjects,
16 however, sputum neutrophil levels increased from 4 hours to 24 hours and were
17 significantly greater than both baseline levels and levels at 24 hours in the $GSTM1$
18 sufficient individuals. Since there was no FA control in the [Alexis et al. \(2009\)](#) study,
19 effects of the exposure other than O_3 itself cannot be ruled out. In general, the findings
20 between studies are inconsistent.

Body Mass Index

21 In a retrospective analysis of data from 541 healthy, nonsmoking, white males between
22 the ages of 18-35 years from 15 studies conducted at the U.S. EPA Human Studies
23 Facility in Chapel Hill, NC, [McDonnell et al. \(2010\)](#) found that increased BMI was
24 associated with enhanced FEV_1 responses to O_3 . The BMI effect was of the same order of
25 magnitude but in the opposite direction of the age effect where by FEV_1 responses
26 diminish with increasing age. In a similar retrospective analysis, [Bennett et al. \(2007\)](#)
27 found enhanced FEV_1 decrements following O_3 exposure with increasing BMI in a group
28 of 75 healthy, nonsmoking, women (age 24 ± 4 years; BMI range 15.7 to 33.4), but not
29 122 healthy, nonsmoking, men (age 25 ± 4 years; BMI range 19.1 to 32.9). In the women,
30 greater O_3 -induced FEV_1 decrements were seen in overweight (BMI >25) than in normal
31 weight (BMI from 18.5 to 25), and in normal weight than in underweight (BMI <18.5)
32 (P trend ≤ 0.022). Together, these results indicate that higher BMI may be a risk factor
33 for pulmonary effects associated with O_3 exposure.

Repeated Ozone Exposure Effects

1 The attenuation of responses observed after repeated consecutive O₃ exposures in
2 controlled human exposure studies has also been referred to in the literature as
3 “adaptation” or “tolerance” (e.g., [Linn et al., 1988](#)). In animal toxicology studies,
4 however, the term tolerance has more classically been used to describe the phenomenon
5 wherein a prior exposure to a low, nonlethal concentration of O₃ provides some
6 protection against death and lung edema at a higher, normally lethal exposure
7 concentration (see [Section 9.3.5 of U.S. EPA, 1986](#)). The term “attenuation” will be used
8 herein to refer to the reduction in responses to O₃ observed with repeated O₃ exposures in
9 controlled human exposure studies. Neither tolerance nor attenuation should be presumed
10 to imply complete protection from the biological effects of inhaled O₃, because
11 continuing injury still occurs despite the desensitization to some responses.

12 The attenuation of responses due to ambient O₃ exposure was first investigated by
13 [Hackney et al. \(1976\)](#); [\(1977a\)](#). Experiencing frequent ambient O₃ exposures, Los
14 Angeles residents were compared to groups having less ambient O₃ exposure. Following
15 a controlled laboratory exposure to 370-400 ppb O₃ for 2 hours with light intermittent
16 exercise (2-2.5 times resting \dot{V}_E), the Los Angeles residents exhibited minimal FEV₁
17 responses relative to groups having less ambient O₃ exposure. Subsequently, [Linn et al.](#)
18 [\(1988\)](#) examined the seasonal variation in Los Angeles residents’ responses to O₃
19 exposure. A group of 8 responders (3M, 5F) and 9 nonresponders (4M, 5F) were exposed
20 to 180 ppb O₃ for 2 hours with heavy intermittent exercise ($\dot{V}_E = 35$ L/min per m² BSA)
21 on four occasions (spring, fall, winter, and the following spring). In responders, relative
22 to the first spring exposures, FEV₁ responses were attenuated in the fall and winter, but
23 returned to similar decrements the following spring. By comparison, the nonresponders,
24 on average, showed no FEV₁ decrements on any of the four occasions. In subjects
25 recruited regardless of FEV₁ responsiveness to O₃ from the area around Chapel Hill, NC,
26 no seasonal effect of ambient O₃ exposure on FEV₁ responses following chamber
27 exposures to O₃ has been observed ([Hazucha et al., 2003](#); [McDonnell et al., 1985b](#)).

28 Based on studies reviewed in previous O₃ AQCDs, several conclusions can be drawn
29 about repeated 1- to 2-h O₃ exposures. Repeated exposures to O₃ causes enhanced
30 (i.e., greater decrements) FVC and FEV₁ responses on the second day of exposure. The
31 enhanced response appears to depend to some extent on the magnitude of the initial
32 response ([Horvath et al., 1981](#)). Small responses to the first O₃ exposure are less likely to
33 result in an enhanced response on the second day of O₃ exposure ([Folinsbee et al., 1994](#)).
34 With continued daily exposures (i.e., beyond the second day) there is a substantial (or
35 even total) attenuation of pulmonary function responses, typically on the third to
36 fifth days of repeated O₃ exposure. This attenuation of responses is lost in 1 week ([Kulle](#)

1 [et al., 1982](#); [Linn et al., 1982b](#)) or perhaps 2 weeks ([Horvath et al., 1981](#)) without O₃
2 exposure. In temporal conjunction with pulmonary function changes, symptoms induced
3 by O₃ (e.g., cough, pain on deep inspiration, and chest discomfort), are also increased on
4 the second exposure day but are attenuated with repeated O₃ exposure thereafter ([U.S.
5 EPA, 1998b](#); [Foxcroft and Adams, 1986](#); [Linn et al., 1982b](#); [Folinsbee et al., 1980](#)). In
6 longer-duration (4-6.6 hours), lower-concentration studies that do not cause an enhanced
7 second-day response, the attenuation of response to O₃ appears to proceed more rapidly
8 ([Folinsbee et al., 1994](#)).

9 Consistent with other investigators, [Frank et al. \(2001\)](#) found FVC and FEV₁ decrements
10 to be significantly attenuated following four consecutive days of exposure to O₃
11 (250 ppb, 2 h). However, the effects of O₃ on the small airways (assessed by a combined
12 index of isovolumetric forced expiratory flow between 25 and 75% of vital capacity
13 [FEF₂₅₋₇₅] and flows at 50% and 75% of FVC) showed a persistent functional reduction
14 from Day 2 through Day 4. Notably, in contrast to FVC and FEV₁ which exhibited a
15 recovery of function between days, there was a persistent effect of O₃ on small airways
16 function such that the baseline function on Day 2 through Day 4 was depressed relative to
17 Day 1. [Frank et al. \(2001\)](#) also found neutrophil (PMN) numbers in BAL remained
18 significantly higher following O₃ (24 hours after last O₃ exposure) compared to FA.
19 Markers from bronchioalveolar lavage fluid (BALF) following 4 consecutive days of
20 both 2-hour ([Devlin et al., 1997](#)) and 4-hour ([Jorres et al., 2000](#); [Christian et al., 1998](#))
21 exposures have indicated ongoing cellular damage irrespective of the attenuation of some
22 cellular inflammatory responses of the airways, lung function and symptoms response.
23 These data suggest that the persistent small airways dysfunction assessed by [Frank et al.
24 \(2001\)](#) is likely induced by both neurogenic and inflammatory mediators, since the
25 density of bronchial C-fibers is much lower in the small than large airways.

Summary of Controlled Human Exposure Studies on Lung Function

26 Responses in humans exposed to ambient O₃ concentrations include: decreased
27 inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing pattern during
28 exercise; and symptoms of cough and pain on deep inspiration ([U.S. EPA, 2006b, 1996a](#)).
29 Discussed in subsequent Section [6.2.2.1](#) and Section [6.2.3.1](#), exposure to O₃ also results
30 in airway hyperresponsiveness, pulmonary inflammation, immune system activation, and
31 epithelial injury ([Que et al., 2011](#); [Mudway and Kelly, 2004a](#)). Reflex inhibition of
32 inspiration results in a decrease in forced vital capacity and, in combination with mild
33 bronchoconstriction, contributes to a decrease in the FEV₁. Healthy young adults exposed
34 to O₃ concentrations ≥ 60 ppb develop statistically significant reversible, transient
35 decrements in lung function and symptoms of breathing discomfort if minute ventilation
36 or duration of exposure is increased sufficiently ([Kim et al., 2011](#); [McDonnell et al.,](#)

1 [2010](#); [Schelegle et al., 2009](#); [Brown et al., 2008](#); [Adams, 2006a](#)). With repeated O₃
2 exposures over several days, FEV₁ and symptom responses become attenuated in both
3 healthy individuals and asthmatics, but this attenuation of responses is lost after about
4 a week without exposure ([Gong et al., 1997a](#); [Folinsbee et al., 1994](#); [Kulle et al., 1982](#)).
5 In contrast to the attenuation of FEV₁ responses, there appear to be persistent O₃ effects
6 on small airways function as well as ongoing cellular damage during repeated exposures.

7 There is a large degree of intersubject variability in lung function decrements
8 ([McDonnell, 1996](#)). However, these lung function responses tend to be reproducible
9 within a given individual over a period of several months indicating differences in the
10 intrinsic responsiveness of individuals ([Hazucha et al., 2003](#); [McDonnell et al., 1985b](#)).
11 In healthy young adults, O₃-induced decrements in FEV₁ do not appear to depend on
12 gender ([Hazucha et al., 2003](#)), body surface area or height ([McDonnell et al., 1997](#)), lung
13 size or baseline FVC ([Messineo and Adams, 1990](#)). There is limited evidence that blacks
14 may experience greater O₃-induced decrements in FEV₁ than age-matched whites ([Que et](#)
15 [al., 2011](#); [Seal et al., 1993](#)). Healthy children experience similar spirometric responses
16 but lesser symptoms from O₃ exposure relative to young adults ([McDonnell et al.,](#)
17 [1985a](#)). On average, spirometric and symptom responses to O₃ exposure appear to decline
18 with increasing age beyond about 18 years of age ([McDonnell et al., 1999b](#); [Seal et al.,](#)
19 [1996](#)). There is a tendency for slightly increased spirometric responses in individuals
20 with mild asthma and allergic rhinitis relative to healthy young adults ([Jorres et al.,](#)
21 [1996](#)). Spirometric responses in asthmatics appear to be affected by baseline lung
22 function, i.e., responses increase with disease severity ([Horstman et al., 1995](#)).

23 Available information on recovery of lung function following O₃ exposure indicates that
24 an initial phase of recovery in healthy individuals proceeds relatively rapidly, with acute
25 spirometric and symptom responses resolving within about 2 to 4 hours ([Folinsbee and](#)
26 [Hazucha, 1989](#)). Small residual lung function effects are almost completely resolved
27 within 24 h. One day following O₃ exposure, persistent effects on the small airways
28 assessed by decrements in FEF₂₅₋₇₅ and altered ventilation distribution have been reported
29 ([Frank et al., 2001](#); [Foster et al., 1997](#)).

6.2.1.2 Epidemiology

30 The O₃-induced lung function decrements consistently demonstrated in controlled human
31 exposure studies (Section [6.2.1.1](#)) provide biological plausibility for the epidemiologic
32 evidence consistently linking short-term increases in ambient O₃ concentration with lung
33 function decrements in diverse populations. In the 1996 and 2006 O₃ AQCDs, coherence
34 with controlled human exposure study results was found not only for epidemiologic

1 associations observed in groups with expected higher ambient O₃ exposures and higher
2 exertion levels, including children attending summer camps and adults exercising or
3 working outdoors, but also for associations observed in children and individuals with
4 asthma ([U.S. EPA, 2006b, 1996a](#)). Recent epidemiologic studies focused more on
5 children with asthma rather than groups with increased outdoor exposures or other
6 healthy populations. Whereas recent studies contributed less consistent evidence, the
7 cumulative body of evidence indicates decreases in lung function in association with
8 increases in ambient O₃ concentration in children with asthma. Collectively, studies in
9 adults with asthma and individuals without asthma found both O₃-associated decreases
10 and increases in lung function. Recent studies did provide additional data to assess
11 whether particular lags of O₃ exposure were more strongly associated with decrements in
12 lung function; whether O₃ associations were confounded by copollutant exposures; and
13 whether associations were modified by factors such as corticosteroid (CS) use, genetic
14 polymorphisms, and elevated BMI.

Populations with Increased Outdoor Exposures

15 Epidemiologic studies primarily use ambient O₃ concentrations to represent exposure;
16 however, few studies have accounted for time spent outdoors, which has been shown to
17 influence the relationship between ambient concentrations and individual exposures to O₃
18 (Section [4.3.3](#)). Epidemiologic studies of individuals engaged in outdoor recreation,
19 exercise, or work are noteworthy for the likely greater extent to which ambient O₃
20 concentrations represent ambient O₃ exposures. Ambient O₃ concentrations, locations,
21 and time periods for epidemiologic studies of populations with increased outdoor
22 exposures are presented in [Table 6-2](#). Most of these studies measured ambient O₃ at the
23 site of subjects' outdoor activity and related lung function changes to the O₃
24 concentrations measured during outdoor activity, which have contributed to higher O₃
25 personal exposure-ambient concentration correlations and ratios (Section [4.3.3](#)). Because
26 of improved O₃ exposure estimates, measurement of lung function before and after
27 discrete periods of outdoor activity, and examination of O₃ effects during exertion when
28 the dose of O₃ reaching the lungs may be higher due to higher ventilation and inhalation
29 of larger volumes of air, epidemiologic studies of populations with increased outdoor
30 exposures are more comparable to controlled human exposure studies. Further, these
31 epidemiologic studies provide strong evidence for respiratory effects in children and
32 adults related to ambient O₃ exposure. Similar to findings from controlled human
33 exposure studies, the collective body of epidemiologic evidence clearly demonstrates
34 decrements in lung function in association with increases in ambient O₃ exposure during
35 periods of outdoor activity ([Figure 6-3](#) to [Figure 6-5](#) and [Table 6-3](#) to [Table 6-5](#)).

Table 6-2 Mean and upper percentile ozone concentrations in epidemiologic studies of lung function in populations with increased outdoor exposures.

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|-----------------------------------|--------------------------------------|---|---|---|
| Thurston et al. (1997) | Connecticut River Valley, CT | June 1991-1993 | 1-h max | 83.6 | Max: 160 |
| Berry et al. (1991) | Mercer County, NJ | July 1988 | 1-h max ^a | NR | Max: 204 |
| Spektor and Lippmann (1991) | Fairview Lake, NJ | July-August 1988 | 1-h avg ^b | 69 | Max: 137 |
| Avol et al. (1990) | Idyllwild, CA | June-August 1988 | 1-h avg ^b | 94 | Max: 161 |
| Burnett et al. (1990) | Lake Couchiching, Ontario, Canada | June-July 1983 | 1-h avg ^b | 59 | Max: 95 |
| Higgins et al. (1990) | San Bernardino, CA | June-July 1987 | 1-h avg ^b | 123 | Max: 245 |
| Raizenne et al. (1989) | Lake Erie, Ontario, Canada | July-August 1986 | 1-h avg ^b | 71 | Max: 143 |
| Spektor et al. (1988a) | Fairview Lake, NJ | July-August 1984 | 1-h avg ^b | 53 | Max: 113 |
| Neas et al. (1999) | Philadelphia, PA | July-September 1993 | 12-h avg ^a (9 a.m. - 9 p.m.) | 57.5 (near Camp 1) 55.9 (near Camp 2) | Max (near Camp 1): 106 |
| Nickmilder et al. (2007) | Southern Belgium | July-August 2002 | 1-h max 8-h max | NR | Max (across 6 camps): 24.5-112.7 ^c Max (across 6 camps): 18.9-81.1 ^c |
| Girardot et al. (2006) | Great Smoky Mountain NP, TN | August-October 2002 June-August 2003 | Hike-time avg (2-9 h) ^d | 48.1 | Max: 74.2 |
| Korrick et al. (1998) | Mt. Washington, NH | Summers 1991, 1992 | Hike-time avg (2-12 h) ^d | 40 | Max: 74 |
| Hoppe et al. (2003) | Munich, Germany | Summers 1992-1995 | 30-min max (1-4 p.m.) | High O ₃ days: 65.9 Control O ₃ days: 27.2 | Max (high O ₃ days): 86 |
| Spektor et al. (1988b) | Tuxedo, NY | June-August 1985 | Exercise-time avg (15 - 55 min) | NR | Max: 124 |
| Selwyn et al. (1985) | Houston, TX | May-October 1981 | Exercise-time 15-min max (4-7 p.m.) | 47 | Max: 135 |
| Brunekreef et al. (1994) | Eastern Netherlands | June-August 1981 | Exercise-time avg ^a (10-145 min) | 42.8 ^c | Max: 99.5 ^c |
| Braun-Fahrlander et al. (1994) | Southern Switzerland | May-October 1989 | Exercise-time 30-min avg | NR | Max: 80 ^c |
| Castillejos et al. (1995) | Mexico City, Mexico | June 1990-October 1991 | 1-h max ^a | 179 | Max: 365 |
| Hoek et al. (1993) | Wageningen, Netherlands | May-July 1989 | 1-h max ^a | NR | Max: 122 ^c |

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|---------------------------------------|--------------------------|------------------------|--|---|---------------------------------------|
| Hoppe et al. (1995) | Munich, Germany | Summers 1992-1995 | 30-min max (1-4 p.m.) | High O ₃ days: 64 Control O ₃ days: 32 | Max (high O ₃ days): 77 |
| Chan and Wu (2005) | Taichung City, Taiwan | November-December 2001 | 8-h avg (9 a.m.-5 p.m.) 1-h max | 35.6 52.6 | Max: 65.1 95.5 |
| Brauer et al. (1996) | British Columbia, Canada | June-August 1993 | 1-h max ^a | 40 | Max: 84 |
| Romieu et al. (1998b) | Mexico City, Mexico | March-August 1996 | Work-shift avg (6 - 12 h) ^a | 67.3 | 95th: 105.8 |
| Thaller et al. (2008) | Galveston, TX | Summer 2002-2004 | 1-h max | 35 (median) | Max: 118 |

* Note: Studies presented in order of first appearance in the text of this section.

NR = not reported.

^aSome or all measurements obtained from monitors located off site of outdoor activity.

^b1-h avg, preceding lung function measurement, as reported in the pooled analysis by [Kinney et al. \(1996\)](#).

^cConcentrations converted from µg/m³ to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

^dIndividual-level estimates calculated from concentrations measured in different segments of hiking trail.

Children Attending Summer Camps

1 Studies of children attending summer camps, most of which were discussed in the 1996
2 O₃ AQCD, have provided important evidence of the impact of ambient O₃ exposure on
3 respiratory effects in young, healthy children. In addition to the improved exposure
4 assessment as described above, these studies were noted for their daily assessment of
5 lung function by trained staff over 1- to 2-week periods in the mornings and late
6 afternoons before and after hours of outdoor activity ([Thurston et al., 1997](#); [Berry et al.,](#)
7 [1991](#); [Spektor and Lippmann, 1991](#); [Avol et al., 1990](#); [Burnett et al., 1990](#); [Higgins et al.,](#)
8 [1990](#); [Raizenne et al., 1989](#); [Spektor et al., 1988a](#)).

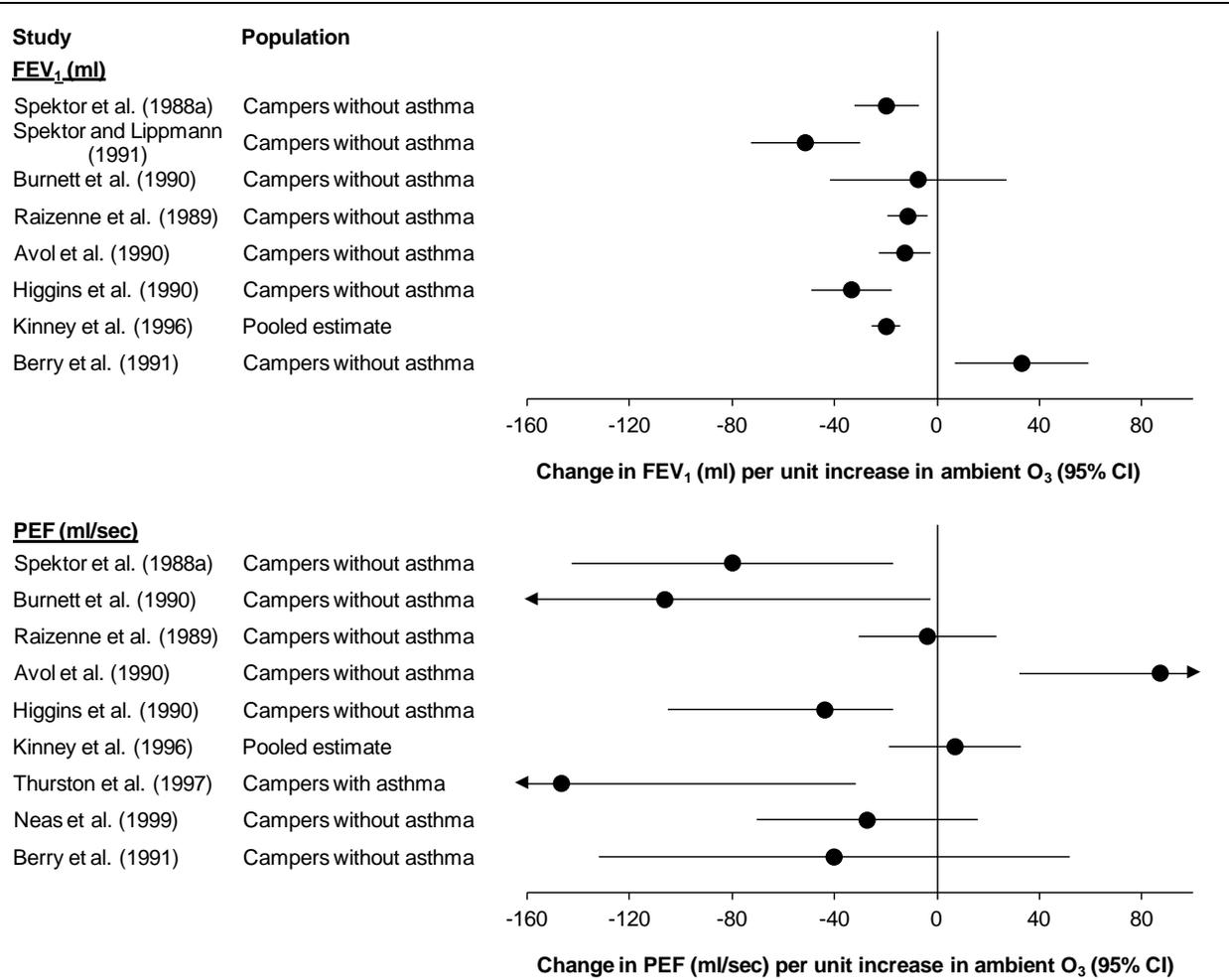
9 In groups mostly comprising healthy children (ages 7-17 years), decrements in FEV₁
10 were associated consistently with increases in ambient O₃ concentration averaged over
11 the 1-12 hours preceding lung function measurement ([Figure 6-3](#) and [Table 6-3](#)). [Kinney](#)
12 [et al. \(1996\)](#) corroborated this association in a re-analysis combining 5,367 lung function
13 measurements collected from 616 healthy children from six studies ([Spektor and](#)
14 [Lippmann, 1991](#); [Avol et al., 1990](#); [Burnett et al., 1990](#); [Higgins et al., 1990](#); [Raizenne et](#)
15 [al., 1989](#); [Spektor et al., 1988a](#)). Based on uniform statistical methods, a -20 ml (95% CI:
16 -25, -14) change in afternoon FEV₁ was estimated for a 40-ppb increase in O₃
17 concentration averaged over the 1 hour before lung function measurement ([Kinney et al.,](#)
18 [1996](#)) (all effect estimates are standardized to increments specific to the O₃ averaging
19 time as detailed in [Section 2.1](#)). All of the studies in the pooled analysis were conducted

1 during summer months but were diverse in locations examined (i.e., Northeast U.S.,
2 Canada, California), range in ambient concentrations of O₃ (presented within [Table 6-2](#))
3 and other pollutants measured, and magnitudes of association observed. Study-specific
4 effect estimates ranged between a 0.76 and 48 mL decrease or a 0.3% to 2.2% decrease in
5 study mean FEV₁ per 40-ppb increase in 1-h avg O₃.

6 Among camp studies included the pooled analysis plus others, associations for peak
7 expiratory flow (PEF) were more variable than were those for FEV₁, as indicated by the
8 wider range in effect estimates and wider 95% CIs ([Figure 6-3](#) and [Table 6-3](#)).

9 Nonetheless, in most cases, increases in ambient O₃ concentration were associated with
10 decreases in PEF. The largest O₃-associated decrease in PEF (mean 2.8% decline per
11 40-ppb increase in 1-h max O₃) was found in a group of campers with asthma, in whom
12 an increase in ambient O₃ concentration also was associated with increases in chest
13 symptoms and bronchodilator use ([Thurston et al., 1997](#)).

14 For both FEV₁ and PEF, the magnitude of association was not related to the study mean
15 ambient 1-h avg or max O₃ concentration. With exclusion of results from [Spektor and](#)
16 [Lippmann \(1991\)](#), larger O₃-associated FEV₁ decrements were found in populations with
17 lower mean FEV₁. No trend was found with mean PEF. Sufficient data were not provided
18 to assess whether the temporal variability in O₃ concentrations, activity levels of subjects,
19 or associations with other pollutants contributed to between-study heterogeneity in O₃
20 effect estimates.



Note: Results generally are presented in order of increasing mean ambient O₃ concentration. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 1-h avg or 1-h max O₃ concentration and a 30-ppb increase for 12-h avg O₃ concentration.

Figure 6-3 Changes in FEV₁ (mL) or PEF (mL/sec) in association with ambient ozone concentrations among children attending summer camp.

Table 6-3 Additional characteristics and quantitative data for studies represented in Figure 6-3.

| Study | Location | Population, Mean FEV ₁ (mL) or PEF (mL/sec) | Standardized Percent Change (95% CI) ^a | Standardized Effect Estimate (95% CI) ^a |
|---|--|--|---|--|
| | | | | FEV₁ |
| | | | | (mL) |
| Spektor et al. (1988a) | Fairview Lake, NJ | 91 campers without asthma ages 8-15 yr, 2,140 | -0.93 (-1.5, -0.35) ^b | -20.0 (-32.5, -7.5) ^b |
| Spektor and Lippmann (1991) | Fairview Lake, NJ | 46 campers without asthma ages 8-14 yr, 2,390 | -2.2 (-3.0, -1.3) ^b | -51.6 (-72.8, -30.4) ^b |
| Burnett et al. (1990) | Lake Couchiching, Ontario, Canada | 29 campers without asthma ages 7-15 yr, 2,410 | -0.32 (-1.7, 1.1) ^b | -7.6 (-42.1, 26.9) ^b |
| Raizenne et al. (1989) | Lake Erie, Ontario, Canada | 112 campers without asthma mean age 11.6 yr, 2,340 | -0.50 (-0.83, -0.16) ^b | -11.6 (-19.4, -3.8) ^b |
| Avol et al. (1990) | Pine Springs, CA | 295 campers without asthma ages 8-17 yr, 2,190 | -0.58 (-1.0, -0.12) ^b | -12.8 (-23.0, -2.6) ^b |
| Higgins et al. (1990) | San Bernardino, CA | 43 campers without asthma ages 7-13 yr, 2,060 | -1.6 (-2.4, -0.87) ^b | -33.6 (-49.3, -17.9) ^b |
| Kinney et al. (1996) | Pooled analysis of preceding 6 studies | 616 campers without asthma ages 7-17 yr, 2,300 | -0.87 (-1.1, -0.63) | -20.0 (-25.5, -14.5) ^b |
| Berry et al. (1991) | Hamilton, NJ | 14 campers without asthma 58% age <14 yr, NA | NA | 32.8 (6.9, 58.7) |
| | | | | PEF |
| | | | | (mL/sec) |
| Spektor et al. (1988a) | Fairview Lake, NJ | 91 campers without asthma ages 8-15 yr, 4,360 | -1.8 (-3.3, -0.40) | -80.0 (-142.7, -17.3) ^b |
| Burnett et al. (1990) | Lake Couchiching, Ontario, Canada | 29 campers without asthma ages 7-15 yr, 5,480 | -1.9 (-3.8, -0.05) | -106.4 (-209.9, -2.9) ^b |
| Raizenne et al. (1989) | Lake Erie, Ontario, Canada | 112 campers without asthma mean age 11.6 yr, 5,510 | -0.07 (-0.56, 0.41) | -4.0 (-30.7, 22.7) ^b |
| Avol et al. (1990) | Pine Springs, CA | 295 campers without asthma ages 8-17 yr, 4,520 | 1.9 (0.71, 3.1) | 86.8 (31.9, 142) ^b |
| Higgins et al. (1990) | San Bernardino, CA | 43 campers without asthma ages 7-13 yr, 5,070 | -0.87 (-2.1, 0.34) | -44.0 (-105, 17.2) ^b |
| Kinney et al. (1996) | Pooled analysis of preceding 6 studies | 616 campers without asthma ages 7-17 yr, 4,222 | 0.31 (-0.88, 1.5) | 6.8 (-19.1, 32.7) ^b |
| Thurston et al. (1997) | CT River Valley, CT | 166 campers with asthma ages 7-13 yr, 5,333 | -2.8 (-4.9, -0.59) | -146.7 (-261.7, -31.7) |
| Neas et al. (1999) | Philadelphia, PA | 156 campers without asthma ages 6-11 yr, 4,717 | -0.58 (-1.5, 0.33) | -27.5 (-70.8, 15.8) |
| Berry et al. (1991) | Hamilton, NJ | 14 campers without asthma 58% age <14 yr, NA | NA | -40.4 (-132.1, 51.3) |

*Includes studies from [Figure 6-3](#).

NA = Data not available.

^aAll results are standardized to a 40-ppb increase in 1-h avg or 1-h max O₃, except that from [Neas et al. \(1999\)](#), which is standardized to a 30-ppb increase in 12-h avg (9 a.m.-9 p.m.) O₃.

^bEffect estimates were reported in the pooled analysis by [Kinney et al. \(1996\)](#).

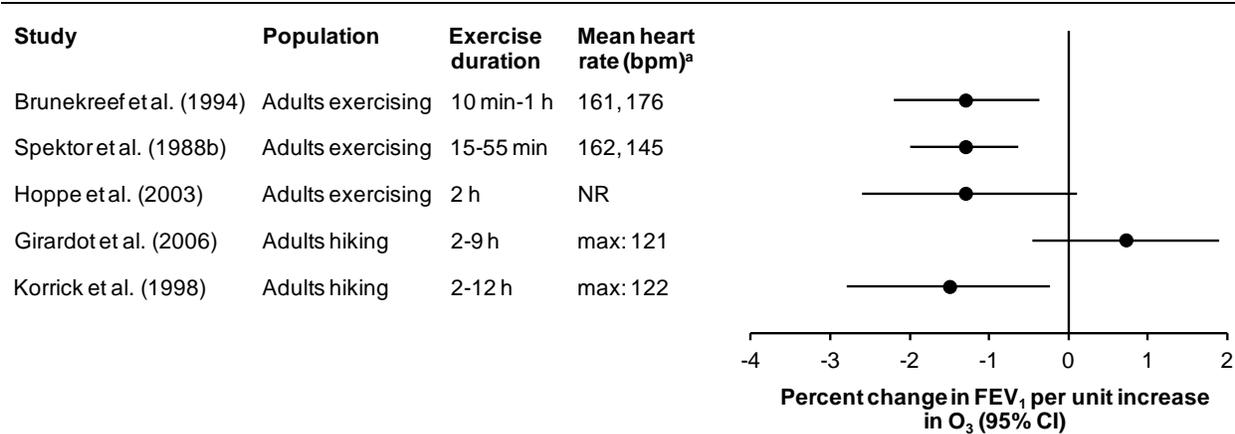
1 Similar to controlled human exposure studies, camp studies found interindividual
2 variability in the magnitude of O₃-associated changes in lung function. Based on separate
3 regression analyses of data from individual subjects, increases in ambient O₃
4 concentration were associated with a wide range of changes in lung function across
5 subjects ([Berry et al., 1991](#); [Higgins et al., 1990](#); [Spektor et al., 1988a](#)). For example,
6 among children attending camp in Fairview Lake, NJ, 36% of subjects had statistically
7 significant O₃-associated decreases in FEV₁, and the 90th percentile of response was a
8 6.3% decrease in FEV₁ per a 40-ppb increase in 1-h avg O₃ ([Spektor et al., 1988a](#)).

9 In contrast with previous studies, a recent study of children attending six different
10 summer camps in Belgium did not find an association between ambient O₃ concentration
11 and lung function ([Nickmilder et al., 2007](#)). This study examined similar ambient O₃
12 concentrations as did previous studies ([Table 6-2](#)) but used a less rigorous methodology.
13 Lung function was measured only once in each subject, and mean lung function was
14 compared among camps. Children at camps with higher daily 1-h max or 8-h max O₃
15 concentrations did not consistently have larger decreases in mean intraday FEV₁ or
16 FEV₁/FVC ([Nickmilder et al., 2007](#)).

Populations Exercising Outdoors

17 As discussed in the 1996 and 2006 O₃ AQCDs, epidemiologic studies of adults exercising
18 outdoors have provided evidence for lung function decrements in healthy adults
19 associated with increases in ambient O₃ exposure during exercise with durations (10 min
20 to 12 h) and intensities (heart rates 121-190 beats per min) in the range of those examined
21 in controlled human exposure studies ([Table 6-1](#)). As in the camp studies, lung function
22 was measured before and after exercise by trained staff. Collectively, studies of adults
23 found FEV₁ decrements of 1.3 to 1.5% per unit increase in O₃¹ ([Figure 6-4](#) and
24 [Table 6-4](#)). The magnitude of association did not appear to be related to study mean
25 ambient O₃ concentrations ([Table 6-2](#)), exercise duration, or the mean heart rate
26 measured during exercise ([Figure 6-4](#) and [Table 6-4](#)). Increases in ambient O₃
27 concentration also were associated with decreases in lung function in children exercising
28 outdoors ([Table 6-4](#)).

¹Effect estimates were standardized to a 40-ppb increase in O₃ averaged over 15 min to 1 h and a 30-ppb increase for O₃ averaged over 2 to 12 h.



Note: Studies generally are presented in order of increasing duration of outdoor exercise. Data refer to the maximum or mean measured during exercise or in different groups or conditions as described in Table 6-4.

^abpm = beats per minute. NR = Not reported. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for O₃ concentrations averaged over 15 minutes to 1 hour and a 30-ppb increase for O₃ concentrations averaged over 2 to 12 hours.

Figure 6-4 Percent change in FEV₁ in association with ambient ozone concentrations among adults exercising outdoors.

Table 6-4 Additional characteristics and quantitative data for studies represented in Figure 6-4 plus results from studies in children exercising outdoors.

| Study* | Location | Population | Exercise Duration, Mean Heart Rate | O ₃ Averaging Time | Parameter | Standardized Percent Change (95% CI) ^a |
|---|-------------------------|--|--|--|-------------------------|---|
| Studies of adults | | | | | | |
| Brunekreef et al. (1994) | Netherlands | 29 adults exercising, ages 18-37 yr | 10 min - 2.4 h, HR: 161 bpm (training), 176 bpm (races) | Exercise duration | FEV ₁ PEF | -1.3 (-2.2, -0.37) -2.5 (-3.8, -1.2) |
| Spektor et al. (1988b) | Tuxedo, NY | 30 adults exercising, ages 21-44 yr | 15 - 55 min, HR: 162 bpm if $\dot{V}_E > 100$ L, 145 bpm if \dot{V}_E 60-100 L | 30-min avg | FEV ₁ | -1.31 (-2.0, -0.65) |
| Hoppe et al. (2003) | Munich, Germany | 43 adults and children exercising, ages 13-38 yr | 2 h, HR: NR | 30-min max (1-4 p.m.) | FEV ₁ PEF | -1.3 (-2.6, 0.10) -2.8 (-5.9, 0.31) |
| Girardot et al. (2006) | Great Smoky Mt, TN | 354 adult day hikers, ages 18-82 yr | 2-9 h, max HR: 121 bpm | Hike duration | FEV ₁ PEF | 0.72 (-0.46, 1.90) 3.5 (-0.11, 7.2) |
| Korrick et al. (1998) | Mt. Washington, NH | 530 adult day hikers, ages 18-64 yr | 2-12 h, max HR: 122 bpm | Hike duration | FEV ₁ PEF | -1.5 (-2.8, -0.24) -0.54 (-4.0, 2.9) |
| Selwyn et al. (1985) | Houston, TX | 24 adults exercising, ages 29-47 yr | Duration: NR, max HR: 179 bpm in males, 183 bpm in females | 15-min max | FEV ₁ | -16 mL (-28.8, -3.2) ^b |
| Studies of children not included in Figure 6-4 | | | | | | |
| Braun-Fahrlander et al. (1994) | Switzerland | 128 children exercising, ages 9-11 yr | 10 min, max HR: 180 bpm | 30-min avg | PEF | -3.8 (-6.7, -0.96) |
| Castillejos et al. (1995) | Mexico City, Mexico | 40 children exercising, ages 7-11 yr | 2 15 min with 15 min rest periods, max HR: <190 bpm | 1-h avg over full exercise-rest period | FEV ₁ | -0.48 (-0.72, -0.24) |
| Hoek et al. (1993) | Wageningen, Netherlands | 65 children exercising, ages 7-12 yr | 25 min-1.5 h, HR: NR | 1-h max | PEF | -2.2 (-4.9, 0.54) |

*Includes studies from [Figure 6-4](#), plus others.

HR = heart rate, bpm = beats per minute, \dot{V}_E = minute ventilation, NR = Not reported.

^aEffect estimates are standardized to a 40-ppb increase for O₃ concentrations averaged over 15 minutes to 1 hour and a 30-ppb increase for O₃ concentrations averaged over 2 to 12 hours.

^bResults not included in the figure because data were not provided to calculate percent change in lung function.

1 Compared with the studies of individuals exercising outdoors described above, analyses
 2 of day-hikers assessed lung function only on one day per subjects but examined longer
 3 periods of outdoor activity and included much larger sample sizes. Studies of adult day-
 4 hikers had similar design but produced contrasting results ([Girardot et al., 2006](#); [Korrick
 5 et al., 1998](#)). Among 530 hikers on Mt. Washington, NH, [Korrick et al. \(1998\)](#) reported

1 posthike declines in FEV₁ and FVC of 1.5% and 1.3%, respectively, per a 30-ppb
2 increase in 2- to 12-h avg O₃. Associations with FEV₁/FVC, FEF_{25-75%}, and PEF were
3 weaker. In contrast, among 354 hikers on Great Smoky Mt, TN, [Girardot et al. \(2006\)](#)
4 found that higher O₃ concentrations were associated with posthike increases in many of
5 the same lung function indices ([Figure 6-4](#) and [Table 6-4](#)). These studies were similar in
6 the examination of a mostly white, healthy population and of changes in lung function
7 associated with ambient O₃ concentrations measured on site during multihour (2-12 h)
8 periods of outdoor exercise. Mean O₃ concentrations were similar as were the population
9 mean and variability in lung function. However, [Girardot et al. \(2006\)](#) differed from
10 [Korrick et al. \(1998\)](#) in several aspects, including a shorter hike time (maximum: 9 versus
11 12 h), older age of subjects (maximum: 82 versus 64 yr), and measurement of lung
12 function by a larger number of less well-trained technicians. The impact of these
13 differences on the heterogeneity in results between the studies was not examined.

14 Similar to the camp studies, some studies of outdoor exercise examined and found
15 interindividual variability in the magnitude of O₃-associated decreases in lung function.
16 In [Korrick et al. \(1998\)](#), although a 30-ppb increase in 2- to 12-h avg ambient O₃
17 concentration was associated with a group mean decrement in FEF_{25-75%} of -0.81%
18 (95% CI: -4.9, 3.3), some individuals experienced a >10% decline. The odds of >10%
19 decline in FEF_{25-75%} increased with increasing ambient O₃ concentration (OR: 2.3
20 [95% CI: 1.2, 6.7] per 30-ppb increase in 2- to 12-h avg O₃). Likewise, [Hoppe et al.](#)
21 [\(2003\)](#) found that compared with days with 30-min max (1-4 p.m.) ambient O₃
22 concentrations <40 ppb, on days with O₃ >50 ppb, 14% of athletes had at least a 10%
23 decrease in lung function or 20% increase in airway resistance.

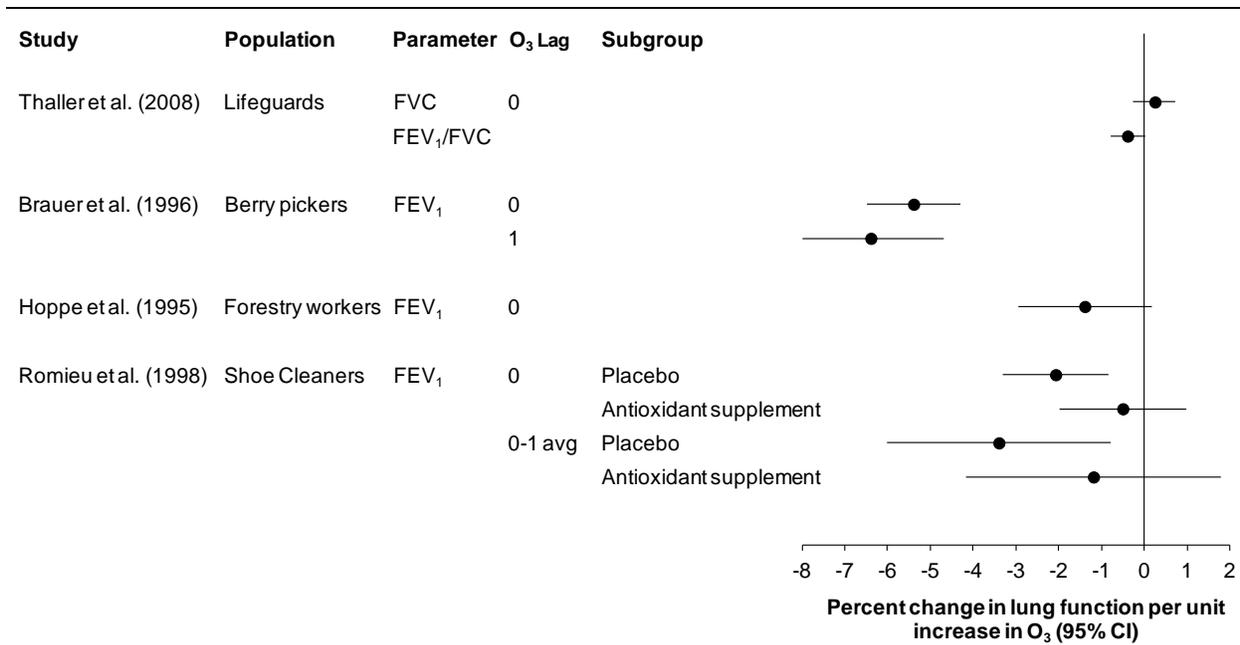
Outdoor Workers

24 Consistent findings in outdoor workers add to the evidence that short-term increases in
25 ambient O₃ exposure decrease lung function in healthy adults ([Figure 6-5](#) and [Table 6-5](#)).
26 Except for [Hoppe et al. \(1995\)](#), studies used central site ambient O₃ concentrations.
27 However, in outdoor workers, ambient concentrations have been more highly correlated
28 with and similar in magnitude to personal exposures (Section [4.3.3](#)) likely because
29 workers spend long periods of time outdoors (6-14 hours across studies) and the O₃
30 averaging times examined correspond to periods of outdoor work. For example, in a
31 subset of berry pickers, the correlation and ratio of personal to ambient 24-h avg O₃
32 concentrations (15 km from work site) were 0.64 and 0.96, respectively ([Brauer and](#)
33 [Brook, 1997](#)). The 6-h avg personal-ambient ratio in a population of shoe cleaners in
34 Mexico City was 0.56 ([O'Neill et al., 2003](#)). Many studies of outdoor workers found that
35 in addition to same-day concentrations, O₃ concentrations lagged 1 or 2 days ([Chan and](#)

1 [Wu, 2005](#); [Brauer et al., 1996](#)) or averaged over 2 days ([Romieu et al., 1998b](#)) were
2 associated with equal or larger decrements in lung function ([Figure 6-5](#) and [Table 6-5](#)).

3 Similar to other populations with increased outdoor exposure, most of the magnitudes of
4 O₃-associated lung function decrements in outdoor workers were small, i.e., <1% to 3.4%
5 per unit increase in O₃ concentration¹. The magnitude of decrease was not found to
6 depend strongly on duration of outdoor work or ambient O₃ concentration. The largest
7 decrease (6.4% per 40-ppb increase in 1-h max O₃) was observed in berry pickers in
8 British Columbia who were examined during a period of relatively low ambient O₃
9 concentrations (work shift mean: 26.0 ppb [SD: 11.8]) but had longer daily periods of
10 outdoor work (8-14 hours) ([Brauer et al., 1996](#)) ([Figure 6-5](#) and [Table 6-5](#)). However, a
11 much smaller O₃-associated decrease in FEV₁ was found in shoe cleaners in Mexico City
12 who were examined during a period of higher O₃ concentrations (work shift mean:
13 67.3 ppb [SD: 24]) but had period of outdoor work that was as long as that of the berry
14 pickers. The smallest magnitude of decrease (-0.4% [95% CI: -0.8, 0] in afternoon
15 FEV₁/FVC per 40-ppb increase in 1-h max O₃) was observed in lifeguards in Galveston,
16 TX ([Thaller et al., 2008](#)) whose outdoor work periods were shorter than those of the berry
17 pickers but characterized by a similar range of ambient O₃ concentrations. Not all studies
18 provided information on ventilation rate or pulse rate, thus it was not possible to ascertain
19 whether differences in the magnitude of O₃-associated lung function decrement across
20 studies were related to differences in the level of exertion of workers.

¹Effect estimates were standardized to a 40-ppb increase for O₃ averaged over 30 min to 1 h and a 30-ppb increase for O₃ averaged over 8 or 12 h.



Note: Studies generally are presented in order of increasing mean ambient O₃ concentration. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 30-min, 1-h avg, or 1-h max O₃ concentrations.

Figure 6-5 Percent change in FEV₁ or FEV₁/FVC in association with ambient ozone concentrations among outdoor workers.

Table 6-5 Additional characteristics and quantitative data for studies represented in Figure 6-5.

| Study* | Location | Population | Parameter | Duration of Outdoor Work | O ₃ Averaging Time | O ₃ Lag | Subgroup | Standardized Percent Change (95% CI) ^a |
|--|--------------------------|--|-----------------------|--------------------------|--|--------------------|-------------|---|
| Thaller et al. (2008) | Galveston, TX | 142 lifeguards, ages 16-27 yr | FVC | 6-8 h | 1-h max | 0 | | 0.24 (-0.28, 0.72) |
| | | | | | 12-h avg | | | 0.15 (-0.06, 0.36) |
| | | | FEV ₁ /FVC | | 1-h max | | | -0.40 (-0.80, 0) |
| | | | | | 12-h avg | | | -0.60 (-1.2, 0) |
| Brauer et al. (1996) | British Columbia, Canada | 58 berry pickers, ages 10-69 yr | FEV ₁ | 8-14 h | 1-h max | 0 | | -5.4 (-6.5, -4.3) |
| | | | | | | 1 | | -6.4 (-8.0, -4.7) |
| Hoppe et al. (1995) | Munich, Germany | 41 forestry workers, ages 20-60 yr | FEV ₁ | Not reported | 30-min max (1 - 4 p.m.) | 0 | | -1.4 (-3.0, 0.16) |
| Romieu et al. (1998b) | Mexico City, Mexico | 47 male shoe cleaners, mean (SD) age: 38.9 (10) yr | FEV ₁ | Mean (SD): 9 h (1) | 1-h avg before lung function measurement | 0 | Placebo | -2.1 (-3.3, -0.85) |
| | | | | | | | Antioxidant | -0.52 (-2.0, 0.97) |
| | | | | | | 0-1 avg | Placebo | -3.4 (-6.0, -0.78) |
| | | | | | | 1 | Antioxidant | -1.2 (-4.2, 1.8) |
| Chan and Wu (2005)^b | Taichung City, Taiwan | 43 mail carriers. Mean (SD) age: 39 (8) yr | PEF | 8 h | 1-h max | 0 | | -1.3 (-1.7, -0.92) |
| | | | | | | 1 | | -1.4 (-1.7, -1.2) |
| | | | | | 8-h avg (9 a.m. - 5 p.m.) | 0 | | -1.6 (-2.2, -1.1) |
| | | | | | | 1 | | -1.9 (-2.5, -1.3) |

*Includes studies from [Figure 6-5](#), plus others.

^aEffect estimates are standardized to a 40-ppb increase for 30-min, 1-h avg, or 1-h max O₃ and a 30-ppb increase for 8-h avg or 12-h avg O₃.

^bPEF results not included in figure.

Associations at Lower Ozone Concentrations

1 In some studies of populations with increased outdoor exposures, O₃-associated lung
2 function decrements were observed when maximum or average ambient O₃
3 concentrations over 30 minutes to 12 hours did not exceed 80 ppb ([Chan and Wu, 2005](#);
4 [Korrick et al., 1998](#); [Hoppe et al., 1995](#); [Braun-Fahrlander et al., 1994](#)) (presented within
5 [Table 6-2](#)). [Korrick et al. \(1998\)](#) found associations between hike-time average (2-12 h)
6 O₃ concentrations and lung function between concentrations 40 and 74 ppb but not
7 <40 ppb. Several other studies that included higher maximum ambient O₃ concentrations
8 restricted analyses to observations with 10-min to 1-hour average O₃ concentrations
9 <80 ppb ([Table 6-6](#)). [Higgins et al. \(1990\)](#) found that O₃-associated lung function
10 decrements in children attending camp were limited largely to 1-h avg ambient
11 concentrations >120 ppb; however, many other studies found associations in the lower
12 range of O₃ concentrations ([Table 6-6](#)). Among adults exercising outdoors, [Spektor et al.](#)

1 [\(1988b\)](#) found that for most lung function parameters, effect estimates in analyses
 2 restricted to 30-min max ambient O₃ concentrations <80 ppb were similar to those
 3 obtained for the full range of O₃ concentrations ([Table 6-6](#)). In a study of children
 4 attending summer camp, similar effects were estimated for the full range of 1-h avg O₃
 5 concentrations and those <60 ppb ([Spektor et al., 1988a](#)). [Brunekreef et al. \(1994\)](#) found
 6 increases in ambient O₃ concentration (10-min to 1-h) during outdoor exercise to be
 7 associated with decreases in FEV₁ in analyses restricted to concentrations <61
 8 ([Table 6-6](#)) and <51 ppb (quantitative results not reported). Whereas [Brunekreef et al.](#)
 9 ([1994](#)) found that effect estimates were near zero with O₃ concentrations <41 ppb
 10 ([Brunekreef et al., 1994](#)), [Brauer et al. \(1996\)](#) found that associations persisted with
 11 1-h max O₃ concentrations <40 ppb (quantitative results not provided).

Table 6-6 Associations between ambient ozone concentration and FEV₁ decrements in different ranges of ambient ozone concentrations.

| Study | Location | Population | O ₃ Averaging Time | O ₃ Concentration Range | Standardized Percent Change (95% CI) ^a |
|--|--------------------|--|---|--|---|
| Brunekreef et al. (1994) | Netherlands | 29 adults exercising, ages 18-37 yr | 10-min to 1-hour average during exercise | Full range O ₃ <61 ppb | -1.3 (-2.2, -0.37) -2.1 (-4.5, 0.32) |
| Spektor et al. (1988a) | Fairview Lake, NJ | 91 children without asthma at camp, ages 8-15 yr | 1-hour average before afternoon FEV ₁ measurement | Full range O ₃ <60 ppb O ₃ <80 ppb | -2.7 (-3.3, -2.0) -2.2 (-3.7, -0.80) -1.4 (-2.5, -0.34) |
| Spektor et al. (1988b) | Tuxedo, NY | 30 adults exercising, ages 21-44 yr | 30-min average during exercise | Full range O ₃ <80 ppb | -1.3 (-2.0, -0.64) -1.3 (-2.4, -0.08) |
| 1998) | Mt. Washington, NH | 53 adult day hikers, ages 18-64 yr | Hike duration (2-12 h) | Full range O ₃ 40-74 ppb | -1.5 (-2.8, -0.24) -2.6 (-4.9, -0.32) |
| Higgins et al. (1990) | San Bernardino, CA | 43 children without asthma at camp, ages 7-13 yr | 1-hour average in the 6-hours before FEV ₁ measurement | >120 ppb <120 ppb | -1.4 (-2.8, 0.03) 0.34 (-1.3, 2.0) |

^aResults are presented in order of increasing maximum O₃ concentration included in models. Effect estimates are standardized to a 40-ppb increase for O₃ concentrations averaged over 10 min to 1 h and a 30-ppb increase for O₃ concentrations averaged over 2 to 12 h.

Children with Asthma

12 Increases in ambient O₃ concentration are associated with lung function decrements in
 13 children with asthma in epidemiologic studies conducted across diverse geographical
 14 locations and a range of ambient O₃ concentrations ([Table 6-7](#)). Whereas most studies of
 15 populations with increased outdoor exposures monitored O₃ concentrations at the site of
 16 subjects' outdoor activities and used trained staff to measure lung function, studies of

1 children with asthma relied more on O₃ measured at central monitoring sites and lung
 2 function measured by subjects. Nonetheless, compared with the camp studies, studies of
 3 children with asthma have provided an understanding of the changes in lung function
 4 associated with patterns of outdoor activity and ambient O₃ exposure that likely better
 5 represent those of children in the general population. Further, these studies have provided
 6 more information on factors that potentially may increase the risk of O₃-associated
 7 respiratory effects and on potential confounding by copollutant exposure or meteorology.

Table 6-7 Mean and upper percentile concentrations of ozone in epidemiologic studies of lung function in children with asthma.

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|---|--|--|-------------------------------|---|--|
| Jalaludin et al. (2000) | Sydney, Australia | February-December 1994 | 15-h avg (6 a.m.-9 p.m.) | 12 | Max: 43 |
| | | | 1-h max | 26 | 91 |
| Lewis et al. (2005) | Detroit, MI | February 2001-May 2002 | 24-h avg | 27.6, 26.5 ^a | Overall max: 66.3 ^a |
| | | | 8-h max | 40.4, 41.4 ^a | Overall max: 92.0 ^a |
| Just et al. (2002) | Paris, France | April-June 1996 | 24-h avg | 30.0 ^b | Max: 61.7 ^b |
| Hoppe et al. (2003) | Munich, Germany | Summers 1992-1995 | 30-min max (1-4 p.m.) | High O ₃ days: 66.9 ^c Control O ₃ days: 32.5 ^c | Max: 91 (high O ₃ days) ^c 39 (control O ₃ days) ^c |
| Thurston et al. (1997) | CT River Valley, CT | June 1991-1993 | 1-h max | 83.6 ^c | Max: 160 ^c |
| Romieu et al. (2006); (2004b; 2002) | Mexico City, Mexico | October 1998-April 2000 | 8-h max | 69 | Max: 184 |
| | | | 1-h max | 102 | Max: 309 |
| Romieu et al. (1997) | Southern Mexico City, Mexico | April-July 1991; November 1991-February 1992 | 1-h max | 196 | Max: 390 |
| Romieu et al. (1996) | Northern Mexico City, Mexico | April-July 1991; November 1991-February 1992 | 1-h max | 190 | Max: 370 |
| O'Connor et al. (2008) | Boston, MA; Bronx, Manhattan NY; Chicago, IL; Dallas, TX, Seattle, WA; Tucson, AZ (ICAS) | August 1998-July 2001 | 24-h avg | NR | NR |
| Mortimer et al. (2002) (2000) | Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO (NCICAS) | June-August 1993 | 8-h avg (10 a.m.-6 p.m.) | 48 | NR |
| Gielen et al. (1997) | Amsterdam, Netherlands | April-July 1995 | 8-h max | 34.2 ^b | Max: 56.5 ^b |

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|----------------------|--|-------------------------------|---------------------------------|---|
| Dales et al. (2009) (2009a) | Windsor, ON, Canada | October-December 2005 | 24-h avg 1-h max | 13.0 27.2 | 75th: 26.0 75th: 32.8 |
| Rabinovitch et al. (2004) | Denver, CO | November-March 1999-2002 | 1-h max | 28.2 | 75th: 36.0, Max 70.0 |
| Barraza-Villarreal et al. (2008) | Mexico City, Mexico | June 2003-June 2005 | 8-h moving avg | 31.6 | Max: 86.3 |
| Wiwatanadate and Trakultivakorn (2010) | Chiang Mai, Thailand | August 2005-June 2006 | 24-h avg | 17.5 | 90th: 26.82, Max: 34.65 |
| Delfino et al. (2004) | Alpine, CA | September-October 1999; April-June 2000 | 8-h max | 62.9 | 90th: 83.9, Max: 105.9 |
| Hernández-Cadena et al. (2009) | Mexico City, Mexico | May-September 2005 | 24-h avg 1-h max | 26.3 74.5 | 75th: 35.3; Max: 62.8 75th: 92.5; Max: 165 |

*Note: Studies presented in order of first appearance in the text of this section.

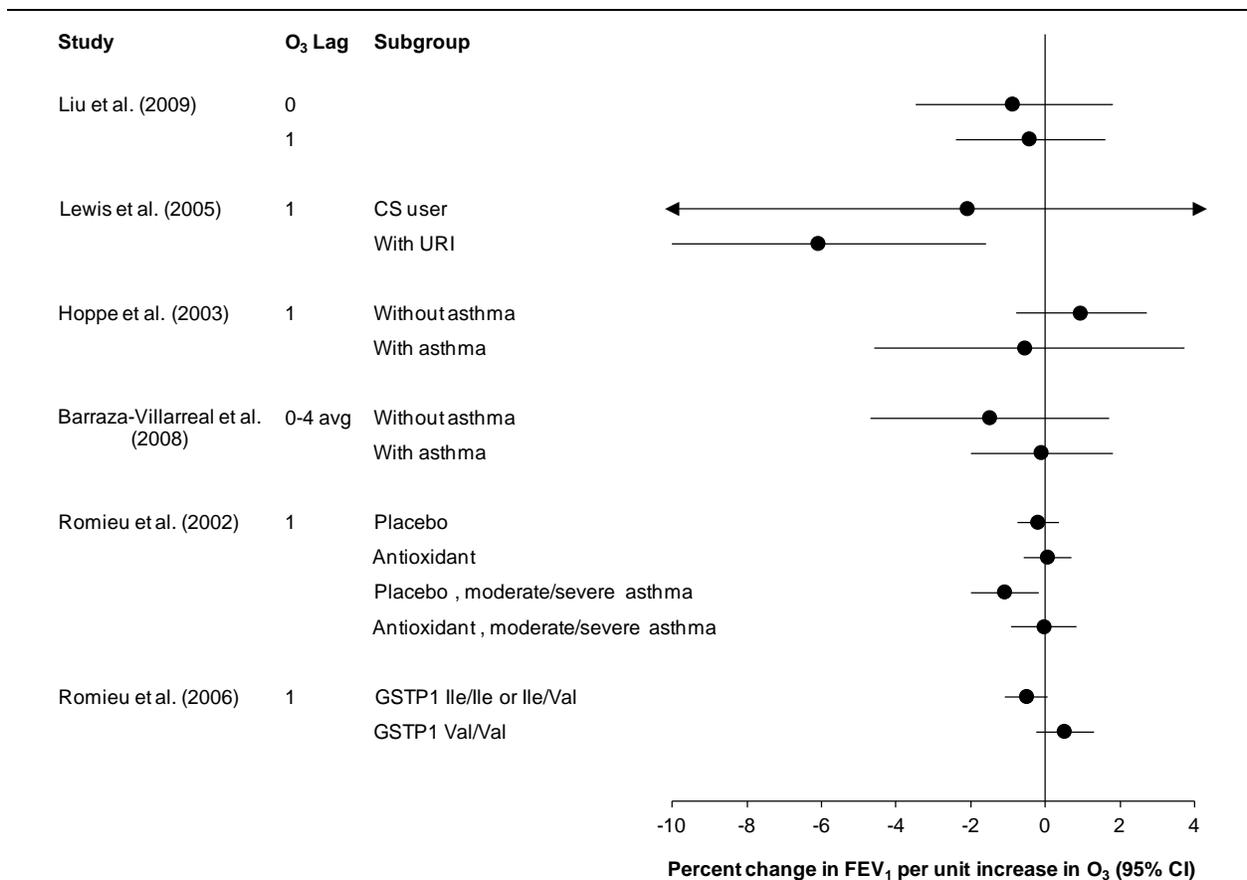
ICAS = Inner City Asthma Study, NR = Not Reported, NCICAS = National Cooperative Inner-City Asthma Study.

^aMeasurements at two sites established by investigators and located within 5 km of most subjects' residences.

^bConcentrations converted from µg/m³ to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

^cMeasured where subjects spent daytime hours.

1 In a majority of studies, including large U.S. multicity studies and several smaller studies
2 conducted in the U.S., Mexico City, and Europe, an increase in ambient O₃ concentration
3 (various averaging times and lags) was associated with a decrement in FEV₁ ([Figure 6-6](#)
4 and [Table 6-8](#)) or PEF ([Figure 6-7](#) and [Table 6-9](#)) in children with asthma. Results were
5 more variable for FEV₁, which typically was measured on nonconsecutive days, than for
6 PEF, which was measured daily. Further, associations with FEV₁ were found in specific
7 subgroups. Some studies found that increases in ambient O₃ concentration were
8 associated with greater lung function variability, i.e., a deviation from a baseline level.
9 These results pointed to associations of O₃ with poorer lung function, as indicated by a
10 decrease from the individual's mean lung function over the study period ([Jalaludin et al.,](#)
11 [2000](#)), a decrease in lung function over the course of the day ([Lewis et al., 2005](#)), or a
12 decrease in the lowest daily measurement ([Just et al., 2002](#)). Within many studies,
13 increases in O₃ concentration were associated concurrently (at the same or similar lag)
14 with decreases in lung function and increases in respiratory symptoms ([Just et al., 2002](#);
15 [Mortimer et al., 2002](#); [Gielen et al., 1997](#); [Romieu et al., 1997](#); [Thurston et al., 1997](#);
16 [Romieu et al., 1996](#)) (see [Figure 6-11](#) and [Table 6-20](#) for symptom results).



Note: Results generally are presented in order of increasing mean ambient O₃ concentration. CS = Corticosteroid, URI = Upper respiratory infection. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 30-min or 1-h max O₃ concentrations, a 30-ppb increase for 8-h max or 8-h avg O₃ concentrations, and a 20-ppb increase for 24-h avg O₃ concentrations.

Figure 6-6 Percent change in FEV₁ in association with ambient ozone concentrations among children with asthma.

Table 6-8 Characteristics and quantitative data for studies represented in Figure 6-6, of FEV₁ or FVC in children with asthma.

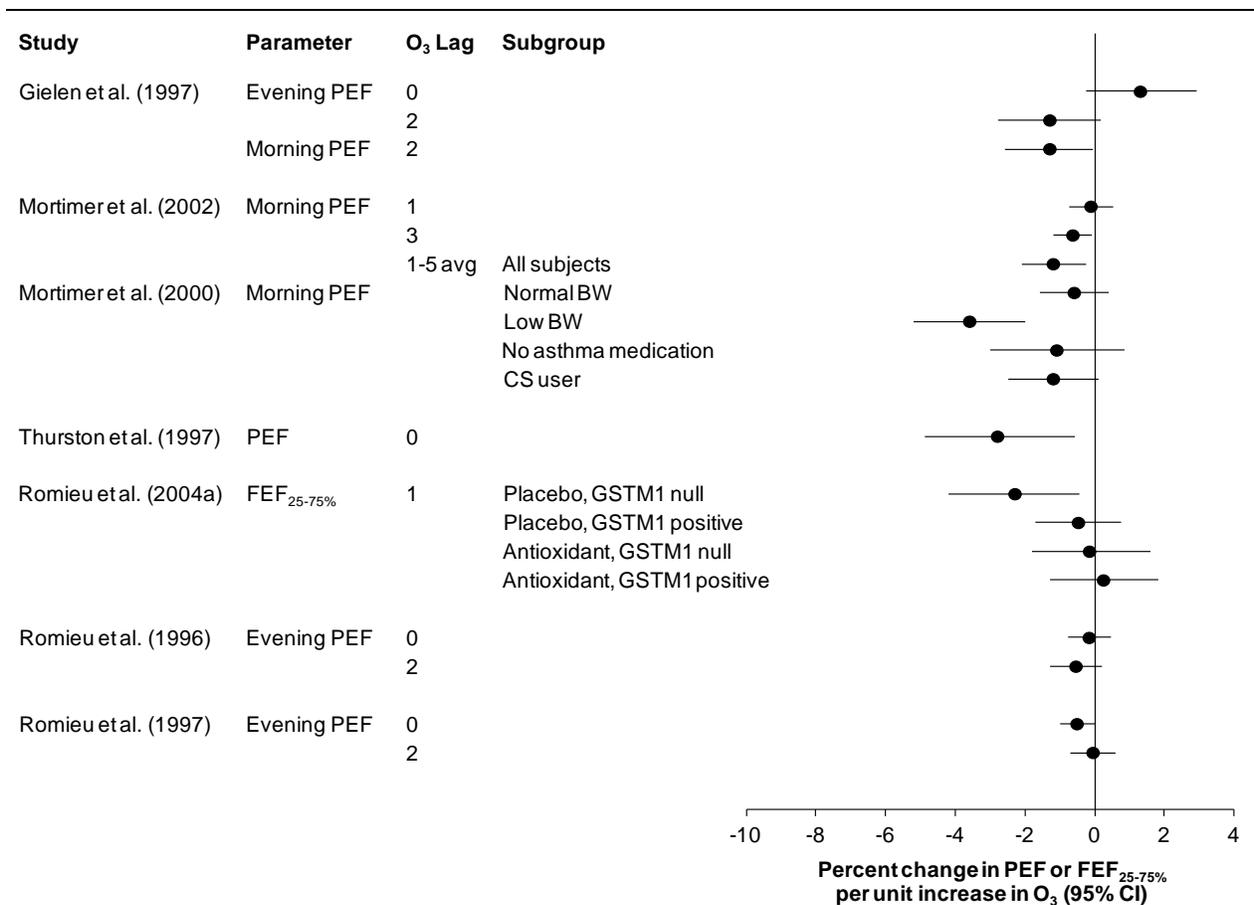
| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Parameter | Subgroup | Standardized Percent Change (95% CI) ^a |
|---|---|-------------------------------|--------------------|---|---|---|
| Liu et al. (2009a) | Windsor, ON, Canada 182 children with asthma, ages 9-14 yr | 24-h avg | 0 | FEV ₁ | | -0.89 (-3.5, 1.8) |
| | | | 1 | | | -0.44 (-2.4, 1.6) |
| Lewis et al. (2005) | Detroit, MI 86 children with asthma, mean (SD) age 9.1 (1.4) yr | 8-h max | 1 | Lowest daily FEV ₁ | CS user | -2.1 (-11.4, 8.3) |
| | | | 2 | | With URI | -6.1 (-10.4, -1.6) |
| Hoppe et al. (2003) | Munich, Germany 43 children, ages 12-23 yr | 30-min max (1-4 p.m.) | 1 | Afternoon FEV ₁ | Without asthma | 0.93 (-0.80, 2.7) |
| | | | | | With asthma | -0.56 (-4.6, 3.7) |
| Barraza-Villarreal et al. (2008) | Mexico City, Mexico 208 children, ages 6-14 yr | 8-h avg | 0-4 avg | FEV ₁ | 50 without asthma | -1.5 (-4.7, 1.7) |
| | | | | | 158 with asthma | -0.12 (-2.0, 1.8) |
| Romieu et al. (2002) | Mexico City, Mexico 158 children with asthma, ages 6-17 yr | 1-h max | 1 | FEV ₁ | Placebo | -0.21 (-0.77, 0.36) |
| | | | | | Antioxidant supplement | 0.05 (-0.60, 0.69) |
| | | | | | Placebo, moderate/severe asthma | -1.1 (-2.0, -0.19) |
| | | | | | Antioxidant supplement, moderate/severe asthma | -0.04 (-0.92, 0.83) |
| Romieu et al. (2006) | Mexico City, Mexico 151 children with asthma, mean age 9 yr | 1-h max | 1 | FEV ₁ | GSTP1 Ile/Ile or Ile/Val | -0.51 (-1.1, 0.05) |
| | | | | | GSTP1 Val/Val | 0.50 (-0.25, 1.3) |
| Studies not included in Figure 6-6^b | | | | | | |
| Dales et al. (2009) | Windsor, ON, Canada 182 children with asthma, ages 9-14 yr | 1-h max | 0 | Evening percent predicted FEV ₁ | | -0.47 (-1.9, 0.95) |
| Rabinovitch et al. (2004) | Denver, CO 86 children with asthma, ages 6-12 yr | 1-h max | 0-2 avg | Morning FEV ₁ (mL) | | 55 (-2.4, 108) |
| O'Connor et al. (2008) | Boston, MA; Bronx, Manhattan NY; Chicago, IL; Dallas, TX, Seattle, WA; Tucson, AZ 861 children with asthma, mean (SD) age 7.7 (2.0) yr | 24-h avg | 1-5 avg | Change in percent predicted FEV ₁ | | -0.41 (-1.0, 0.21) |

*Includes studies in [Figure 6-6](#), plus others

CS = corticosteroid, URI = Upper respiratory infection.

^aEffect estimates are standardized to a 40-ppb increase for 30-min or 1-h max O₃, a 30-ppb increase for 8-h max or 8-h avg O₃, and a 20-ppb increase for 24-h avg O₃.

^bResults not presented in [Figure 6-6](#) because a different form of FEV₁ with a different scale was examined or because sufficient data were not provided to calculate percent change in FEV₁.



Note: Results generally are presented in order of increasing mean ambient O₃ concentration. BW = birth weight, CS = Corticosteroid. Effect estimates are from single pollutant models and are standardized to a 40-ppb increase for 1-h max O₃ concentrations and a 30-ppb increase for 8-h max or 8-h avg O₃ concentrations.

Figure 6-7 Percent change in PEF or FEF_{25-75%} in association with ambient ozone concentrations among children with asthma.

Table 6-9 Characteristics and quantitative data for studies represented in Figure 6-7, of PEF or FEF_{25-75%} in children with asthma.

| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Parameter | Subgroup | Standardized Percent Change (95% CI) ^a |
|--|---|-------------------------------------|-----------------------|------------------------|--------------------------------|--|
| Gielen et al. (1997) | Amsterdam, Netherlands 61 children with asthma, ages 7-13 yr | 8-h max | 0 | Evening PEF | | -1.3 (-0.25, 2.9) |
| | | | | Evening PEF | | -1.3 (-2.8, 0.16) |
| | | | | Morning PEF | | -1.3 (-2.6, -0.08) |
| Mortimer et al. (2002) | Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO 846 children with asthma, ages 4-9 yr | 8-h avg (10 a.m.-6 p.m.) | 1 3 1-5 avg | Morning PEF | All subjects | -0.12 (-0.76, 0.52) |
| | | | | | | -0.64 (-1.2, -0.10) |
| Mortimer et al. (2000) | Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO 846 children with asthma, ages 4-9 yr | 8-h avg (10 a.m.-6 p.m.) | 1-5 avg | Morning PEF | Normal BW | -0.60 (-1.6, 0.39) |
| | | | | | Low BW (<5.5 lbs.) | -3.6 (-5.2, -2.0) |
| | | | | | No medication | -1.1 (-3.0, 0.84) |
| | | | | | CS user | -1.2 (-2.5, 0.11) |
| Thurston et al. (1997) | CT River Valley, CT 166 children with asthma, ages 7-13 yr | 1-h max | 0 | Intraday change PEF | | -2.8 (-4.9, -0.59) |
| Romieu et al. (2004b) | Mexico City, Mexico 158 children with asthma, mean age 9 yr | 1-h max | 1 | FEF _{25-75%} | Placebo, GSTM1 null | -2.3 (-4.2, -0.44) |
| | | | | | Placebo, GSTM1 positive | -0.48 (-1.7, 0.74) |
| | | | | | Antioxidant, GSTM1 null | -0.16 (-1.8, 1.6) |
| | | | | | Antioxidant, GSTM1 positive | 0.24 (-1.3, 1.8) |
| Romieu et al. (1996) | Northern Mexico City, Mexico 71 children with asthma, ages 5-7 yr | 1-h max | 0 | Evening PEF | | -0.17 (-0.79, 0.46) |
| Romieu et al. (1997) | Southern Mexico City, Mexico 65 children with asthma, ages 5-13 yr | 1-h max | 0 | Evening PEF | | -0.55 (-1.3, 0.19) |
| | | | | | | |
| | | | | | | -0.06 (-0.70, 0.58) |

| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Parameter | Subgroup | Standardized Percent Change (95% CI) ^a |
|--|---|-------------------------------|--------------------|---------------------------------|----------|--|
| Studies not included in Figure 6-7^b | | | | | | |
| Jalaludin et al. (2000) | Sydney, Australia 20 children with asthma and AHR, mean (SD) age 9.6 (0.9) yr | 24-h avg 1-h max | 0 | Daily deviation from mean PEF | | -2.4 (-5.1, 0.28) ^c -1.3 (-2.8, 0.17) ^c |
| Wiwatanadate and Trakultivakorn (2010) | Chiang Mai, Thailand 31 children with asthma, ages 4-11 yr | 24-h avg | 0 5 | Daily avg PEF (L/min) | | 1.0 (-1.6, 3.6) -2.6 (-5.2, 0) |
| O'Connor et al. (2008) | Boston, MA; Bronx, Manhattan NY; Chicago, IL; Dallas, TX, Seattle, WA; Tucson, AZ 861 Children with asthma, mean (SD) age 7.7 (2.0) yr | 24-h avg | 1-5 avg | Change in percent predicted PEF | | -0.22 (-0.86, 0.43) |
| Just et al. (2002) | Paris, France 82 children with asthma, mean (SD) age 10.9 (2.5) yr | 8-h avg | 0-2 avg | Percent variability PEF | | 15.6 (0, 31.2) |

*Includes studies in [Figure 6-7](#), plus others

BW = birth weight, CS = corticosteroid, AHR = Airway hyperresponsiveness.

^aEffect estimates are standardized to a 40-ppb increase for 1-h max O₃, a 30-ppb increase for 8-h max or avg O₃, and a 20-ppb increase for 24-h avg O₃.

^bResults are not presented in [Figure 6-7](#) because a different form of PEF with a different scale was examined or because sufficient data were not provided to calculate percent change in PEF.

^cOutcome defined as the normalized percent deviation from individual mean PEF during the study period. Quantitative results from generalized estimating equations were provided only for models that included PM₁₀ and NO₂.

1 The most geographically representative data were provided by the large, multi-U.S. city
2 National Cooperative Inner City Asthma Study (NCICAS) ([Mortimer et al., 2002](#); [2000](#))
3 and Inner-City Asthma Study (ICAS) ([O'Connor et al., 2008](#)). Although the two studies
4 differed in the cities, seasons, racial distribution of subjects, and lung function indices
5 examined, results were fairly similar. In ICAS, which included children with asthma and
6 atopy (i.e., allergic sensitization) and year-round examinations of lung function, a 20-ppb
7 increase in the lag 1-5 average of 24-h avg O₃ was associated with a 0.41-point decrease
8 in percent predicted FEV₁ (95% CI: -1.0, 0.21) and a 0.22-point decrease in percent
9 predicted PEF (95% CI: -0.86, 0.43) ([O'Connor et al., 2008](#)).

10 Increases in lag 1-5 avg O₃ (8-h avg, 10 a.m.-6 p.m.) also were associated with declines
11 in PEF in NCICAS, which included different U.S. cities, summer-only measurements,
12 larger proportions of Black and Hispanic children, and fewer subjects with atopy (79%)
13 ([Mortimer et al., 2002](#)). Ozone concentrations lagged 3 to 5 days were associated with
14 larger PEF decrements than were O₃ concentrations lagged 1 to 2 days ([Figure 6-7](#) and
15 [Table 6-9](#)). NCICAS additionally identified groups potentially at increased risk of
16 O₃-associated PEF decrements, namely, males, children of Hispanic ethnicity, children
17 living in crowded housing, and as indicated in [Figure 6-7](#) and [Table 6-9](#), children with

1 birth weight <5.5 lbs ([Mortimer et al., 2000](#)). Somewhat paradoxically, O₃ was associated
2 with a larger decrease in PEF among subjects taking cromolyn, medication typically used
3 to treat asthma due to allergy, but a smaller decrease among subjects with positive atopy
4 (as determined by skin prick test). NCICAS also indicated robust associations with
5 consideration of other sources of heterogeneity. Except for Baltimore, MD, effect
6 estimates were similar across the study cities (1.1 to 1.7% decrease in PEF per 30-ppb
7 increase in lag 1-5 avg of 8-h avg O₃). Results were similar with O₃ averaged from all
8 available city monitors and concentrations averaged from the three monitors closest to
9 subject ZIP code centroid (1.2% and 1.0%, respectively, per 30-ppb increase in O₃). At
10 concentrations <80 ppb, a 30-ppb increase in lag 1-5 of 8-h avg O₃ was associated with a
11 1.4% decrease (95% CI: -2.6, -0.21) in PEF, which was similar to the effect estimated for
12 the full range of O₃ concentrations ([Figure 6-7](#) and [Table 6-9](#)). In a study of children with
13 asthma in the Netherlands, [Gielen et al. \(1997\)](#) estimated similar effects for the full range
14 of 8-h max O₃ concentrations and concentrations <51 ppb.

15 Several but not all controlled human exposure studies have reported slightly larger
16 O₃-induced FEV₁ decrements in adults with asthma (Section [6.2.1.1](#)). However, in the
17 few epidemiologic studies that compared children with and without asthma, evidence did
18 not conclusively indicate that children with asthma were at increased risk of
19 O₃-associated lung function decrements. [Hoppe et al. \(2003\)](#) and [Jalaludin et al. \(2000\)](#)
20 generally found larger O₃-associated lung function decrements in children with asthma;
21 whereas [Raizenne et al. \(1989\)](#) did not consistently demonstrate differences between
22 campers with and without asthma. In their study of children in Mexico City, [Barraza-
23 Villarreal et al. \(2008\)](#) estimated larger O₃-associated decreases in children without
24 asthma; however, 72% of these children had atopy. These findings indicate that children
25 with atopy, who also have airway inflammation and similar respiratory symptoms, may
26 experience respiratory effects from short-term ambient O₃ exposure.

27 As shown in [Figure 6-6](#) and [Figure 6-7](#) and [Table 6-8](#) and [Table 6-9](#), lung function
28 decrements in children with asthma mostly ranged from <1% to 2% per unit increase in
29 ambient O₃ concentration¹. Larger magnitudes of decrease, were found in children with
30 asthma who were using CS, had a concurrent upper respiratory infection (URI), were
31 GSTM1 null, had airway hyperresponsiveness, or had increased outdoor exposure
32 ([Romieu et al., 2006](#); [Lewis et al., 2005](#); [Romieu et al., 2004b](#); [Jalaludin et al., 2000](#)) than
33 among children with asthma overall ([Barraza-Villarreal et al., 2008](#); [Lewis et al., 2005](#);
34 [Delfino et al., 2004](#); [Romieu et al., 2002](#)). For example, [Jalaludin et al. \(2000\)](#) estimated a
35 -5.2% deviation from mean FEV₁ per a 20-ppb increase in 24-h avg O₃ concentration
36 among children with asthma and airway hyperresponsiveness and a much smaller -0.71%

¹Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max or avg, and 24-h avg O₃.

1 deviation among children with asthma without airway hyperresponsiveness. In a group of
2 86 children with asthma in Detroit, MI, [Lewis et al. \(2005\)](#) reported that associations
3 between ambient O₃ concentration and FEV₁ were confined largely to children with
4 asthma who used CS or had a concurrent URI, 8.0% and 5.4% decreases, respectively, in
5 the mean of lowest daily FEV₁ per 30-ppb increase in 8-h max ambient O₃ concentration.

6 Heterogeneity in response to O₃ exposure also was demonstrated by observations that
7 some individuals experienced larger O₃-associated lung function decrements than the
8 population mean effect estimate. Similar observations were made in controlled human
9 exposure studies (Section [6.2.1.1](#)). [Mortimer et al. \(2002\)](#) found that for a 30-ppb
10 increase in lag 1-5 avg of 8-h avg O₃, there was a 30% (95% CI: 4, 61) higher incidence
11 of >10% decline in PEF. Likewise, [Hoppe et al. \(2003\)](#) found that while the percentages
12 of lung function decrements were variable and small, 47% of children with asthma
13 experienced >10% decline in FEV₁, FVC, or PEF or 20% increase in airway resistance on
14 days with 30-min (1-4 p.m.) max ambient O₃ concentrations >50 ppb relative to days
15 with <40 ppb O₃.

Effect modification by corticosteroid use

16 In controlled human exposure studies, CS treatment of subjects with asthma generally has
17 not prevented O₃-induced FEV₁ decrements (Section [6.2.1.1](#)). Epidemiologic evidence is
18 equivocal, with findings that use of inhaled CS attenuated ([Hernández-Cadena et al.,](#)
19 [2009](#)), increased ([Lewis et al., 2005](#)), and did not affect ([Mortimer et al., 2000](#)), ambient
20 O₃-associated lung function decrements. In winter-only studies, consideration of CS use
21 largely did not influence associations between ambient O₃ and various lung function
22 indices ([Liu et al., 2009a](#); [Rabinovitch et al., 2004](#)). Similarly equivocal evidence was
23 found for modification of associations with respiratory symptoms (Section [6.2.4.1](#)). The
24 assessment of effect modification by CS use has been hampered by differences in the
25 severity of asthma among CS users and the definition of CS use. Additionally,
26 investigators did not assess adherence to reported CS regimen, and misclassification of
27 CS use may bias findings. For example, [Mortimer et al. \(2000\)](#) classified children by no
28 or any CS use at baseline but did not measure daily use during the study period. [Lewis et](#)
29 [al. \(2005\)](#) defined CS use as use for at least 50% of study days and estimated larger
30 O₃-associated FEV₁ decrements among CS users ([Figure 6-6](#) and [Table 6-8](#)) than among
31 CS nonusers (quantitative results not reported). In this study, most children with
32 moderate to severe asthma (91%) were classified as CS users. However, CS users had a
33 higher percent predicted FEV₁. In contrast, [Hernández-Cadena et al. \(2009\)](#) observed
34 larger O₃-related decrements in FEV₁ among the 60 CS nonusers than among the 25 CS
35 users. A definition for CS use was not provided; however, children with persistent asthma

1 were included among the group of CS nonusers. Thus, across studies, both CS use and
2 nonuse have been used to indicate more severe, uncontrolled asthma.

Effect modification by antioxidant capacity

3 Ozone is a powerful oxidant whose secondary oxidation products have been described to
4 initiate the key modes of action that mediate decreases in lung function, including the
5 activation of neural reflexes (Section [5.3.2](#)). Additionally, O₃ exposure of humans and
6 animals has induced changes in the levels of antioxidants in the ELF (Section [5.3.3](#)).
7 These observations provide biological plausibility for diminished antioxidant capacity to
8 increase the risk of O₃-associated respiratory effects and for augmented antioxidant
9 capacity to decrease risk. Controlled human exposure studies have demonstrated the
10 protective effects of α -tocopherol (vitamin E) and ascorbate (vitamin C) supplementation
11 on O₃-induced lung function decrements (Section [6.2.1.1](#)), and epidemiologic studies of
12 children with asthma conducted in Mexico City produced similar findings. Particularly
13 among children with moderate to severe asthma, increases in ambient O₃ concentration
14 were associated with a smaller decrease in FEV₁ in the group supplemented with vitamin
15 C and E as compared with the placebo group ([Romieu et al., 2002](#)) ([Figure 6-6](#) and
16 [Table 6-8](#)). [Romieu et al. \(2009\)](#) also demonstrated an interaction between dietary
17 antioxidant intake and ambient O₃ concentrations by finding that the main effect of diet
18 was modified by ambient O₃ concentrations. Diets high in antioxidant vitamins and/or
19 omega-3 fatty acids protected against FEV₁ decrements at 8-h max O₃ concentrations
20 ≥ 38 ppb. Results for the main effect of O₃ on FEV₁ or effect modification by diet were
21 not presented.

22 Antioxidant capacity also can be characterized by variants in genes encoding xenobiotic
23 metabolizing enzymes with altered enzymatic activity. Ambient O₃-associated FEF_{25-75%}
24 decrements were larger among children with asthma with the GSTM1 null genotype,
25 which is associated with lack of oxidant metabolizing activity ([Romieu et al., 2004b](#)).
26 The difference in association between GSTM1 null and positive subjects was minimal in
27 children supplemented with antioxidant vitamins ([Figure 6-7](#) and [Table 6-9](#)). Although
28 these findings are biologically plausible given the well-characterized evidence for the
29 secondary oxidation products of O₃ mediating effects, it is important to note that a larger
30 body of controlled human exposure studies has not consistently found larger O₃-induced
31 lung function decrements in GSTM1 null subjects (Section [6.2.1.1](#)). Effect modification
32 by GSTP1 variants is less clear. [Romieu et al. \(2006\)](#) observed larger O₃-associated
33 decreases in FEV₁ in children with asthma with the GSTP1 Ile/Ile or Ile/Val variant,
34 which are associated with relatively higher oxidative metabolism activity ([Figure 6-6](#) and
35 [Table 6-8](#)). An increase in ambient O₃ concentration was associated with an increase in
36 FEV₁ among children with the GSTP1 Val/Val variant, which is associated with reduced

1 oxidative metabolism. Rather than reflecting effect modification by the GSTP1 variant,
2 these results may reflect effect modification by asthma severity, as 77% of subjects with
3 the GSTP1 Ile/Ile genotype had moderate to severe asthma. In support of this alternate
4 hypothesis, another analysis of the same cohort indicated a larger O₃-associated
5 decrement in FEV₁ among children with moderate to severe asthma than among all
6 subjects with asthma ([Romieu et al., 2002](#)).

Exposure Measurement Error

7 Across the studies of children with asthma, lung function decrements were associated
8 with ambient O₃ concentrations assigned to subjects using various exposure assessment
9 methods. As described in Section [4.3.3](#), exposure measurement error due to use of
10 ambient concentrations measured at central sites has varied, depending on the population
11 and season examined. Because there are a limited number of studies of each method, it is
12 difficult to conclude that a particular method of exposure assessment produced stronger
13 results.

14 Seasonal differences have been observed in the personal-ambient O₃ relationship
15 (Section [4.3.3](#)); however, in children with asthma, O₃-associated lung function
16 decrements were found in studies conducted in summer months and over multiple
17 seasons. Lung function was associated with O₃ measured on site of subjects' daytime
18 hours in summer months ([Hoppe et al., 2003](#); [Thurston et al., 1997](#)), factors that have
19 contributed to higher personal-ambient O₃ ratios and correlations. Many year-round
20 studies in Mexico City ([Romieu et al., 2006](#); [2004b](#); [2002](#); [1997](#); [1996](#)) and a study in
21 Detroit, MI ([Lewis et al., 2005](#)) found associations with O₃ measured at sites within 5 km
22 of children's home or school. Children with asthma examined by [Romieu et al. \(2006\)](#);
23 ([2004b](#); [2002](#)) had a personal-ambient ratio and correlation for 48- to 72-h avg O₃
24 concentrations were 0.17 and 0.35, respectively ([Ramírez-Aguilar et al., 2008](#)). These
25 findings indicate that the effects of personal O₃ exposure on lung function decrements
26 may have been underestimated in the children in Mexico City. Associations were found
27 with O₃ concentrations averaged across multiple community monitoring sites ([O'Connor](#)
28 [et al., 2008](#); [Just et al., 2002](#); [Mortimer et al., 2002](#); [Jalaludin et al., 2000](#)) and measured
29 at a single site ([Gielen et al., 1997](#)), O₃ measured at multiple sites within a region have
30 shown high temporal correlation ([Darrow et al., 2011a](#); [Gent et al., 2003](#)).

31 Studies of children with asthma restricted to winter months provided little evidence of an
32 association between various single- and multi-day lags of ambient O₃ concentration and
33 lung function decrements with several studies reporting O₃-associated increases in lung
34 function ([Dales et al., 2009](#); [Liu et al., 2009a](#); [Rabinovitch et al., 2004](#)). One explanation
35 for these results may be lower indoor than outdoor O₃ concentrations, variable indoor to

1 outdoor ratios, and lower correlations between personal and ambient O₃ concentrations in
2 non-summer months (Section [4.3.2](#) and Section [4.3.3](#)). As noted for other respiratory
3 endpoints such as respiratory hospital admissions, ED visits, and mortality, associations
4 with O₃ generally are lower in colder seasons.

Adults with Respiratory Disease

5 Relative to studies in children with asthma, studies of adults with asthma or COPD have
6 been limited in number. Details from these studies regarding location, time period, and
7 ambient O₃ concentrations are presented in [Table 6-10](#). Increases in ambient O₃
8 concentration were not consistently associated with lung function decrements in adults
9 with respiratory disease. Several different exposure assessment methods were used,
10 including monitoring personal exposures ([Delfino et al., 1997](#)), monitoring on site of
11 outdoor activity ([Girardot et al., 2006](#); [Korrick et al., 1998](#)), and using measurements
12 from one ([Peacock et al., 2011](#); [Wiwatanadate and Liwsrisakun, 2011](#); [Thaller et al.,](#)
13 [2008](#); [Ross et al., 2002](#)) to several central monitors ([Khatri et al., 2009](#); [Lagorio et al.,](#)
14 [2006](#); [Park et al., 2005a](#)). There was not a clear indication that differences in exposure
15 assessment methodology contributed to inconsistencies in findings.

Table 6-10 Mean and upper percentile concentrations of ozone in epidemiologic studies of lung function in adults with respiratory disease.

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|-----------------------------|--------------------------------------|-----------------------------------|--|--|
| Delfino et al. (1997) | Alpine, CA | May-July 1994 | 12-h avg personal (8 a.m.-8 p.m.) | 18 | 90th: 38 Max: 80 |
| Girardot et al. (2006) | Great Smoky Mountain NP, TN | August-October 2002 June-August 2003 | Hike-time avg (2-9 h) | 48.1 | Max: 74.2 |
| Korrick et al. (1998) | Mt. Washington, NH | Summer 1991, 1992 | Hike-time avg (2-12 h) | 40 | Max: 74 |
| Peacock et al. (2011) | London, England | All-year 1995-1997 | 8-h max | 15.5 | Autumn/Winter Max: 32 Spring/Summer Max: 74 |
| Wiwatanadate and Liwsrisakun (2011) | Chiang Mai, Thailand | August 2005-June 2006 | 24-h avg | 17.5 | 90th: 26.82 Max: 34.65 |
| Thaller et al. (2008); Brooks (2010) | Galveston, TX | Summer 2002-2004 | 1-h max | 35 (median) | Max: 118 |
| Ross et al. (2002) | East Moline, IL | April-October 1994 | 8-h avg | 41.5 | Max: 78.3 |
| Khatri et al. (2009) | Atlanta, GA | May-September 2003, 2005, 2006 | 8-h max | With asthma: 61 (median) ^a No asthma: 56 (median) ^a | 75th (all subjects): 74 ^a |
| Lagorio et al. (2006) | Rome, Italy | May-June, November-December 1999 | 24-h avg | Spring: 36.2 ^b Winter: 8.0 ^b | Overall max: 48.6 ^b |
| Park et al. (2005a) | Incheon, Korea | March-June 2002 | 24-h avg | Dust event days: 23.6 Control days: 25.1 | NR |

* Note: Studies presented in order of first appearance in the text of this section.

NR = Not reported.

^aIndividual-level estimates were calculated based on time spent in the vicinity of various O₃ monitors.

^bConcentrations converted from µg/m³ to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

1 Comparisons of adults with asthma (8-18% of study population) and without asthma did
 2 not conclusively demonstrate that adults with asthma had larger ambient O₃-associated
 3 lung function decrements. Several studies examined on-site or central-site ambient O₃
 4 concentrations measured while subjects were outdoors, and ambient O₃ measured during
 5 time spent outdoors has been closer in magnitude and more correlated with personal
 6 exposures (Section 4.3.3). In a panel study of lifeguards (ages 16-27 years) in Galveston,
 7 TX, a larger O₃-associated decrement in FEV₁/FVC was found among the 16 lifeguards
 8 with asthma (-1.6% [95% CI: -2.8, -0.4] per 40 ppb increase in 1-h max O₃) than among
 9 the 126 lifeguards without asthma (-0.40% [95% CI: -0.80, 0] per 40-ppb increase in

1 1-h max O₃) [Brooks \(2010\)](#). In [Korrick et al. \(1998\)](#), hikers with a history of asthma or
2 wheeze had larger O₃-associated lung function decrements (e.g. -4.4% [95% CI: -7.5,
3 -1.2] in FEV₁ per 30-ppb increase in 2-12 h avg O₃). In contrast, [Girardot et al. \(2006\)](#)
4 generally did not find O₃-associated lung function decrements in hikers with or without
5 respiratory disease history. In a cross-sectional study of 38 adults with asthma and
6 13 adults without asthma, [Khatri et al. \(2009\)](#) used central site O₃ measurements but
7 aimed to account for spatial variability by calculating an average of concentrations
8 measured at sites closest to each subject's location during each hour. Investigators
9 reported a larger O₃-associated decrease in percent predicted FEV₁/FVC in the 38
10 subjects with atopy (with or without asthma) (-12 points [95% CI: -21, -3] per 30-ppb
11 increase in 8-h max O₃) than in subjects with asthma (-4.7 points [95% CI: -11, 2.3]).
12 Among adults with asthma, O₃ was associated with an increase in FEV₁.

13 In panel studies that exclusively examined adults with asthma, increases in ambient O₃
14 concentrations, across the multiple lags examined, generally were associated with
15 increases in lung function ([Wiwatanadate and Liwsrisakun, 2011](#); [Lagorio et al., 2006](#);
16 [Park et al., 2005a](#)). These studies were conducted in Europe and Asia during periods of
17 low ambient O₃ concentrations, including one conducted in Korea during a period of dust
18 storms ([Park et al., 2005a](#))

19 Some studies included children and adults with asthma. Among subjects ages 9-46 years
20 (41% adults) in Alpine, CA with low personal 12-h avg O₃ exposures (55% samples
21 below limit of detection) and a majority of sampling hours spent indoors (mean 71%),
22 [Delfino et al. \(1997\)](#) reported that neither 12-h avg personal exposure nor ambient O₃
23 concentration was associated with a decrease in PEF. [Ross et al. \(2002\)](#) examined
24 subjects ages 5-49 years (proportion of adults not reported) in East Moline, IL and found
25 that a 20-ppb increase in lag 0 of 24-h avg O₃ was associated with a 2.6 L/min decrease
26 (95% CI: -4.3, -0.90) in evening PEF. In this population with asthma, an increase in lag 0
27 O₃ also was associated with an increase in symptom score.

28 Controlled human exposure studies have found diminished, statistically nonsignificant
29 O₃-induced lung function responses in older adults with COPD (Section [6.2.1.1](#)).
30 Similarly, epidemiologic studies do not provide strong evidence that short-term increases
31 in ambient O₃ exposure result in lung function decrements in adults with COPD.
32 Inconsistent associations were reported for PEF, FEV₁, and FVC in a study that followed
33 94 adults with COPD (ages 40-83 years) in London, England daily over two years
34 ([Peacock et al., 2011](#)). For example, a 30-ppb increase in 8-h max O₃ was associated with
35 a 1.7 L/min decrease (95% CI: -3.1, -0.39) in PEF in an analysis of summer 1996 but not
36 summer 1997 (-0.21 L/min [95% CI: -2.4, 2.0]). Further, in this study, an increase in
37 ambient O₃ concentration was associated with lower odds of a large PEF decrement (OR

1 for a >20% drop from an individual's median value: 0.89 [95% CI: 0.72, 1.10] per
 2 30-ppb increase in lag 1 of 8-h max O₃) and was not consistently associated with
 3 increases in respiratory symptoms ([Peacock et al., 2011](#)). Inconsistent associations also
 4 were reported in a small panel study of 11 adults with COPD (mean age 67 years) in
 5 Rome, Italy ([Lagorio et al., 2006](#)).

Populations Not Restricted to Individuals with Asthma

6 Several studies have examined associations between ambient O₃ concentrations and lung
 7 function in groups that included children with and without asthma; however, a limited
 8 number of studies have examined groups of children or adults restricted to healthy
 9 individuals. Details from studies not restricted to individuals with asthma regarding
 10 location, time period, and ambient O₃ concentrations are presented in [Table 6-11](#).

Table 6-11 Mean and upper percentile concentrations of ozone in epidemiologic studies of lung function in populations not restricted to individuals with asthma.

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|-------------------------------------|---------------------------------------|---------------------------------------|---|---|
| Avol et al. (1998b) | 6 southern CA communities | Spring and summer 1994 | 24-h avg personal | NR | NR |
| Hoppe et al. (2003) | Munich, Germany | Summers 1992-1995 | 30-min max (1-4 p.m.) | High O ₃ days: 70.4 ^a Control O ₃ days: 29.8 ^a | Max (high O ₃ days): 99 ^a Max (control O ₃ days): 39 ^a |
| Chen et al. (1999) | 3 Taiwan communities | May-January, 1995-1996 | 1-h max (8 a.m.-6 p.m.) | NR | Max: 110.3 ^a |
| Gold et al. (1999) | Mexico City, Mexico | January-November 1991 | 24-h avg | 52.0 ^a | Max: 103 ^a |
| Ward et al. (2002) | Birmingham and Sandwell, England | January-March and May-July 1997 | 24-h avg | Winter median: 13.0 Summer median: 22.0 | Winter Max: 33 Summer Max: 41 |
| Ulmer et al. (1997) | Freudenstadt and Villingen, Germany | March-October 1994 | 30-min avg | Freudenstadt median: 50.6 Villingen median: 32.1 | Freudenstadt 95th: 89.8 Villingen 95th: 70.1 |
| Linn et al. (1996) | Rubidoux, Upland, Torrence, CA | September-June 1992-1994 | 24-h avg personal 24-h avg ambient | 5 23 | Max: 16 Max: 53 |
| Scarlett et al. (1996) | Surrey, England | June-July 1994 | 8-h max | 50.7a | Max: 128a |
| Neuberger et al. (2004) | Vienna, Austria | June-October 1999, January-April 2000 | NR | NR | NR |
| Alexeeff et al. (2008); (2007) | Greater Boston, MA; NAS | January 1995-June 2005 | 48-h avg | 24.4b | NR |

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|--------------------------|----------------------------------|-------------------------------|---------------------------------|---------------------------------------|
| Steinvil et al. (2009) | Tel Aviv, Israel | September 2002- November 2007 | 8-h avg (10 a.m.-6 p.m.) | 41.1 | 75th: 48.7 Max: 72.8 |
| Naeher et al. (1999) | Multiple communities, VA | May-September 1995-1996 | 8-h max | 53.7 | Max: 87.6 |
| Son et al. (2010) | Ulsan, Korea | All-year, 2003- 2007 | 8-h max | 35.86 (avg of 13 monitors) | Max: 59.53 |

* Note: Studies presented in order of first appearance in the text of this section.

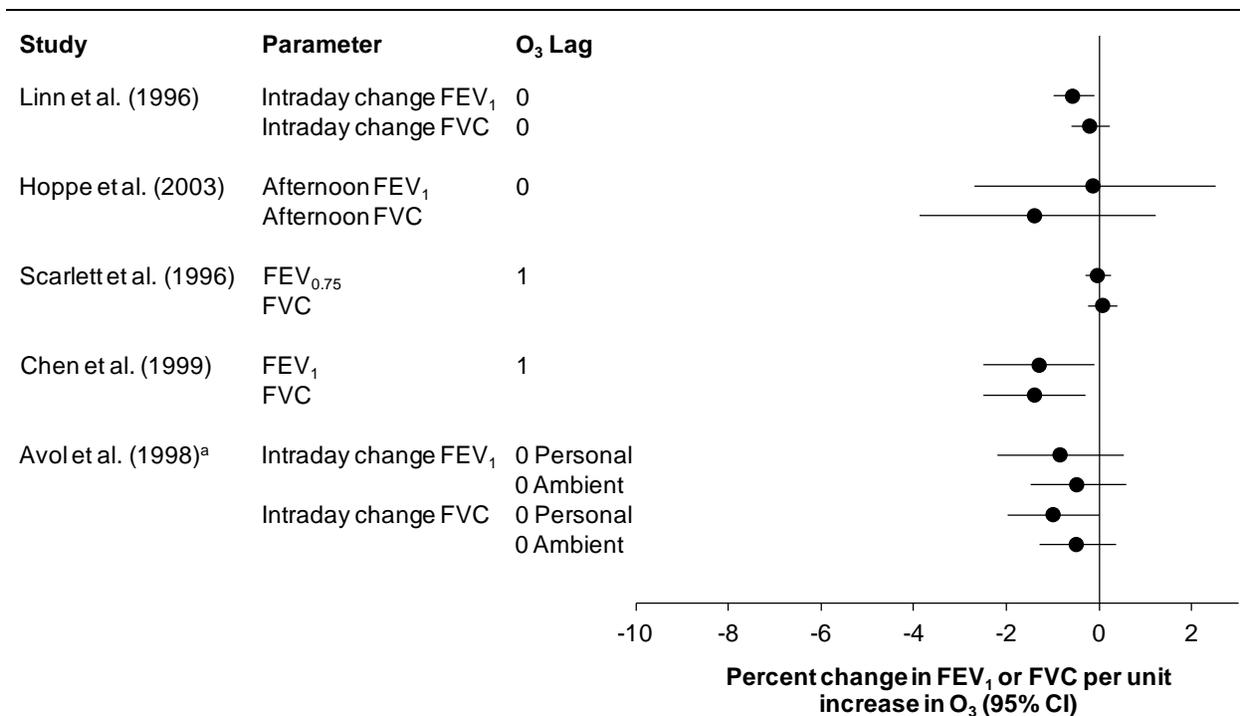
NAS = Normative Aging Study, NR = Not Reported.

^aMeasured at subjects' schools where lung function was measured.

^bMeasured at central monitoring sites established by investigators. Concentrations were averaged across four monitors.

Children

1 Based on studies available at the time of the 2006 O₃ AQCD, evidence consistently links
2 increases in ambient O₃ concentration with decrements in FEV₁ and PEF in children
3 ([U.S. EPA, 2006b](#)) ([Figure 6-8](#) and [Table 6-12](#)). These associations were found with
4 personal O₃ exposures ([Avol et al., 1998b](#)), ambient O₃ measured at children's schools
5 where lung function was measured ([Hoppe et al., 2003](#); [Chen et al., 1999](#); [Gold et al.,](#)
6 [1999](#)), and ambient O₃ measured at sites within the community ([Ward et al., 2002](#); [Ulmer](#)
7 [et al., 1997](#); [Linn et al., 1996](#)). Among children in California who spent a mean 2-3 hours
8 outdoors per day and whose personal-ambient O₃ correlation was 0.28 across multiple
9 seasons, [Avol et al. \(1998b\)](#) found slightly larger O₃-associated decrements in FEV₁ and
10 FVC for 24-h avg personal exposures than for 1-h max ambient measurements
11 ([Figure 6-8](#) and [Table 6-12](#)). The effect estimates for personal exposures were similar in
12 magnitude to those found in other studies for ambient O₃ measured at schools ([Hoppe et](#)
13 [al., 2003](#); [Chen et al., 1999](#)). In another study of children in California, [Linn et al. \(1996\)](#)
14 did not present results for personal O₃ exposures but found FEV₁ decrements in
15 association with increases in ambient O₃ concentrations in children who spent 1-2 hours
16 per day outdoors and whose personal-ambient correlations were 0.61. Because of
17 between-study heterogeneity in populations and ambient O₃ concentrations examined, it
18 is difficult to assess how the method of exposure assessment may have influenced
19 findings.



Note: The 95% CI was constructed using a standard error that was estimated from the p-value. Results generally are presented in order of increasing mean ambient O₃ concentration. Effect estimates are from single-pollutant models and are standardized to a 40-, 30-, and 20-ppb increase for a 1-hour (or 30-min) max, 8-h max, and 24-h avg O₃ concentrations, respectively.

Figure 6-8 Percent change in FEV₁ or FVC in association with ambient ozone concentrations in studies of children in the general population.

Table 6-12 Characteristics and quantitative data for studies represented in Figure 6-8, of lung function in children.

| Study* | Location/ Population | O ₃ Averaging Time | O ₃ Lag | Parameter | Standardized Percent Change (95% CI) ^a |
|---|--|--|--------------------|--|--|
| Linn et al. (1996) | 3 southern CA communities 269 children, 4th and 5th grades | 24-h avg | 0 | Intraday change FEV ₁ Intraday change FVC | -0.58 (-1.0, -0.13) -0.21 (-0.62, 0.20) |
| Hoppe et al. (2003) | Munich, Germany 44 children, ages 6-8 yr | 30-min max (1 - 4 p.m.) | 0 | Afternoon FEV ₁ Afternoon FVC | -0.14 (-2.7, 2.5) -1.4 (-3.9, -1.2) |
| Scarlett et al. (1996) | Surrey, England 154 children, ages 7-11 yr | 8-h max | 1 | FEV _{0.75} FVC | -0.04 (-0.32, 0.23) 0.07 (-0.25, 0.39) |
| Chen et al. (1999) | 3 Taiwan communities 941 children, mean (SD) age 9.8 (1.6) yr | 1-h max | 1 | FEV ₁ FVC | -1.5 (-2.8, -0.12) -1.6 (-2.9, -0.33) |
| Avol et al. (1998b) | 3 southern CA communities 195 children, ages 10-12 yr | 24-h avg personal 1-h max ambient 24-h avg personal 1-h max ambient | 0 | Intraday change FEV ₁ Intraday change FEV ₁ Intraday change FVC Intraday change FVC | -0.85 (-2.2, 0.53) ^b -0.49 (-1.5, 0.57) ^b -1.0 (-2.0, 0) ^b -0.50 (-1.3, 0.35) ^b |
| Studies of children not included in Figure 6-8^c | | | | | |
| Ulmer et al. (1997) | Freudenstadt and Villingen, Germany 135 children, ages 8-10 yr | 30-min max | 1 | FEV ₁ (mL) | -59 (-103, 14) ^b |
| Ward et al. (2002) | Birmingham and Sandwell, England 162 children, age 9 yr | 24-h avg | 0 2 | Daily deviation from mean PEF (L/min) | -3.2 (-8.3, 2.0) ^d -6.7 (-12, -1.4) ^d |
| Gold et al. (1999) | Mexico City, Mexico 40 children, ages 8-11 yr | 24-h avg | 0 1-10 avg | Intraday change PEF (% change) | -0.47 (-1.1, 0.11) -3.4 (-5.4, -1.5) |

*Includes studies in [Figure 6-8](#) plus others.

^aEffect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h (or 30-min) max, 8-h max, and 24-h avg O₃, respectively.

^bThe 95% CI was constructed using a standard error that was estimated from the p-value.

^cResults are not presented in [Figure 6-8](#) because sufficient data were not provided to calculate percent change in FEV₁ or PEF was analyzed.

^dEffect estimates are from analyses restricted to summer months.

1 In the limited number of studies that examined only healthy children, increases in
2 ambient O₃ concentration were associated with decreases ([Hoppe et al., 2003](#)) or no
3 change in lung function ([Neuberger et al., 2004](#)). Several studies that included small
4 proportions (4-10%) of children with history of respiratory disease or symptoms found
5 associations between increases in ambient O₃ concentration and lung function decrements
6 ([Chen et al., 1999](#); [Ulmer et al., 1997](#); [Scarlett et al., 1996](#)). Based on analysis of
7 interaction terms for O₃ concentration and asthma/wheeze history, [Avol et al. \(1998b\)](#)

1 and [Ward et al. \(2002\)](#) did not find differences in O₃-associated lung function decrements
2 between children with history of asthma or wheeze and healthy children. Combined,
3 these lines of evidence indicate that the ambient O₃-associated lung function decrements
4 in children were not solely due to effects in children with asthma, and that increases in
5 ambient O₃ exposure may decrease lung function in healthy children.

6 Among the studies of children, the magnitudes of decrease in lung function per unit
7 increase in ambient O₃ concentration¹ ranged from <1 to 4%, a range similar to that
8 estimated in children with asthma. Comparable data were not adequately available to
9 assess whether mean lung function differed between groups of children with asthma and
10 healthy children. In contrast with children with asthma, O₃-associated decreases in lung
11 function were not consistently accompanied by O₃-associated increases in respiratory
12 symptoms in children in the general population. For example, [Gold et al. \(1999\)](#) found
13 O₃-associated decreases in PEF and increases in phlegm; however, the increase in phlegm
14 was associated with lag 1 O₃ concentrations whereas the PEF decrement was found with
15 single-day lags 2 to 4 of O₃. Also, O₃ was weakly associated with cough and shortness of
16 breath among children in England ([Ward et al., 2002](#)) and was associated with a decrease
17 in respiratory symptom score among children in California ([Linn et al., 1996](#)).

Adults

18 Compared with children, in a more limited body of studies, O₃ was less consistently
19 associated with lung function decrements in populations of adults not restricted to healthy
20 subjects ([Table 6-13](#)). In studies that included only healthy adults, increases in ambient
21 O₃ concentration were associated with decreases ([Naeher et al., 1999](#)) and increases in
22 lung function ([Steinvil et al., 2009](#)). Contrasting results also were found in studies of
23 older adults ([Alexeeff et al., 2008](#); [Alexeeff et al., 2007](#); [Hoppe et al., 2003](#)).

¹Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max (or 30-min max), 8-h max, and 24-h avg O₃.

Table 6-13 Associations between ambient ozone concentration and lung function in studies of adults.

| Study ^a | Location/Population | O ₃ Averaging Time | O ₃ Lag | Parameter | O ₃ Assessment Method/Subgroup | Standardized Effect Estimate (95% CI) ^b |
|--|--|----------------------------------|--------------------|--|--|---|
| Son et al. (2010) | Ulsan, Korea 2,102 children and adults, ages 7-97 yr | 8-h max | 0-2 avg | Change in percent predicted FEV ₁ | All monitor avg Nearest monitor IDW Kriging | -1.4 (-2.7, -0.08) -0.76 (-1.8, 0.25) -1.1 (-2.2, 0.05) -1.4 (-2.6, -0.11) |
| Steinvil et al. (2009) | Tel Aviv, Israel 2,380 healthy adults, mean age 43 yr, 75th percentile: 52 yr | 8-h avg (10 a.m. - 6 p.m.) | 0 0-6 avg | FEV ₁ (mL) | | 60 (0, 120) 141 (33, 234) |
| Naeher et al. (1999) | Multiple communities, VA 473 healthy women, ages 19 - 43 yr | 24-h avg | 0 0-2 avg | Evening PEF (L/min) | | -1.7 (-3.4, 0.03) -3.0 (-4.4, -1.7) |
| Hoppe et al. (2003) | Munich, Germany 61 older adults, ages 69-95 yr | 30-min max (1-4 p.m.) | 0 1 | % change in afternoon FEV ₁ | | 0.75 (-2.1, 3.7) 1.2 (-1.3, 3.6) |
| Alexeeff et al. (2008) | Greater Boston, MA 1,015 older adults, mean (SD) age: 68.8 (7.2) yr at baseline | 24-h avg | 0-1 avg | % change in FEV ₁ | GSTP1 Ile/Ile GSTP1 Ile/Val or Val/Val | -1.0 (-2.2, 0.20) -2.3 (-3.5, -1.0) |
| Alexeeff et al. (2007) | Greater Boston, MA 904 older adults, mean (SD) age: 68.8 (7.3) yr at baseline | 24-h avg | 0-1 avg | % change in FEV ₁ | BMI <30 BMI ≥ 30 No AHR AHR BMI ≥ 30 and AHR | -1.5 (-2.5, -0.51) -3.5 (-5.1, -1.9) -1.7 (-2.7, -0.73) -4.0 (-6.2, -1.8) -5.3 (-8.2, -2.3) |

^aResults generally are presented in order of increasing mean ambient O₃ concentration.

IDW = Inverse distance weighting, BMI = Body mass index, AHR = airway hyperresponsiveness.

^bEffect estimates are standardized to a 40-ppb increase for 30-min max O₃, 30-ppb increase for 8-h max or 8-h avg O₃, and 20-ppb increase for 24-h avg O₃.

1 Despite mixed results overall, lung function decrements in adults were associated with
2 increases in ambient O₃ concentrations assigned to subjects using various methods with
3 potentially varying degrees of measurement error. These methods included the average of
4 multiple intra-city monitors, nearest monitor, estimates from spatial interpolation ([Son et](#)
5 [al., 2010](#)), average of monitors in multiple towns ([Alexeeff et al., 2008; 2007](#)), and one
6 site for multiple towns ([Naeher et al., 1999](#)). In a large cross-sectional study, conducted
7 in 2,102 children and adults (mean age: 45 years) living near a petrochemical plant in
8 Ulsan, Korea, [Son et al. \(2010\)](#) did not find a consistent difference in the magnitude of
9 association with lung function among ambient O₃ concentrations averaged across 13 city
10 monitors, concentrations from the nearest monitor, inverse distance-weighted

1 concentrations, and estimates from kriging across the various lags examined
2 ([Table 6-13](#)). Ozone concentrations were similar (<10% difference) and highly correlated
3 ($r = 0.84-96$) among the methods. Although the health status of subjects was not reported,
4 the study population mean percent predicted FEV₁ was 82.85%, indicating a large
5 proportion of subjects with underlying airway obstruction. Results from this study were
6 not adjusted for meteorological factors and thus, confounding cannot be ruled out.
7 Importantly, the similarities among exposure assessment methods in [Son et al. \(2010\)](#)
8 may apply mostly to populations living within the same region of a city. The majority of
9 women examined by [Naeher et al. \(1999\)](#) lived >60 miles from the single available
10 central site monitor. However, in the nonurban (southwest Virginia) study area, O₃
11 concentrations may be more spatially homogeneous ([Section 4.6.2.1](#)), and the
12 concentrations measured at the single site may capture temporal variability in ambient
13 exposures.

14 The inconsistent findings for older adults parallel observations from controlled human
15 exposure studies ([Section 6.2.1.1](#)). In a study that followed adults ages 69-95 years over a
16 summer in Germany, [Hoppe et al. \(2003\)](#) did not find decreases in lung function in
17 association with ambient O₃ measured at subjects' retirement home. However, recently,
18 the Normative Aging Study found decrements in FEV₁ and FVC in a group of older men
19 (mean [SD] age = 68.9 [7.2] years) in association with ambient O₃ concentrations
20 averaged from four town-specific monitors ([Alexeeff et al., 2008](#)), which may less well
21 represent spatial heterogeneity in ambient O₃ exposures. Among all subjects, who were
22 examined once every three years for ten years, associations were found with several lags
23 of 24-h avg O₃ concentration, i.e., 1- to 7-day avg ([Alexeeff et al., 2008](#)). Additionally,
24 larger effects were estimated in adults with airway hyperresponsiveness, higher BMI (\geq
25 30), and GSTP1 Ile/Val or Val/Val genetic variants (Val/Val variant produces enzyme
26 with reduced oxidative metabolism activity) ([Alexeeff et al., 2008](#); [Alexeeff et al., 2007](#))
27 ([Table 6-13](#)). Larger O₃-related decrements in FEV₁ and FVC also were observed in
28 subjects with long GT dinucleotide repeats in the promoter region of the gene for the
29 antioxidant enzyme heme oxygenase-1 ([Alexeeff et al., 2008](#)), which has been associated
30 with reduced inducibility ([Hiltermann et al., 1998](#)). In this cohort, O₃ also was associated
31 with decreases in lung function in adults without airway hyperresponsiveness and those
32 with BMI <30, indicating effects of O₃ on lung function in healthy older adults. However,
33 the findings may be generalizable only to this study population of older, predominately
34 white men.

Confounding in epidemiologic studies of lung function

35 The 1996 O₃ AQCD noted uncertainty regarding confounding by temperature and pollen
36 ([U.S. EPA, 1996a](#)); however, collective evidence does not indicate that these factors fully

1 account for the associations observed between increases in ambient O₃ concentration and
2 lung function decrements. Across the populations examined, most studies that found
3 ambient O₃-associated lung function decrements, whether conducted in multiple seasons
4 or only in summer, included temperature in statistical analyses. Some summer camp
5 studies conducted detailed analysis of temperature. In most of these studies, temperature
6 and O₃ were measured at the camps. In two Northeast U.S. studies, an increase in
7 temperature was associated with an increase in lung function ([Thurston et al., 1997](#);
8 [Berry et al., 1991](#)). This positive association likely accounted for the nearly 2-fold greater
9 decrease in O₃-associated PEF found by [Thurston et al. \(1997\)](#) with temperature in the
10 model than with O₃ alone. In another Northeast U.S. camp study, [Spektor et al. \(1988a\)](#)
11 estimated similar effects for O₃ in a model with and without a temperature-humidity
12 index. In the re analysis of six camp studies, investigators did not include temperature in
13 models because temperature within the normal ambient range had not been shown to
14 affect O₃-induced lung function responses in controlled human exposure studies ([Kinney](#)
15 [et al., 1996](#)).

16 Pollen was evaluated in far fewer studies. Camp studies that examined pollen found that
17 pollen independently was not associated with lung function decrements ([Thurston et al.,](#)
18 [1997](#); [Avol et al., 1990](#)). Many studies of children with asthma with follow-up over
19 multiple seasons found O₃-associated decrements in lung function in models that adjusted
20 for pollen counts ([Just et al., 2002](#); [Ross et al., 2002](#); [Jalaludin et al., 2000](#); [Gielen et al.,](#)
21 [1997](#)). In these studies, large proportions of subjects had atopy (22-98%), with some
22 studies examining large proportions of subjects specifically with pollen allergy and thus
23 would be more responsive to pollen exposure ([Ross et al., 2002](#); [Gielen et al., 1997](#)).

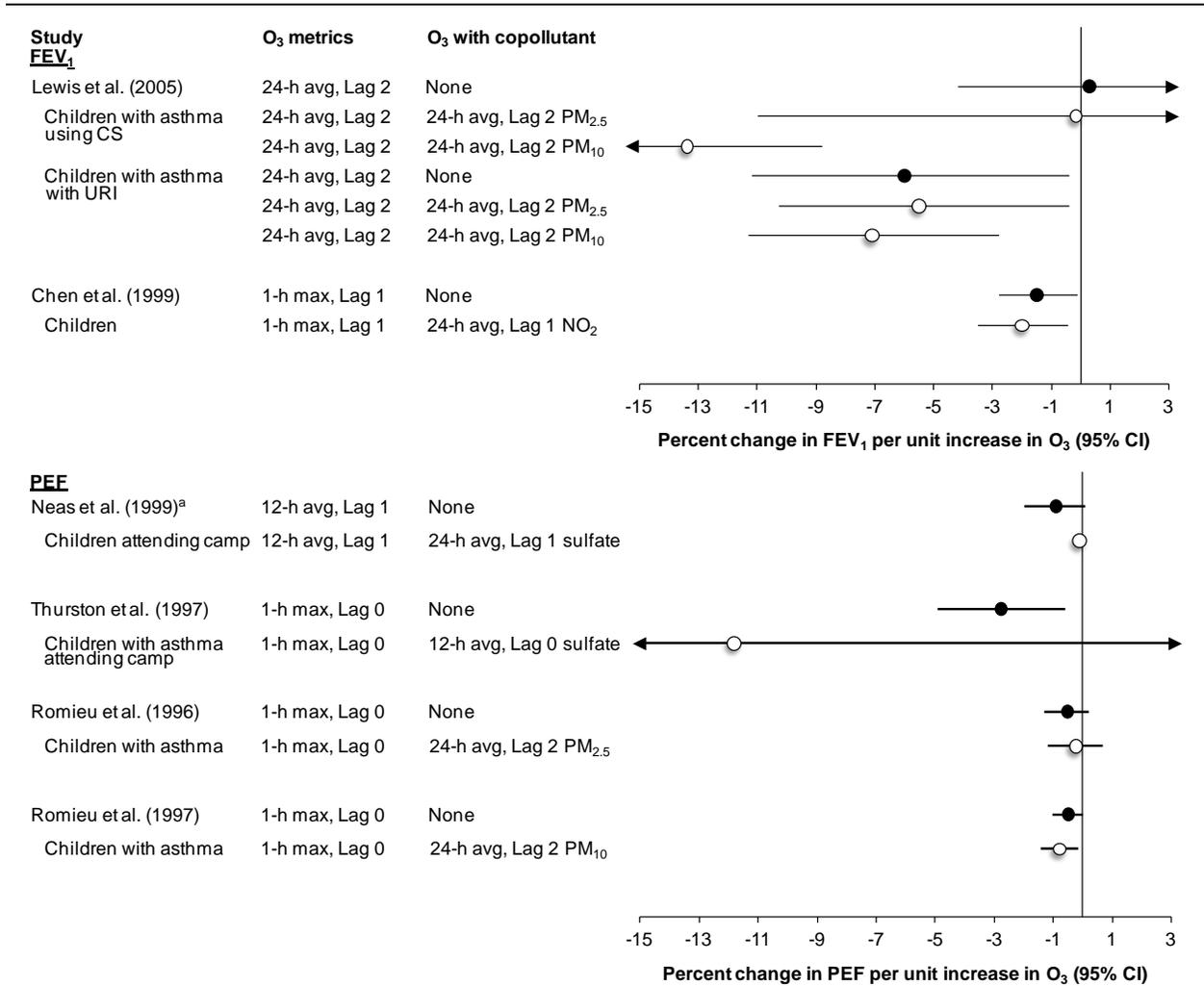
24 A relatively larger number of studies provided information on potential confounding by
25 copollutants such as PM_{2.5}, PM₁₀, NO₂, or SO₂. While studies were varied in how they
26 evaluated confounding, most indicated that O₃-associated lung function decrements were
27 not solely due to copollutant confounding. Some studies of subjects exercising outdoors
28 indicated that ambient concentrations of copollutants such as NO₂, SO₂, or acid aerosol
29 were low and thus, not likely to confound associations observed for O₃ ([Hoppe et al.,](#)
30 [2003](#); [Brunekreef et al., 1994](#); [Hoek et al., 1993](#)). In other studies of children with
31 increased outdoor exposures, O₃ was consistently associated with decreases in lung
32 function, whereas other pollutants such as PM_{2.5}, sulfate, and acid aerosol individually
33 showed variable associations across studies ([Thurston et al., 1997](#); [Castillejos et al., 1995](#);
34 [Berry et al., 1991](#); [Avol et al., 1990](#); [Spektor et al., 1988a](#)). Most of these studies
35 measured ambient pollutants on site of subjects' outdoor activity and related lung
36 function changes to the pollutant concentrations measured during outdoor activity. Thus,
37 the degree of exposure measurement error likely is comparable for O₃ and copollutants.

1 Studies that conducted copollutant modeling generally found O₃-associated lung function
2 decrements to be robust; most copollutant-adjusted effect estimates fell within the
3 95% CI of the single-pollutant effect estimates ([Figure 6-9](#) and [Table 6-14](#)). These studies
4 used central site measurements for both O₃ and copollutants. There may be residual
5 confounding because of differential exposure measurement error for O₃ and copollutants
6 due to differing spatial heterogeneity and indoor-outdoor ratios; however, the limited
7 available evidence indicates that personal O₃ exposures are weakly correlated with
8 personal PM_{2.5} and NO₂ exposures (Section [4.3.4.1](#)). Whereas a few studies used the same
9 averaging time for copollutants ([Lewis et al., 2005](#); [Jalaludin et al., 2000](#)), more
10 examined 1-h max or 8-h max O₃ and 24-h avg copollutant concentrations ([Son et al.,](#)
11 [2010](#); [Chen et al., 1999](#); [Romieu et al., 1997](#); [Romieu et al., 1996](#)). In a Philadelphia-area
12 summer camp study, [Neas et al. \(1999\)](#) was among the few studies to find that the effect
13 estimate for O₃ was attenuated to near zero in a copollutant model (24-h avg sulfate in
14 this study) ([Figure 6-9](#) and [Table 6-14](#)).

15 Ambient O₃ concentrations showed a wide range of correlations with copollutant
16 concentrations (r = -0.31 to 0.74). In Sydney, Australia, [Jalaludin et al. \(2000\)](#) found low
17 correlations of O₃ with PM₁₀ (r = 0.13) and NO₂ (r = -0.31), all averaged over 24 hours.
18 In two-pollutant models, PM₁₀ and NO₂ remained associated with increases in PEF, and
19 O₃ remained associated with decreases in PEF in children with asthma. In Detroit, MI, O₃
20 was moderately correlated with PM_{2.5} (Pearson r = 0.57) and PM₁₀ (Pearson r = 0.59), all
21 averaged over 24 hours ([Lewis et al., 2005](#)). Adjustment for PM₁₀ or PM_{2.5} resulted in a
22 large change in the O₃-associated FEV₁ decrement in children with asthma, but only in
23 CS users and not in children with concurrent URI ([Figure 6-9](#) and [Table 6-14](#)). Studies
24 conducted in Mexico City found small changes in O₃-associated PEF decrements with
25 copollutant adjustment although different averaging times were used for copollutants
26 ([Romieu et al., 1997](#); [Romieu et al., 1996](#)) ([Figure 6-9](#) and [Table 6-14](#)). In these studies,
27 O₃ was moderately correlated with copollutants such as NO₂ and PM₁₀ (range of Pearson
28 r = 0.38-0.58). Studies conducted in Asia also found that associations between O₃ and
29 lung function were robust to adjustment for weakly- to moderately-correlated
30 copollutants; effect estimates for copollutants generally were attenuated, indicating that
31 O₃ may confound associations of copollutants ([Son et al., 2010](#); [Chen et al., 1999](#)).

32 In a summer camp study conducted in Connecticut, [Thurston et al. \(1997\)](#) found ambient
33 concentrations of 1-h max O₃ and 12-h avg sulfate to be highly correlated (r = 0.74),
34 making it difficult to separate their independent effects. With sulfate in the model, a
35 larger decrease in PEF was estimated for O₃; however, the 95% CI was much wider
36 ([Figure 6-9](#) and [Table 6-14](#)). Investigators found that the association for sulfate was due
37 to one day when the ambient concentrations of both pollutants were at their peak. With
38 the removal of this peak day, the sulfate effect was attenuated, whereas O₃ effects

1 remained robust ([Thurston et al., 1997](#)). Among children with asthma in Thailand, the
 2 O₃-associated decrease in PEF was robust to adjustment of SO₂; however, different lags
 3 were examined for O₃ (lag 5) and SO₂ (lag 4) ([Wiwatanadate and Trakultivakorn, 2010](#)).



Note: Results are presented first for FEV₁ then for PEF and then in order of increasing mean ambient O₃ concentration. ^aInformation was not available to calculate 95% CI of the copollutant model. CS = corticosteroid, URI = Upper respiratory infection. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 12-h avg, and 24-h avg O₃, respectively. Black circles represent O₃ effect estimates from single pollutant models, and open circles represent O₃ effect estimates from copollutant models.

Figure 6-9 Comparison of ozone-associated changes in lung function in single- and co-pollutant models.

Table 6-14 Additional characteristics and quantitative data for studies represented in Figure 6-9.

| Study* | Location/Population | Parameter | O ₃ -associated Percent Change in Single-Pollutant Model (95% CI) ^a | O ₃ -associated Percent Change in Copollutant Model (95% CI) ^a |
|--|--|-------------------------------|---|---|
| PEF | | | | |
| Neas et al. (1999) | Philadelphia, PA 156 Children at summer camp, ages 6 - 11 yr | Morning PEF | For 12-h avg, Lag 1 -0.94 (-2.0, 0.08) | With 24-h avg, Lag 1 sulfate -0.10 ^b |
| Thurston et al. (1997) | CT River Valley 166 Children with asthma at summer camp, ages 7-13 yr | Intraday change PEF | For 1-h max, Lag 0 -2.8 (-4.9, -0.59) | With 12-h avg, Lag 0 sulfate -11.8 (-31.6, 8.1) |
| Romieu et al. (1996) | Mexico City, Mexico 71 children with asthma, ages 5-7 yr | Evening PEF | For 1-h max, Lag 2 -0.55 (-1.3, 0.19) | With 24-h avg, Lag 2 PM _{2.5} -0.24 (-1.2, 0.68) |
| Romieu et al. (1997) | Mexico City, Mexico 65 children with asthma, ages 5-13 yr | Evening PEF | For 1-h max, Lag 0 -0.52 (-1.0, -0.01) | With 24-h avg, Lag 0 PM ₁₀ -0.79 (-1.4, -0.16) |
| FEV₁ | | | | |
| Lewis et al. (2005) | Detroit, MI Children with asthma using CS 393 person-days | Lowest daily FEV ₁ | For 24-h avg, Lag 2 0.29 (-4.2, 5.0) | With 24-h avg, Lag 2 PM _{2.5} -0.18 (-11.0, 11.9) With 24-h avg, Lag 2 PM ₁₀ -13.4 (-17.8, -8.8) |
| | Children with asthma with URI 231 person-days Overall mean (SD) age 9.1 (1.4 yr) | | For 24-h avg, Lag 2 -6.0 (-11.2, -0.41) | With 24-h avg, Lag 2 PM _{2.5} -5.5 (-10.3, -0.42) With 24-h avg, Lag 2 PM ₁₀ -7.1 (-11.3, -2.8) |
| Chen et al. (1999) | 3 Taiwan communities 941 children, mean (SD) age 9.8 (1.6) yr | FEV ₁ | For 1-h max, Lag 1 -1.5 (-2.8, -0.12) | With 24-h avg, Lag 1 NO ₂ -2.0 (-3.5, -0.43) |

| Study* | Location/Population | Parameter | O ₃ -associated Percent Change in Single-Pollutant Model (95% CI) ^a | O ₃ -associated Percent Change in Copollutant Model (95% CI) ^a |
|--|---|--|---|---|
| Results not included in Figure 6-9^c | | | | |
| Jalaludin et al. (2000) | Sydney, Australia 125 children with asthma or wheeze, mean (SD) age 9.6 (1.0) yr | Daily deviation from mean PEF | For 24-h avg, Lag 0 -1.8 (-3.5, -0.19) | With 24-h avg, Lag 0 PM ₁₀ , -1.8 (-3.5, -0.19) With 24-h avg, Lag 0 NO ₂ -1.8 (-3.4, -0.11) |
| Wiwatanadate and Trakultivakorn (2010) | Chiang Mai, Thailand 31 children with asthma, ages 4-11 yr | Evening PEF (L/min) | For 24-h avg, Lag 5 -2.6 (-5.2, 0) | With 24-h avg, Lag 4 SO ₂ -3.2 (-6.2, -0.2) |
| Son et al. (2010) | Ulsan, Korea 2,102 children and adults, ages 7-97 yr | Change in percent predicted FEV ₁ | For 8-h max, Lag 0-2 avg (kriging) -1.4 (-2.6, -0.11) | With 24-h avg, Lag 2 PM ₁₀ (kriging) -1.8 (-3.4, -0.25) |

*Includes studies in [Figure 6-9](#) plus others.

CS = Corticosteroid, URI = Upper respiratory infection.

^aEffect estimates are standardized to a 40-ppb increase for 1-h max O₃, 30-ppb increase for 8-h max or 12-h avg O₃, and 20-ppb increase for 24-h avg O₃.

^bInformation was not available to calculate 95% CI.

^cResults are not presented in [Figure 6-9](#) because sufficient data were not provided to calculate percent change in lung function.

1 Some studies did not provide quantitative results but reported that O₃-associated lung
2 function decrements remained statistically significant in models that included
3 copollutants such as PM₁₀, NO₂, sulfate, nitrate, or ammonium ([Romieu et al., 1998b](#);
4 [Brauer et al., 1996](#); [Linn et al., 1996](#); [Spektor et al., 1988b](#)).

5 Several studies estimated robust O₃-associated lung function decrements in multipollutant
6 models that most often included O₃, NO₂, and either PM_{2.5} or PM₁₀ ([O'Connor et al.,](#)
7 [2008](#); [Thaller et al., 2008](#); [Chan and Wu, 2005](#); [Romieu et al., 2002](#); [Korrick et al., 1998](#);
8 [Higgins et al., 1990](#)). However, the independent effects of O₃ are more difficult to assess
9 in relation to incremental changes in more than one copollutant.

Summary of Epidemiologic Studies of Lung Function

10 The cumulative body of epidemiologic evidence indicates that short-term increases in
11 ambient O₃ concentration are associated with decrements in lung function in children
12 with asthma ([Figure 6-6](#) and [Figure 6-7](#) and [Table 6-8](#) and [Table 6-9](#)) and without
13 asthma. In contrast with results from controlled human exposure studies, within-study
14 epidemiologic comparisons did not consistently indicate larger ambient O₃-associated
15 lung function decrements in groups with asthma (children or adults) than in groups
16 without asthma. Notably, most epidemiologic studies were not designed to assess

1 between-group differences. Based on comparisons between studies, differences were
2 noted between children with and without asthma in so far as in studies of children with
3 asthma, an increase in ambient O₃ concentration was associated concurrently with lung
4 function decrements and increases in respiratory symptoms ([Just et al., 2002](#); [Mortimer et
5 al., 2002](#); [Ross et al., 2002](#); [Gielen et al., 1997](#); [Romieu et al., 1997](#); [Thurston et al.,
6 1997](#); [Romieu et al., 1996](#)). In studies of children in the general population, O₃-associated
7 decreases in lung function were not accompanied by O₃-associated increases in
8 respiratory symptoms ([Ward et al., 2002](#); [Gold et al., 1999](#); [Linn et al., 1996](#)).

9 Across studies of children, there was no clear indication that a particular exposure
10 assessment method using central site measurements produced stronger findings, despite
11 potential differences in exposure measurement error. In children, lung function was
12 associated with ambient O₃ concentrations measured on site of children's daytime hours
13 ([Hoppe et al., 2003](#); [Thurston et al., 1997](#)), at children's schools ([Chen et al., 1999](#); [Gold
14 et al., 1999](#)), at the closest site ([Romieu et al., 2006](#); [Lewis et al., 2005](#); [Romieu et al.,
15 2004b](#); [2002](#); [1997](#); [1996](#)), at multiple community sites then averaged ([O'Connor et al.,
16 2008](#); [Just et al., 2002](#); [Mortimer et al., 2002](#); [Jalaludin et al., 2000](#)), and at a single site
17 ([Ward et al., 2002](#); [Gielen et al., 1997](#); [Ulmer et al., 1997](#); [Linn et al., 1996](#)). Among
18 children in California, \ found slightly larger O₃-associated lung function decrements for
19 24-h avg personal exposures than for 1-h max ambient concentrations.

20 As noted in the 1996 and 2006 O₃ AQCDs, evidence clearly demonstrates ambient
21 O₃-associated lung function decrements in children and adults engaged in outdoor
22 recreation, exercise, or work. Moreover, several results indicated associations with 10-
23 min to 12-h avg O₃ concentrations <80 ppb. These studies are noteworthy for their
24 measurement of ambient O₃ on site of and at the time of subjects' outdoor activity,
25 factors that have contributed to higher O₃ personal exposure-ambient concentration
26 correlations and ratios (Section [4.3.3](#)). These epidemiologic results are well supported by
27 observations from controlled human exposure studies of lung function decrements
28 induced by O₃ exposure during exercise (Section [6.2.1.1](#)). Although investigation was
29 relatively limited, increases in ambient O₃ concentration were not consistently associated
30 with lung function decrements in adults with respiratory disease, healthy adults, or older
31 adults.

32 Across the diverse populations examined, most effect estimates ranged from a <1 to 2%
33 decrease in lung function per unit increase in O₃ concentration¹. Heterogeneity in
34 O₃-associated respiratory effects within populations was indicated by observations of
35 larger decreases (3-8%) in children with asthma with CS use or concurrent URI ([Lewis et
36 al., 2005](#)) and older adults with airway hyperresponsiveness and/or BMI >30 ([Alexeeff et](#)

¹ Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O₃.

1 [al., 2007](#)). Among children in Mexico City, high dietary antioxidant intake attenuated
2 O₃-associated lung function decrements ([Romieu et al., 2004b](#); [2002](#)), similar to results
3 from controlled human exposure studies. Each of these potential effect modifiers was
4 examined in one to two populations; thus, firm conclusions about their influences are not
5 warranted. Adding to the evidence for heterogeneity in response, [Hoppe et al. \(2003\)](#) and
6 [Mortimer et al. \(2002\)](#) found that increases in ambient O₃ concentration were associated
7 with increased incidence of >10% decline in lung function in children with asthma.

8 Collectively, epidemiologic studies examined and found lung function decrements in
9 association with single-day O₃ concentrations lagged from 0 to 7 days and concentrations
10 averaged over 2-10 days. More studies found associations with O₃ concentrations lagged
11 0 or 1 day ([Son et al., 2010](#); [Alexeeff et al., 2008](#); [Lewis et al., 2005](#); [Ross et al., 2002](#);
12 [Jalaludin et al., 2000](#); [Chen et al., 1999](#); [Romieu et al., 1997](#); [Brauer et al., 1996](#); [Romieu](#)
13 [et al., 1996](#); [Spektor et al., 1988b](#)) than those lagged 5-7 days ([Wiwatanadate and](#)
14 [Trakultivakorn, 2010](#); [Hernández-Cadena et al., 2009](#); [Steinvil et al., 2009](#)). Associations
15 with multiday average concentrations ([Son et al., 2010](#); [Liu et al., 2009a](#); [Barraza-](#)
16 [Villarreal et al., 2008](#); [O'Connor et al., 2008](#); [Alexeeff et al., 2007](#); [Mortimer et al., 2002](#);
17 [Ward et al., 2002](#); [Gold et al., 1999](#); [Naehler et al., 1999](#); [Neas et al., 1999](#)) indicate that
18 elevated exposures over several days may be important. Within studies, O₃
19 concentrations for multiple lag periods were associated with lung function decrements,
20 possibly indicating that multiple modes of action may be involved in the responses.
21 Activation of bronchial C-fibers (Section [5.3.2](#)) may lead to decreases in lung function as
22 an immediate response to O₃ exposure, and increased airway hyperresponsiveness to
23 antigens resulting from sensitization of airways by O₃ (Section [5.3.5](#)) may mediate lung
24 function responses associated with lagged or multiday O₃ exposures ([Peden, 2011](#)).

25 For single- and multi-day average O₃ concentrations, lung function decrements were
26 associated with 1-h max, 8-h max, and 24-h avg O₃, with no strong difference in the
27 consistency or magnitude of association among the averaging times. For example, among
28 studies that examined multiple averaging times, [Spektor and Lippmann \(1991\)](#) found a
29 larger magnitude of association for 1-h max O₃ than for 24-h avg O₃. However, other
30 studies found larger magnitudes of association for longer averaging times [8-h max in
31 [Chan and Wu \(2005\)](#) and 12-h avg in [Thaller et al. \(2008\)](#)] than for 1-h max O₃. Other
32 studies found no clear difference among O₃ averaging times ([Jalaludin et al., 2000](#); [Chen](#)
33 [et al., 1999](#); [Scarlett et al., 1996](#); [Berry et al., 1991](#)).

34 Several studies found that associations with lung function decrements persisted at lower
35 ambient O₃ concentrations. For O₃ concentrations averaged up to 1 hour during outdoor
36 recreation or exercise, associations were found in analyses restricted to O₃ concentrations
37 <80 ppb ([Spektor et al., 1988a](#); [Spektor et al., 1988b](#)), 60 ppb ([Brunekreef et al., 1994](#);

1 [Spektor et al., 1988a](#)), and 50 ppb ([Brunekreef et al., 1994](#)). Among outdoor workers,
2 [Brauer et al. \(1996\)](#) found a robust association using daily 1-h max O₃ concentrations
3 <40 ppb. [Ulmer et al. \(1997\)](#) found a robust association in schoolchildren using 30-min
4 max O₃ concentrations <60 ppb. For 8-hour avg O₃ concentrations, associations with lung
5 function decrements in children with asthma were found to persist at concentrations
6 <80 ppb in a U.S. multicity study (for lag 1-5 avg) ([Mortimer et al., 2002](#)) and <51 ppb in
7 a study conducted in the Netherlands (for lag 2) ([Gielen et al., 1997](#)).

8 Evidence did not demonstrate strong confounding by meteorological factors and
9 copollutant exposures. Most O₃ effect estimates for lung function were robust to
10 adjustment for temperature, humidity, and copollutants such as PM_{2.5}, PM₁₀, NO₂, or SO₂.
11 Although examined in few epidemiologic studies, O₃ was associated with decreases in
12 lung function with adjustment for pollen or acid aerosols. The consistency of association
13 in the collective body of evidence with and without adjustment for ambient copollutant
14 concentrations and meteorological factors combined with evidence from controlled
15 human exposure studies for the direct effects of O₃ exposure provide strong support for
16 the independent effects of short-term ambient O₃ exposure on lung function decrements.

6.2.1.3 Toxicology: Lung Function

17 The 2006 O₃ AQCD concluded that pulmonary function decrements occur in a number of
18 species with acute exposures (≤ 1 week), ranging from 0.25 to 0.4 ppm O₃ ([U.S. EPA,](#)
19 [2006b](#)). Early work has demonstrated that during acute exposure of ~0.2 ppm O₃ in rats,
20 the most commonly observed alterations are increased frequency of breathing and
21 decreased tidal volume (i.e., rapid, shallow breathing). Decreased lung volumes are
22 observed in rats with acute exposures to 0.5 ppm O₃. At concentrations of ≥ 1 ppm,
23 breathing mechanics (compliance and resistance) are also affected. Exposures of 6 h/day
24 for 5 days create a pattern of attenuation of pulmonary function decrements in both rats
25 and humans without concurrent attenuation of lung injury and morphological changes,
26 indicating that the attenuation did not result in protection against all the effects of O₃
27 ([Tepper et al., 1989](#)). A number of studies examining the effects of O₃ on pulmonary
28 function in rats, mice, and dogs are described in Table 6-13 on page 6-91 ([U.S. EPA,](#)
29 [1996m](#)) of the 1996 O₃ AQCD, and Table AX5-11 on page AX5-34 ([U.S. EPA, 2006f](#)) of
30 the 2006 O₃ AQCD ([U.S. EPA, 2006b, 1996a](#)). Lung imaging studies using
31 hyperpolarized ³He provide evidence of ventilation abnormalities in rats following
32 exposure to 0.5 ppm O₃ ([Crémillieux et al., 2008](#)). Rats were exposed to 0.5 ppm O₃ for 2
33 or 6 days, either continuously (22 h/day) or alternately (12 h/day). Dynamic imaging of
34 lung filling (2 mL/sec) revealed delayed and incomplete filling of lung segments and
35 lobes. Abnormalities were mainly found in the upper regions of the lungs and proposed to

1 be due to the spatial distribution of O₃ exposure within the lung. Although the small
2 number of animals used in the study (n = 3 to 7/group) makes definitive conclusions
3 difficult, the authors suggest that the delayed filling of lung lobes or segments is likely a
4 result of an increase in airway resistance brought about by narrowing of the peripheral
5 small airways.

6.2.2 Airway Hyperresponsiveness

6 Airway hyperresponsiveness refers to a condition in which the conducting airways
7 undergo enhanced bronchoconstriction in response to a variety of stimuli. Airway
8 responsiveness is typically quantified by measuring changes in pulmonary function
9 (e.g., FEV₁ or specific airway resistance [sRaw]) following the inhalation of an
10 aerosolized specific (allergen) or nonspecific (e.g., methacholine) bronchoconstricting
11 agent or another stimulus such as exercise or cold air. Asthmatics are generally more
12 sensitive to bronchoconstricting agents than nonasthmatics, and the use of an airway
13 challenge to inhaled bronchoconstricting agents is a diagnostic test in asthma. Standards
14 for airway responsiveness testing have been developed for the clinical laboratory ([ATS,
15 2000a](#)), although variation in methodology for administering the bronchoconstricting
16 agent may affect the results ([Cockcroft et al., 2005](#)). There is a wide range of airway
17 responsiveness in nonasthmatic people, and responsiveness is influenced by a wide range
18 of factors, including cigarette smoke, pollutant exposures, respiratory infections,
19 occupational exposures, and respiratory irritants. Airways hyperresponsiveness in
20 response to O₃ exposure has not been examined widely in epidemiologic studies; such
21 evidence is derived primarily from controlled human exposure and toxicological studies.

6.2.2.1 Controlled Human Exposures

22 Beyond its direct effect on lung function, O₃ exposure causes an increase in airway
23 responsiveness in human subjects. Increased airway responsiveness is an important
24 consequence of exposure to ambient O₃, because the airways are then predisposed to
25 narrowing upon inhalation of a variety of ambient stimuli.

26 Increases in airway responsiveness have been reported for exposures to 80 ppb O₃ and
27 above. [Horstman et al. \(1990\)](#) evaluated airway responsiveness to methacholine in young
28 healthy adults (22 M) exposed to 80, 100, and 120 ppb O₃ (6.6 hours, quasi continuous
29 moderate exercise, 39 L/min). Dose-dependent decreases of 33, 47, and 55% in the
30 cumulative dose of methacholine required to produce a 100% increase in sRaw after
31 exposure to O₃ at 80, 100, and 120 ppb, respectively, were reported. [Molfino et al. \(1991\)](#)

1 reported increased allergen-specific airway responsiveness in mild asthmatics exposed to
2 120 ppb O₃ (1 hour resting exposure). Due to safety concerns, however, the exposures in
3 the [Molfino et al. \(1991\)](#) study were not randomized with FA conducted first and O₃
4 exposure second. Attempts to reproduce the findings of [Molfino et al. \(1991\)](#) using a
5 randomized exposure design have not found statistically significant changes in airway
6 responsiveness at such low levels of O₃ exposure. At a considerably higher exposure to
7 250 ppb O₃ (3 h, light-to-moderate intermittent exercise, 30 L/min), [Jorres et al. \(1996\)](#)
8 found significant increases in specific and non-specific airway responsiveness of mild
9 asthmatics 3 hours following O₃ exposure. [Kehrl et al. \(1999\)](#) found increased reactivity
10 to house dust mite antigen in mild atopic asthmatics 16-18 hours after exposure to
11 160 ppb O₃ (7.6 hours, light quasi continuous exercise, 25 L/min). [Holz et al. \(2002\)](#)
12 demonstrated that repeated daily exposure to lower concentrations of 125 ppb O₃ (3 hours
13 for four consecutive days; intermittent exercise, 30 L/min) causes an increased response
14 to allergen challenge at 20 hours postexposure in allergic airway disease.

15 Ozone exposure of asthmatic subjects, who characteristically have increased airway
16 responsiveness at baseline relative to healthy controls (by nearly two orders of
17 magnitude), can cause further increases in responsiveness ([Kreit et al., 1989](#)). Similar
18 relative changes in airway responsiveness are seen in asthmatics and healthy control
19 subject exposed to O₃ despite their markedly different baseline airway responsiveness.
20 Several studies ([Kehrl et al., 1999](#); [Jorres et al., 1996](#); [Molfino et al., 1991](#)) have
21 suggested an increase in specific (i.e., allergen-induced) airway reactivity. An important
22 aspect of increased airway responsiveness after O₃ exposure is that this may provide
23 biological plausibility for associations observed between increases in ambient O₃
24 concentrations and increased respiratory symptoms in children with asthma
25 (Section [6.2.4.1](#)) and increased hospital admissions and ED visits for asthma
26 (Section [6.2.7](#)).

27 Changes in airway responsiveness after O₃ exposure appear to resolve more slowly than
28 changes in FEV₁ or respiratory symptoms ([Folinsbee and Hazucha, 2000](#)). Studies
29 suggest that O₃-induced increases in airway responsiveness usually resolve 18 to 24 hours
30 after exposure, but may persist in some individuals for longer periods ([Folinsbee and](#)
31 [Hazucha, 1989](#)). Furthermore, in studies of repeated exposure to O₃, changes in airway
32 responsiveness tend to be somewhat less susceptible to attenuation with consecutive
33 exposures than changes in FEV₁ ([Gong et al., 1997a](#); [Folinsbee et al., 1994](#); [Kulle et al.,](#)
34 [1982](#); [Dimeo et al., 1981](#)). Increases in airway responsiveness do not appear to be
35 strongly associated with decrements in lung function or increases in symptoms ([Aris et](#)
36 [al., 1995](#)). Recently, [Que et al. \(2011\)](#) assessed methacholine responsiveness in healthy
37 young adults (83M, 55 F) one day after exposure to 220 ppb O₃ and FA for 2.25 hours
38 (alternating 15 min periods of rest and brisk treadmill walking). Increases in airways

1 responsiveness at 1 day post-O₃ exposure were not correlated with FEV₁ responses
2 immediately following the O₃ exposure nor with changes in epithelial permeability
3 assessed 1 day post-O₃ exposure.

6.2.2.2 Toxicology: Airway Hyperresponsiveness

4 In addition to human subjects, a number of species, including nonhuman primates, dogs,
5 cats, rabbits, and rodents, have been used to examine the effect of O₃ exposure on airway
6 hyperresponsiveness (see Table 6-14 on page 6-93 ([U.S. EPA, 1996n](#)) of the 1996 O₃
7 AQCD and Table AX5-12 on page AX5-36 ([U.S. EPA, 2006g](#)) of the 2006 O₃ AQCD).
8 With a few exceptions, commonly used animal models have been guinea pigs, rats, or
9 mice acutely exposed to O₃ concentrations of 1 to 3 ppm to induce airway
10 hyperresponsiveness. These animal models are helpful for determining underlying
11 mechanisms of general airway hyperresponsiveness and are relevant for understanding
12 airway responses in humans. Although 1-3 ppm may seem like a high exposure
13 concentration, based on ¹⁸O₃ (oxygen-18-labeled O₃) in the BALF of humans and rats, an
14 exposure of 0.4 ppm O₃ in exercising humans appears roughly equivalent to an exposure
15 of 2 ppm in resting rats ([Hatch et al., 1994](#)).

16 A limited number of studies have observed airway hyperresponsiveness in rodents and
17 guinea pigs after exposure to less than 0.3 ppm O₃. As previously reported in the 2006 O₃
18 AQCD, one study demonstrated that a very low concentration of O₃ (0.05 ppm for 4 h)
19 induced airway hyperresponsiveness in some of the nine strains of rats tested ([Depuydt et
20 al., 1999](#)). This effect occurred at a concentration of O₃ that was much lower than has
21 been reported to induce airway hyperresponsiveness in any other species. Similar to the
22 effects of O₃ on other endpoints, these observations suggest a genetic component plays an
23 important role in O₃-induced airway hyperresponsiveness in this species and warrants
24 verification in other species. More recently, [Chhabra et al. \(2010\)](#) demonstrated that
25 exposure of ovalbumin (OVA)-sensitized guinea pigs to 0.12 ppm for 2 h/day for
26 4 weeks produced specific airway hyperresponsiveness to an inhaled OVA challenge.
27 Interestingly, in this study, dietary supplementation of the guinea pigs with vitamins C
28 and E ameliorated a portion of the airway hyperresponsiveness as well as indices of
29 inflammation and oxidative stress. Larsen and colleagues conducted an O₃ C-R study in
30 mice sensitized by 10 daily inhalation treatments with an OVA aerosol ([Larsen et al.,
31 2010](#)). Although airway responsiveness to methacholine was increased in non-sensitized
32 animals exposed to a single 3-hour exposure to 0.5, but not 0.1 or 0.25 ppm O₃, airway
33 hyperresponsiveness was observed after exposure to 0.1 and 0.25 ppm O₃ in OVA-
34 sensitized mice.

1 In order to evaluate the ability of O₃ to enhance specific and non-specific airway
2 responsiveness, it is important to take into account the phenomenon of attenuation in the
3 effects of O₃. Several studies have clearly demonstrated that some effects caused by acute
4 exposure are absent after repeated or prolonged exposures to O₃. The ability of the
5 pulmonary system to adapt to repeated insults to O₃ is complex, however, and
6 experimental findings for attenuation to O₃-induced airway hyperresponsiveness are
7 inconsistent. Airway hyperresponsiveness was observed in mice after a 3-hour exposure
8 but not in mice exposed continuously for 72 hours to 0.3 ppm ([Johnston et al., 2005b](#)).
9 However, the Chhabra study demonstrated O₃-induced airway hyperresponsiveness in
10 guinea pigs exposed for 2 h/day for 10 days ([Chhabra et al., 2010](#)). Besides the obvious
11 species disparity, these studies differ in that the mice were exposed continuously for
12 72 hours, whereas the guinea pigs were exposed intermittently over 10 days, suggesting
13 that attenuation might be lost with periods of rest in between O₃ exposures.

14 Overall, numerous toxicological studies have demonstrated that O₃-induced airway
15 hyperresponsiveness occurs in guinea pigs, rats, and mice after either acute or repeated
16 exposure to relevant concentrations of O₃. The mechanisms by which O₃ enhances the
17 airway responsiveness to either specific (e.g., OVA) or non-specific (e.g., methacholine)
18 bronchoprovocation are not clear, but appear to be associated with complex cellular and
19 biochemical changes in the conducting airways. A number of potential mediators and
20 cells may play a role in O₃-induced airway hyperresponsiveness; mechanistic studies are
21 discussed in greater detail in Section [5.3](#).

6.2.3 Pulmonary Inflammation, Injury and Oxidative Stress

22 In addition to physiological pulmonary responses, respiratory symptoms, and airway
23 hyperresponsiveness, O₃ exposure has been shown to result in increased epithelial
24 permeability and respiratory tract inflammation. In general, inflammation can be
25 considered as the host response to injury and the induction of inflammation as evidence
26 that injury has occurred. Inflammation induced by exposure of humans to O₃ can have
27 several potential outcomes: (1) inflammation induced by a single exposure (or several
28 exposures over the course of a summer) can resolve entirely; (2) continued acute
29 inflammation can evolve into a chronic inflammatory state; (3) continued inflammation
30 can alter the structure and function of other pulmonary tissue, leading to diseases such as
31 fibrosis; (4) inflammation can alter the body's host defense response to inhaled
32 microorganisms, particularly in potentially at-risk populations such as the very young and
33 old; and (5) inflammation can alter the lung's response to other agents such as allergens
34 or toxins. Except for outcome (1), the possible chronic responses have only been directly
35 observed in animals exposed to O₃. It is also possible that the profile of response can be

1 altered in persons with preexisting pulmonary disease (e.g., asthma, COPD) or smokers.
2 Oxidative stress has been shown to play a key role in initiating and sustaining O₃-induced
3 inflammation. Secondary oxidation products formed as a result of reactions between O₃
4 and components of the ELF can increase the expression of cytokines, chemokines, and
5 adhesion molecules and enhance airway epithelium permeability (Section [5.3.3](#). and
6 Section [5.3.4](#)).

6.2.3.1 Controlled Human Exposures

7 As reported in studies reviewed in the 1996 and 2006 O₃ AQCDs, acute O₃ exposure
8 initiates an acute inflammatory response throughout the respiratory tract that has been
9 observed to persist for at least 18-24 hours postexposure. A meta-analysis of 21 studies
10 ([Mudway and Kelly, 2004a](#)) for varied experimental protocols (80-600 ppb O₃;
11 1-6.6 hours duration; light to heavy exercise; bronchoscopy at 0-24 hours post-O₃
12 exposure) showed that neutrophils (PMN) influx in healthy subjects was linearly
13 associated (p <0.01) with total O₃ dose (i.e., the product of O₃ concentration, exposure
14 duration, and \dot{V}_E). As with FEV₁ responses to O₃, within individual inflammatory
15 responses to O₃ are generally reproducible and correlated between repeat exposures ([Holz
16 et al., 1999](#)). Some individuals also appear to be intrinsically more susceptible to
17 increased inflammatory responses to O₃ exposure ([Holz et al., 2005](#)).

18 The presence of PMNs in the lung has long been accepted as a hallmark of inflammation
19 and is an important indicator that O₃ causes inflammation in the lungs. Neutrophilic
20 inflammation of tissues indicates activation of the innate immune system and requires a
21 complex series of events that are normally followed by processes that clear the evidence
22 of acute inflammation. Inflammatory effects have been assessed in vivo by lavage
23 (proximal airway and bronchoalveolar), bronchial biopsy, and more recently, induced
24 sputum. A single acute exposure (1-4 hours) of humans to moderate concentrations of O₃
25 (200-600 ppb) while exercising at moderate to heavy intensities results in a number of
26 cellular and biochemical changes in the lung, including an inflammatory response
27 characterized by increased numbers of PMNs, increased permeability of the epithelial
28 lining of the respiratory tract, cell damage, and production of proinflammatory cytokines
29 and prostaglandins ([U.S. EPA, 2006b](#)). These changes also occur in humans exposed to
30 80 and 100 ppb O₃ for 6-8 hours ([Alexis et al., 2010](#); [Peden et al., 1997](#); [Devlin et al.,
31 1991](#)). Significant (p = 0.002) increases in sputum PMN (16-18 hours postexposure)
32 relative to FA responses have been recently reported for 60 ppb O₃ which is the lowest
33 exposure concentration that has been investigated in young healthy adults ([Kim et al.,
34 2011](#)). Soluble mediators of inflammation such as the cytokines (e.g., IL-6, IL-8) and
35 arachidonic acid metabolites (e.g., prostaglandin [PG]E₂, PGF_{2 α} , thromboxane, and

1 leukotrienes [LTs] such as LTB₄) have been measured in the BALF of humans exposed
2 to O₃. In addition to their role in inflammation, many of these compounds have
3 bronchoconstrictive properties and may be involved in increased airway responsiveness
4 following O₃ exposure. The possible relationship between repetitive bouts of acute
5 inflammation in humans caused by O₃ and the development of chronic respiratory disease
6 is unknown.

Asthma

7 Inflammatory responses to O₃ exposure have also been studied in asthmatic subjects.
8 Asthmatics exposed to 200 ppb O₃ for 4-6 hours with exercise show significantly more
9 neutrophils in BALF (18 hours postexposure) than similarly exposed healthy individuals
10 ([Scannell et al., 1996](#); [Basha et al., 1994](#)). In allergic asthmatics who tested positive for
11 *Dermatophagoides farinae* antigen, there was an eosinophilic inflammation (2-fold
12 increase), as well as neutrophilic inflammation (3-fold increase) 18 hours after exposure
13 to 160 ppb O₃ for 7.6 hours with exercise ([Peden et al., 1997](#)). In a study of subjects with
14 intermittent asthma exposed to 400 ppb O₃ for 2 hours, increases in eosinophil cationic
15 protein, neutrophil elastase and IL-8 were found to be significantly increased 16 hours
16 postexposure and comparable in induced sputum and BALF ([Hiltermann et al., 1999](#)). At
17 18 hours post-O₃ exposure (200 ppb, 4 hours with exercise) and corrected for FA
18 responses, [Scannell et al. \(1996\)](#) found significantly increased neutrophils in 18
19 asthmatics (12%) compared to 20 healthy subjects (4.5%). This difference in
20 inflammatory response was observed despite no group differences in spirometric
21 responses to O₃. [Scannell et al. \(1996\)](#) also reported that IL-8 tends to be higher in the
22 BALF of asthmatics compared to nonasthmatics following O₃ exposure, suggesting a
23 possible mediator for the significantly increased neutrophilic inflammation in those
24 subjects. [Bosson et al. \(2003\)](#) found significantly greater epithelial expression of IL-5,
25 IL-8, granulocyte-macrophage colony-stimulating factor and epithelial cell-derived
26 neutrophil-activating peptide-78 in asthmatics compared to healthy subjects following
27 exposure to 200 ppb O₃ for 2 h. In contrast, [Stenfors et al. \(2002\)](#) did not detect a
28 difference in the O₃-induced increases in neutrophil numbers between 15 mild asthmatic
29 and 15 healthy subjects by bronchial wash at the 6 hours postexposure time point.
30 However, the asthmatics were on average 5 years older than the healthy subjects in this
31 study, and it is not yet known how age affects inflammatory responses. It is also possible
32 that the time course of neutrophil influx differs between healthy and asthmatic
33 individuals. Differences between asthmatics and healthy subjects in O₃-mediated
34 activation of innate and adaptive immune responses have been observed in two studies
35 ([Hernandez et al., 2010](#); [Bosson et al., 2003](#)), as discussed in Section [6.2.5.4](#) and
36 Section [5.4.2.2](#).

1 [Vagaggini et al. \(2002\)](#) investigated the effect of prior allergen challenge on responses in
2 mild asthmatics exposed for 2 hours to 270 ppb O₃ or filtered air. At 6 hours
3 postexposure, eosinophil numbers in induced sputum were found to be significantly
4 greater after O₃ than after air exposures. Studies such as this suggest that the time course
5 of eosinophil and neutrophil influx following O₃ exposure can occur at levels detectable
6 within the airway lumen by as early as 6 h. They also suggest that the previous or
7 concurrent activation of proinflammatory pathways within the airway epithelium may
8 enhance the inflammatory effects of O₃. For example, in an in vitro study of primary
9 human nasal epithelial cells and BEAS-2B cell line, cytokine production induced by
10 rhinovirus infection was enhanced synergistically by concurrent exposure to O₃ at
11 200 ppb for 3 hours ([Spannhake et al., 2002](#)).

12 A few studies have evaluated the effects of corticosteroid usage on the response of
13 asthmatics to O₃. [Vagaggini et al. \(2007\)](#) evaluated whether corticosteroid usage would
14 prevent O₃-induced lung function decrements and inflammatory responses in a group of
15 subjects with mild persistent asthma (n = 9; 25 ± 7 years). In this study, asthmatics were
16 randomly exposed on four occasions to 270 ppb O₃ or FA for 2 hours with moderate
17 exercise. Exposures were preceded by four days of treatment with prednisone or placebo.
18 Pretreatment with corticosteroids prevented an inflammatory response in induced sputum
19 at 6 hours postexposure. FEV₁ responses were, however, not prevented by corticosteroid
20 treatment and were roughly equivalent to those observed following placebo. [Vagaggini et
21 al. \(2001\)](#) also found budesonide to decrease airway neutrophil influx in asthmatics
22 following O₃ exposure. In contrast, inhalation of corticosteroid budesonide failed to
23 prevent or attenuate O₃-induced responses in healthy subjects as assessed by
24 measurements of lung function, bronchial reactivity and airway inflammation
25 ([Nightingale et al., 2000](#)). High doses of inhaled fluticasone and oral prednisolone have
26 each been reported to reduce inflammatory responses to O₃ in healthy individuals ([Holz
27 et al., 2005](#)).

28 [Stenfors et al. \(2010\)](#) exposed persistent asthmatics (n = 13; aged 33 years) receiving
29 chronic inhaled corticosteroid therapy to 200 ppb O₃ for 2 hours with moderate exercise.
30 At 18 hours postexposure, there was a significant O₃-induced increase in
31 bronchioalveolar lavage (BAL) neutrophils, but not eosinophils. Bronchial biopsy also
32 showed a significant O₃-induced increase in mast cells. This study suggests that the
33 protective effect of acute corticosteroid therapy against inflammatory responses to O₃ in
34 asthmatics demonstrated by [Vagaggini et al. \(2007\)](#) may be lost with continued treatment
35 regimes.

Associations between Inflammation and FEV₁ responses

1 Studies reviewed in the 2006 O₃ AQCD reported that inflammatory responses do not
2 appear to be correlated with lung function responses in either asthmatic or healthy
3 subjects. In healthy adults (14 M, 6 F) and asthmatic (12 M, 6 F) volunteers exposed to
4 200 ppb O₃ (4 hours with moderate quasi continuous exercise, $\dot{V}_E = 44$ L/min), percent
5 PMN and total protein in BAL fluids were significantly increased in the asthmatics
6 relative to the healthy controls. Spirometric measures of lung function were significantly
7 decreased following the O₃ exposure in both groups, but were not significantly different
8 between the asthmatic and healthy subjects. Effects of O₃ on PMN and total protein were
9 not correlated with changes in FEV₁ or FVC ([Balmes et al., 1997](#); [Balmes et al., 1996](#)).
10 [Devlin et al. \(1991\)](#) exposed healthy adults (18 M) to 80 and 100 ppb O₃ (6.6-hours with
11 moderate quasi continuous exercise, 40 L/min). In BAL fluid collected 18 hours after
12 exposure to 100 ppb O₃, significant increases in PMNs, protein, PGE₂, fibronectin, IL-6,
13 lactate dehydrogenase, and α -1 antitrypsin compared to FA. Similar but smaller increases
14 in all mediators were found after exposure to 80 ppb O₃ except for protein and
15 fibronectin. Changes in BAL markers were not correlated with changes in FEV₁. [Holz et](#)
16 [al. \(1999\)](#) examined inflammatory responses in healthy (n = 21) and asthmatic (n = 15)
17 subjects exposed to 125 and 250 ppb O₃ (3 h, light intermittent exercise, 26 L/min).
18 Significantly increased percent PMN in sputum due to O₃ exposure was observed in both
19 asthmatics and healthy subjects following the 250 ppb exposure. At the lower 125 ppb
20 exposure, only the asthmatic group experienced statistically significant increases in the
21 percent PMN. Significant decrements in FEV₁ were only found following exposure to
22 250 ppb; these changes in FEV₁ did not differ significantly between the asthmatic and
23 healthy groups and were not correlated with changes in PMN levels. [Peden et al. \(1997\)](#)
24 also found no correlation between PMN and FEV₁ responses in 8 individuals with asthma
25 exposed to 160 ppb O₃ for 7.6 hours with light-to-moderate exercise ($\dot{V}_E = 25$ L/min).
26 However, a marginally significant correlation (r = -0.69, two-tailed p = 0.08, n = 7) was
27 observed between increases in the percentage of eosinophils and FEV₁ responses
28 following O₃ exposure.

29 In contrast to these earlier findings, [Vagaggini et al. \(2010\)](#) recently reported a significant
30 (r = 0.61, p = 0.015) correlation between changes in FEV₁ and changes in sputum
31 neutrophils in mild-to-moderate asthmatics (n = 23; 33 ± 11 years) exposed to 300 ppb
32 O₃ for 2 hours with moderate exercise. Eight subjects were categorized as “responders”
33 based on >10% FEV₁ decrements. There were no baseline differences between
34 responders and nonresponders. However, at 6 hours post-O₃ exposure, sputum
35 neutrophils were significantly increased by 15% relative to FA in responders. The
36 neutrophil increase in responders was also significantly greater than the 0.2% increase in
37 nonresponders. Interestingly, the nonresponders in the [Vagaggini et al. \(2010\)](#) study

1 experienced a significant O₃-induced 11.3% increase in sputum eosinophils, while
2 responders had a nonsignificant 2.6% decrease.

Time Course of the Inflammatory Response

3 The time course of the inflammatory response to O₃ in humans has not been fully
4 characterized. Different markers exhibit peak responses at different times. Studies in
5 which lavages were performed 1 hour after O₃ exposure (1 hours at 400 ppb or 4 hours at
6 200 ppb) have demonstrated that the inflammatory responses are quickly initiated ([Torres
7 et al., 1997](#); [Devlin et al., 1996](#); [Schelegle et al., 1991](#)). Inflammatory mediators and
8 cytokines such as IL-8, IL-6, and PGE₂ are greater at 1 hours than at 18 hours post-O₃
9 exposure ([Torres et al., 1997](#); [Devlin et al., 1996](#)). However, IL-8 still remained elevated
10 at 18 hours post-O₃ exposure (4 hours at 200 ppb O₃ versus FA) in healthy subjects
11 ([Balmes et al., 1996](#)). [Schelegle et al. \(1991\)](#) found increased PMNs in the “proximal
12 airway” lavage at 1, 6, and 24 hours after O₃ exposure (4 hours at 200 ppb O₃), with a
13 peak response at 6 hours. However, at 18-24 hours after O₃ exposure, PMNs remain
14 elevated relative to 1 hour postexposure ([Torres et al., 1997](#); [Schelegle et al., 1991](#)).

Genetic Polymorphisms

15 [Alexis et al. \(2010\)](#) recently reported that a 6.6-hour exposure with moderate exercise to
16 80 ppb O₃ caused increased sputum neutrophil levels at 18 hours postexposure in young
17 healthy adults (n = 15; 24 ± 1 years). In a prior study, [Alexis et al. \(2009\)](#) found genotype
18 effects on inflammatory responses to O₃, but not lung function responses following a
19 2-hour exposure to 400 ppb O₃. At 4 hours post-O₃ exposure, both GSTM1 genotypes
20 had significant increases in sputum neutrophils with a tendency for a greater increase in
21 GSTM1-sufficient than null individuals. At 24 hours postexposure, neutrophils had
22 returned to baseline levels in the GSTM1-sufficient individuals. In the GSTM1-null
23 subjects, however, neutrophil levels increased further from 4 hours to 24 hours and were
24 significantly greater than both baseline levels and 24 hours levels in GSTM1-sufficient
25 individuals. [Alexis et al. \(2009\)](#) found that GSTM1-sufficient individuals (n = 19;
26 24 ± 3 years) had a decrease in macrophage levels at 4-24 hours postexposure to 400 ppb
27 O₃ for 2 hours with exercise. These studies also provide evidence for activation of innate
28 immunity and antigen presentation, as discussed in Section [5.3.6](#). Effects of the exposure
29 apart from O₃ cannot be ruled out in the [Alexis et al. \(2010\)](#); ([2009](#)) studies, however,
30 since no FA exposure was conducted.

31 [Vagaggini et al. \(2010\)](#) examined FEV₁ and sputum neutrophils in mild-to-moderate
32 asthmatics (n = 23; 33 ± 11 years) exposed to 300 ppb O₃ for 2 hours with moderate
33 exercise. Six of the subjects were NQO1 wild type and GSTM1 null, but this genotype
34 was not found to be associated with O₃-induced changes in lung function or inflammatory

1 responses to O₃. [Kim et al. \(2011\)](#) showed a significant (p = 0.002) increase in sputum
2 neutrophil levels following a 6.6-hour exposure to 60 ppb O₃ relative to FA in young
3 healthy adults (13 F, 11 M; 25.0 ± 0.5 years). There was no significant effect of GSTM1
4 genotype (half GSTM1-null) on the inflammatory responses observed in these
5 individuals. Previously, inflammatory responses had only been evaluated down to a level
6 of 80 ppb O₃.

Repeated Exposures

7 Markers from BALF following both 2 hours ([Devlin et al., 1997](#)) and 4 hours ([Jorres et](#)
8 [al., 2000](#); [Christian et al., 1998](#)) repeated O₃ exposures (up to 5 days) indicate that there is
9 ongoing cellular damage irrespective of the attenuation of some cellular inflammatory
10 responses of the airways, pulmonary function, and symptom responses. [Devlin et al.](#)
11 [\(1997\)](#) found that several indicators of inflammation (e.g., PMN, IL-6, PGE₂, fibronectin)
12 were attenuated after 5 days of exposure (i.e., values were not different from FA).
13 However, other markers (LDH, IL-8, total protein, epithelial cells) did not show
14 attenuation, suggesting that tissue damage probably continues to occur during repeated
15 exposure. Some cellular responses did not return to baseline levels for more than 10-
16 20 days following O₃ exposure. [Christian et al. \(1998\)](#) showed decreased numbers of
17 neutrophils and a decrease in IL-6 levels in healthy adults after 4 days of exposure versus
18 the single exposure to 200 ppb O₃ for 4 h. [Jorres et al. \(2000\)](#) also found both functional
19 and BALF cellular responses to O₃ were abolished at 24 hours postexposure following
20 the fourth exposure day. However, levels of total protein, IL-6, IL-8, reduced glutathione
21 and ortho-tyrosine were still increased significantly. In addition, visual scores
22 (bronchoscopy) for bronchitis and erythema and the numbers of neutrophils in bronchial
23 mucosal biopsies were increased. Results indicate that, despite an attenuation of some
24 markers of inflammation in BALF and pulmonary function decrements, inflammation
25 within the airways persists following repeated exposure to O₃. The continued presence of
26 cellular injury markers indicates a persistent effect that may not necessarily be recognized
27 due to the attenuation of spirometric and symptom responses.

Epithelial Permeability

28 A number of studies show that O₃ exposures increase epithelial cell permeability through
29 direct (technetium-99m labeled diethylene triamine pentaacetic acid, ^{99m}Tc-DTPA,
30 clearance) and indirect (e.g., increased BALF albumin, protein) techniques. [Kehrl et al.](#)
31 [\(1987\)](#) showed increased ^{99m}Tc-DTPA clearance in healthy young adults (age 20-30 yrs)
32 at 75 minutes postexposure to 400 ppb O₃ for 2 hours. Also in healthy young adults (age
33 26±2 yrs), [Foster and Stetkiewicz \(1996\)](#) have shown that increased ^{99m}Tc-DTPA
34 clearance persists for at least 18-20 hours post-O₃ exposure (130 minutes to average O₃
35 concentration of 240 ppb), and the effect is greater at the lung apices than at the base. In a

1 older group of healthy adults (mean age = 35 yrs), [Morrison et al. \(2006\)](#) observed
2 ^{99m}Tc -DTPA clearance at 1 hours and 6 hours postexposure to O_3 (100 and 400 ppb; 1
3 hour; moderate intermittent exercise, $\dot{V}_E = 40$ L/min) to be similar and not statistically
4 different from ^{99m}Tc -DTPA clearance at 1 hours postexposure to FA (1 h; $\dot{V}_E = 40$
5 L/min).

6 Increased BALF protein, suggesting O_3 -induced changes in epithelial permeability, have
7 also been reported at 1 hour and 18 hours postexposure ([Devlin et al., 1997](#); [Balmes et](#)
8 [al., 1996](#)). Meta-analysis of results from 21 publications ([Mudway and Kelly, 2004a](#)) for
9 varied experimental protocols (80-600 ppb O_3 ; 1-6.6 hours duration; light to heavy
10 exercise; bronchoscopy at 0-24 hours post- O_3 exposure), showed that increased BALF
11 protein is associated with total inhaled O_3 dose (i.e., the product of O_3 concentration,
12 exposure duration, and \dot{V}_E).

13 It has been postulated that changes in permeability associated with acute inflammation
14 may provide increased access of inhaled antigens, particles, and other inhaled substances
15 deposited on lung surfaces to the smooth muscle, interstitial cells, and the blood. Hence,
16 increases in epithelial permeability following O_3 exposure might lead to increases in
17 airway responsiveness to specific and nonspecific agents. [Que et al. \(2011\)](#) investigated
18 this hypothesis in healthy young adults (83M, 55 F) exposed to 220 ppb O_3 for 2.25 hours
19 (alternating 15 min periods of rest and brisk treadmill walking). As has been observed by
20 others for FEV_1 responses, within individual changes in permeability were correlated
21 between sequential O_3 exposures. This indicates intrinsic differences in susceptibility to
22 epithelial damage from O_3 exposure among individuals. Increases in epithelial
23 permeability at 1 day post- O_3 exposure were not correlated with FEV_1 responses
24 immediately following O_3 exposure nor with changes in airway responsiveness to
25 methacholine assessed 1 day post- O_3 exposure. The authors concluded that changes in
26 FEV_1 , permeability, and airway responsiveness following O_3 exposure were relatively
27 constant over time in young healthy adults; although, these responses appear to be
28 mediated by differing physiologic pathways.

6.2.3.2 Epidemiology

29 In the 2006 O_3 AQCD, epidemiologic evidence of associations between short-term
30 increases in ambient O_3 concentration (30-min or 1-h max) and changes in pulmonary
31 inflammation was limited to a few observations of increases in nasal lavage levels of
32 inflammatory cell counts, eosinophilic cationic protein, and myeloperoxidases ([U.S.](#)
33 [EPA, 2006b](#)). In recent years, there has been a large increase in the number of studies
34 assessing ambient O_3 -related changes in pulmonary inflammation and oxidative stress,

1 types of biological samples collected (i.e., lower airway), and types of indicators
2 examined. Most studies collected samples every 1 to 3 weeks resulting in a total of 3 to 8
3 samples per subject. These recent studies form a larger base to establish coherence with
4 findings from controlled human exposure and animal studies that have measured the
5 same or related biological markers. Additionally, these studies provide further biological
6 plausibility for the associations observed between ambient O₃ concentrations and
7 respiratory symptoms and asthma exacerbations.

8 Despite the strengths of studies of inflammation, it is important to note that research in
9 this field continues to develop, and several uncertainties are recognized that may limit
10 inferences of the effects of ambient O₃ exposure. Current areas of development include
11 examination of the clinical relevance of the observed magnitudes of changes in biological
12 markers of pulmonary inflammation ([Murugan et al., 2009](#); [Duramad et al., 2007](#)),
13 characterization of the time course of changes between biomarker levels and other
14 endpoints of respiratory morbidity, development of standardized methodologies for
15 collection, improvement of the sensitivity and specificity of assay methods, and
16 characterization of subject factors (e.g., asthma severity and recent medication use) that
17 contribute to inter-individual variability. These sources of uncertainty may contribute to
18 differences in findings among studies.

19 Although most of the biomarkers examined in epidemiologic studies were not specific to
20 the lung, most studies collected exhaled breath, exhaled breath condensate (EBC), nasal
21 lavage fluid, or induced sputum with the aim of monitoring inflammatory responses in
22 airways, as opposed to monitoring systemic responses in blood. The biomarker most
23 frequently measured was exhaled nitric oxide (eNO), likely related to its ease of
24 collection in the field and automated measurement. Other biological markers were
25 examined in EBC, induced sputum, and nasal lavage fluid, which are hypothesized to
26 represent the fluid lining the lower or upper airways and contain cytokines, cells, and/or
27 markers of oxidative stress that mediate inflammatory responses ([Balbi et al., 2007](#);
28 [Howarth et al., 2005](#); [Hunt, 2002](#)). [Table 6-15](#) presents the locations, time periods, and
29 ambient O₃ concentrations for studies examining associations with biological markers of
30 pulmonary inflammation and oxidative stress. Many studies found that short-term
31 increases in ambient O₃ concentration were associated with increases in pulmonary
32 inflammation and oxidative stress, in particular, studies of children with asthma
33 conducted in Mexico City ([Figure 6-10](#) and [Table 6-16](#) and
34 [Table 6-17](#)).

Table 6-15 Mean and upper percentile ozone concentrations in studies of biological markers of pulmonary inflammation and oxidative stress.

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|---|-----------------------------------|-------------------------------|---|--|
| Barraza-Villarreal et al. (2008) | Mexico City, Mexico | June 2003-June 2005 | 8-h moving avg | 31.6 | Max: 86.3 |
| Berhane et al. (2011) | 13 Southern California Communities | September 2004- June 2005 | 8-h avg (10 a.m.-6 p.m.) | NR | NR |
| Liu et al. (2009a) | Windsor, ON, Canada | October-December 2005 | 24-h avg | 13.0 | 95th: 26.5 |
| Khatri et al. (2009) | Atlanta, GA | May-September 2003, 2005, 2006 | 8-h max | With asthma: 61 (median) ^a No asthma: 56 (median) ^a | 75th (all subjects): 74 ^a |
| Qian et al. (2009) | Boston, MA; New York, NY; Denver, CO; Philadelphia, PA; San Francisco, CA; Madison, WI (SOCS) | February 1997-January 1999 | 8-h max | 33.6 | 75th: 44.4, Max: 91.5 |
| Romieu et al. (2008) | Mexico City, Mexico | January-October 2004 | 8-h max | 31.1 | 75th: 38.3, Max: 60.7 |
| Sienra-Monge et al. (2004) | Mexico City, Mexico | All-year 1999-2000 | 8-h max | 66.2 | Max: 142.5 |
| Ferdinands et al. (2008) | Suburb of Atlanta, GA | August 2004 | 1-h max | 61 (median) | 75th: 67 |
| Chimenti et al. (2009) | Sicily, Italy | November, February, July, year NR | 8-h avg (7 a.m. – 3 p.m.) | November: 32.7 (pre-race), 35.1 (race) ^b February: 37.0 (pre-race), 30.8 (race) ^b July: 51.2 (pre-race), 46.1 (race) ^b | NR |
| Nickmilder et al. (2007) | Southern Belgium | July-August 2002 | 1-h max | NR | Max (across 6 camps): 24.5-112.7 ^b |
| | | | 8-h max | NR | Max (across 6 camps): 18.9-81.1 ^b |
| Delfino et al. (2010a) | Los Angeles, CA | Warm and cold season 2005-2007 | 24-h avg | Warm season: 32.1 (median) ^c Cool season: 19.1 (median) ^c | Max: 76.4 ^c Max: 44.9 ^c |
| Adamkiewicz et al. (2004) | Steubenville, OH | September-December 2000 | 24-h avg | 15.3 | 75th: 20.2, Max: 32.2 |
| | | | 1-h avg ^d | 19.8 | 75th: 27.5, Max: 61.6 |

* Note: Studies presented in order of first appearance in the text of this section.

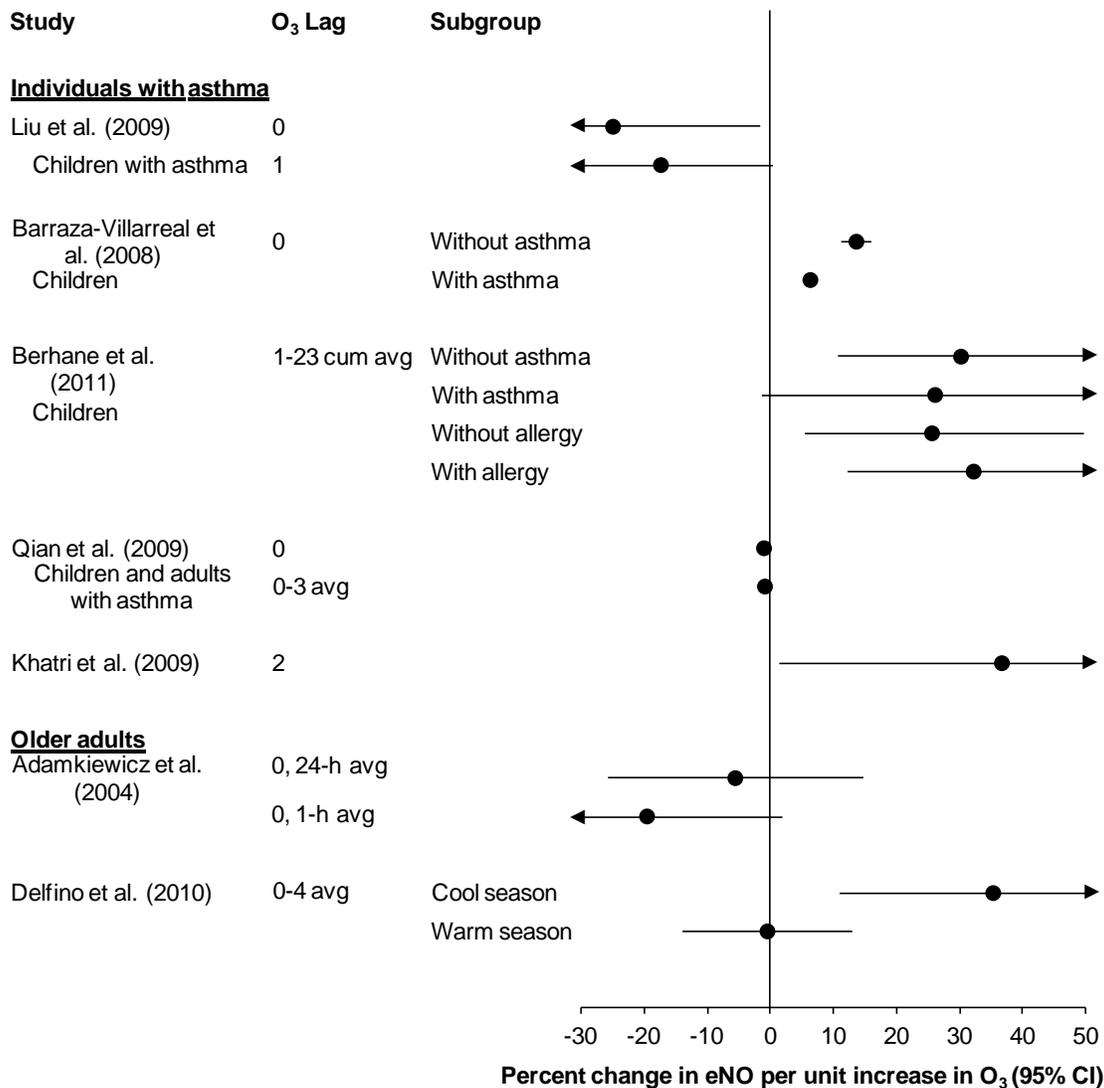
NR = Not Reported, SOCS = Salmeterol Off Corticosteroids Study.

^aIndividual-level estimates were calculated based on time spent in the vicinity of various O₃ monitors.

^bConcentrations converted from µg/m³ to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

^cMeasurements outside subject's residence (retirement home).

^dAverage O₃ concentration in the 1 hour preceding eNO collection.



Note: Results are presented first for children with asthma then for adults with asthma and older adults. Effect estimates are from single-pollutant models and are standardized to a 40-ppb increase for 1-h avg O₃ concentrations, a 30-ppb increase for 8-h max or 8-h avg O₃ concentrations, and a 20-ppb increase for 24-h avg O₃ concentrations.

Figure 6-10 Percent change in exhaled nitric oxide (eNO) in association with ambient ozone concentrations in populations with and without asthma.

Table 6-16 Additional characteristics and quantitative data for studies represented in Figure 6-10.

| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Subgroup | Standardized % Change (95% CI) ^a |
|--|---|-------------------------------|---------------------------|-----------------|---|
| Studies in individuals with asthma | | | | | |
| Liu et al. (2009a) | Windsor, ON, Canada 182 children with asthma, ages 9-14 yr | 24-h avg | 0 | | -25.1 (-42.9, -1.7) |
| | | | 1 | | -17.5 (-32.1, -0.24) |
| Barraza-Villarreal et al. (2008) | Mexico City, Mexico 208 children, ages 6-14 yr | 8-h max | 0 | Without asthma | 13.5 (11.2, 15.8) |
| | | | | With asthma | 6.2 (6.0, 6.5) |
| Berhane et al. (2011) | 13 Southern California communities 2,240 children, ages 6-10 yr | 8-h avg (10 a.m.-6 p.m.) | 1-23 cumulative avg | Without asthma | 30.1 (10.6, 53.2) |
| | | | | With asthma | 26.0 (-1.4, 60.9) |
| | | | | Without allergy | 25.5 (5.3, 49.6) |
| | | | | With allergy | 32.1 (12.0, 55.9) |
| Qian et al. (2009) | Boston, MA; New York, NY; Denver, CO; Philadelphia, PA; San Francisco, CA; Madison, WI 119 children and adults with asthma, ages 12-65 yr | 8-h max | 0 | | -1.2 (-1.7, -0.64) |
| | | | 0-3 avg | | -1.0 (-1.8, -0.26) |
| Khatri et al. (2009) | Atlanta, GA 38 adults with asthma, ages 31-50 yr | 8-h max | 2 | | 36.6 (1.2, 71.9) |
| Studies in older adults | | | | | |
| Adamkiewicz et al. (2004) | Steubenville, Ohio 29 older adults, ages 53-90 yr | 24-h avg | 0 | | -5.7 (-25.9, 14.5) |
| | | 1-h avg ^b | | | -19.7 (-41.3, 1.9) |
| Delfino et al. (2010a) | Los Angeles, CA 60 older adults, ages ≥ 65 yr | 24-h avg | 0-4 avg | Cool season | 35.2 (10.9, 59.5) |
| | | | | Warm season | -0.60 (-14.0, 12.8) |

*Includes studies in [Figure 6-10](#).

^aEffect estimates are standardized to a 40-ppb, 30-ppb, and 20-ppb increase for 1-h avg, 8-h max or avg, and 24-h avg O₃, respectively.

^bAverage O₃ concentration in the 1 hour preceding eNO collection.

Table 6-17 Associations between short-term ambient ozone exposure and biological markers of pulmonary inflammation and oxidative stress.

| Study | Location/Population | O ₃ Averaging Time | O ₃ Lag | Biological Marker | Subgroup | Standardized Effect Estimate (95% CI) ^a |
|--|---|-------------------------------|--------------------|---------------------------------------|----------------|--|
| Liu et al. (2009a) | Windsor, ON, Canada 182 children with asthma, ages 9 - 14 yr | 24-h avg | 0 | EBC 8-isoprostane (% change) | | 16.2 (-14.9, 56.8) |
| | | | | EBC TBARS (% change) | | 11.5 (-27.0, 70.1) |
| Romieu et al. (2008) | Mexico City, Mexico 107 children with asthma, mean (SD) age 9.5 (2.1) yr | 8-h max | 0 | EBC Malondialdehyde ^b | | 1.9 (1.1, 3.5) |
| Barraza-Villarreal et al. (2008) | Mexico City, Mexico 208 children, ages 6-14 yr | 8-h max | 0 | Nasal lavage IL-8 (pg/mL) | Without asthma | 1.6 (1.4, 1.8) |
| | | | | | With asthma | 1.6 (1.4, 1.9) |
| | | | | EBC pH | Without asthma | -0.10 (-0.27, 0.08) ^c |
| | | | | | With asthma | -0.10 (-0.20, 0.01) ^c |
| Sienra-Monge et al. (2004) | Mexico City, Mexico 117 children with asthma, mean age 9 yr | 8-h max | 0-2 avg | Nasal lavage IL-8 ^b | Placebo | 2.2 (1.1, 4.7) |
| | | | | | Antioxidant | 1.0 (0.44, 2.3) |
| | | | | Nasal lavage IL-6 ^b | Placebo | 2.7 (1.4, 5.1) |
| | | | | | Antioxidant | 1.1 (0.53, 2.2) |
| | | | | Nasal lavage Uric acid ^d | Placebo | 0.75 (0.44, 1.3) |
| | | | | | Antioxidant | 1.3 (0.68, 2.4) |
| | | | | Nasal lavage Glutathione ^b | Placebo | 0.79 (0.63, 0.98) |
| | | | | | Antioxidant | 0.80 (0.66, 0.96) |
| Khatri et al. (2009) | Atlanta, GA 38 adults with asthma, ages 31 - 50 yr | 8-h max | 2 | Blood eosinophils (% change) | | 2.4 (0.62, 4.2) |
| Ferdinands et al. (2008) | Atlanta, GA 16 children exercising outdoors, ages 14 - 17 yr | 1-h max | 0 | EBC pH (normalized score) | | 0.80 (-0.20, 1.8) ^c |

Results generally are presented in order of increasing mean ambient O₃ concentration. EBC = exhaled breath condensate, TBARS = thiobarbituric acid reactive substances, IL-8 = interleukin 8, IL-6 = interleukin 6, Antioxidant = group supplemented with vitamins C and E.

^aEffect estimates are standardized to a 40-, 30- and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O₃, respectively.

^bEffect estimates represent the ratio of the geometric means of biological marker per unit increase in O₃ concentration. A ratio <1 indicates a decrease in marker, and a ratio >1 indicates an increase in marker for an increase in O₃.

^cModel analyzed log-transformed O₃. Decreases and increases in pH indicate increases and decreases in pulmonary inflammation, respectively.

Populations with Asthma

Exhaled Nitric Oxide

1 Neither NO nor eNO has been examined in controlled human exposure or toxicological
2 studies of O₃ exposure. However, several lines of evidence support its analysis as an
3 indicator of pulmonary inflammation. Inducible NO synthase can be activated by
4 pro-inflammatory cytokines, and NO can be produced by cells such as neutrophils,
5 eosinophils, and epithelial cells in the lung during an inflammatory response ([Barnes and
6 Liew, 1995](#)). Further, eNO commonly is higher in individuals with asthma and increases
7 during acute exacerbations ([Jones et al., 2001](#); [Kharitonov and Barnes, 2000](#)).

8 As indicated in [Figure 6-10](#) and [Table 6-16](#), short-term increases in ambient O₃
9 concentration (8-h max or avg) were associated with increases in eNO in children with
10 asthma. These studies used different methods to assign exposures using central site O₃
11 measurements: the site closest (within 5 km) to home or school ([Barraza-Villarreal et al.,
12 2008](#)) and a single site per community ([Berhane et al., 2011](#)). Because information on
13 spatial homogeneity of ambient O₃ concentrations and time spent outdoors was not
14 provided, it is not possible to assess whether these two methods differed in personal-
15 ambient O₃ ratios and correlations. [Liu et al. \(2009a\)](#) (described in Section [6.2.1.2](#))
16 reported O₃-associated decreases in eNO; however, this study was restricted to winter.
17 Results for EBC markers of oxidative stress and lung function collectively provided weak
18 evidence of O₃-associated respiratory effects in this study. As described in Section [4.3.3](#),
19 in non-summer months, indoor to outdoor O₃ ratios are lower as are personal-ambient
20 ratios, making it more difficult to detect associations with ambient O₃ concentrations.

21 In contrast with controlled human exposure studies (Section [6.2.3.1](#)), epidemiologic
22 studies did not find larger O₃-associated increases in pulmonary inflammation in groups
23 with asthma than in groups without asthma ([Figure 6-10](#) and [Table 6-16](#)). Among
24 children in Southern California, [Berhane et al. \(2011\)](#) estimated similar associations for a
25 1-23 day cumulative average of 8-h avg (10 a.m.-6 p.m.) O₃ in children with and without
26 asthma. Among children in Mexico City, [Barraza-Villarreal et al. \(2008\)](#) found a larger
27 association (for lag 0 of 8-max O₃) in children without asthma, most of whom had atopy.

28 Studies that included adults with asthma produced contrasting results ([Khatri et al., 2009](#);
29 [Qian et al., 2009](#)). The multicity salmeterol (β-2 agonist) trial (Boston, MA; New York,
30 NY; Denver, CO; Philadelphia, PA; San Francisco, CA; and Madison, WI) involved
31 serial collection of eNO from 119 subjects with asthma, 87% of whom were 20-65 years
32 of age ([Qian et al., 2009](#)). Ambient O₃ concentrations were averaged from all sites within
33 20 miles of subjects' zipcode centroids, which in a repeated measures study, may capture
34 the temporal variation in O₃ reasonably well ([Darrow et al., 2011a](#); [Gent et al., 2003](#)).

1 Among all subjects, increases in 8-h max O₃ at multiple lags (0 to 3 single-day and
2 0-4 avg) were associated with decreases in eNO. Results did not vary among the
3 salmeterol-, CS-, and placebo-treated groups, indicating that the counterintuitive findings
4 for O₃ were not only due to the reduction of inflammation by medication. [Qian et al.](#)
5 [\(2009\)](#) suggested that at higher concentrations, O₃ may transform NO in airways to
6 reactive nitrogen species. However, this hypothesis was not supported by results from
7 [Khatri et al. \(2009\)](#), who in Atlanta, GA examined overall higher 8-h max O₃ ambient
8 concentrations than did [Qian et al. \(2009\)](#) and found that an increase in O₃ was associated
9 with an increase in eNO in adults with asthma (36.6% [95% CI: 1.2, 71.9] per 30-ppb
10 increase in lag 2 of 8-h max O₃). Although [Khatri et al. \(2009\)](#) was cross-sectional and
11 did not adjust for any meteorological factors, it may have better characterized O₃
12 exposures because subjects were examined during warm months, and an 8-h max O₃
13 concentration was calculated for each subject using measurements at the site closest to
14 his/her location each hour.

Other biological markers of pulmonary inflammation and oxidative stress

15 Short-term increases in ambient O₃ concentration were associated with changes in the
16 levels of pro-inflammatory cytokines and cells, indicators of oxidative stress, and
17 antioxidants (

18 Table 6-17). Importantly, any particular biomarker was examined in only one to two
19 studies, and the evidence in individuals with asthma is derived primarily from studies
20 conducted in Mexico City ([Barraza-Villarreal et al., 2008](#); [Romieu et al., 2008](#); [Sierra-
21 Monge et al., 2004](#)). These studies measured ambient O₃ concentrations at sites within 5
22 km of subjects' schools or homes. In a Mexico City cohort of children with asthma,
23 school ambient O₃ concentrations averaged over 48 to 72 hours had a ratio and
24 correlation with personal exposures (48- to 72-h avg) of 0.17 and 0.35, respectively
25 ([Ramírez-Aguilar et al., 2008](#)). These observations suggest that the effects of personal O₃
26 exposure on inflammation may have been underestimated in the Mexico City studies.
27 Despite the limited evidence, the epidemiologic findings are well supported by controlled
28 human exposure and toxicological studies that measured the same or related endpoints.

29 Several of the modes of action of O₃ are mediated by reactive oxygen species (ROS)
30 produced in the airways by O₃ (Section [5.3.3](#)). These ROS are important mediators of
31 inflammation as they regulate cytokine expression and inflammatory cell activity in
32 airways ([Heidenfelder et al., 2009](#)). Controlled human exposure and toxicological studies,
33 frequently have found O₃-induced increases in oxidative stress as shown by increases in
34 prostaglandins (Section [5.3.3](#) and Section [6.2.3.1](#)), which are produced by the
35 peroxidation of cell membrane phospholipids ([Morrow et al., 1990](#)). [Romieu et al. \(2008\)](#)

1 analyzed EBC malondialdehyde (MDA), a thiobarbituric acid reactive substance, which
2 like prostaglandins, is derived from lipid peroxidation ([Janero, 1990](#)). For a 30-ppb
3 increase in lag 0 of 8-h max O₃, the ratio of the geometric means of MDA was 1.3
4 (95% CI: 1.0, 1.7). Similar results were reported for lags 1 and 0-1 avg O₃. A limitation
5 of the study was that 25% of EBC samples had nondetectable levels of MDA, and the
6 random assignment of concentrations between 0 and 4.1 nmol to these samples may have
7 contributed random measurement error to the estimated O₃ effects. Because MDA
8 represents less than 1% of lipid peroxides and is present at low concentrations, its
9 biological relevance has been questioned. However, [Romieu et al. \(2008\)](#) pointed to their
10 observations of statistically significant associations of EBC MDA levels with nasal
11 lavage IL-8 levels to demonstrate its relationship with pulmonary inflammation.

12 Uric acid and glutathione are ROS scavengers that are present in the airway ELF. While
13 the roles of these markers in the inflammatory cascade of asthma are not well defined,
14 they have been observed to be consumed in response to short-term O₃ exposure as part of
15 an antioxidant response in controlled human exposure and animal studies (Section [5.3.3](#)).
16 Results from an epidemiologic study also indicate that a similar antioxidant response may
17 be induced by increases in ambient O₃ exposure. [2004](#) [Sienra-Monge et al. \(2004\)](#) found
18 O₃-associated decreases in nasal lavage levels of uric acid and glutathione in children
19 with asthma not supplemented with antioxidant vitamins (

20 Table 6-17). The magnitudes of decrease were similar for O₃ concentrations lagged 2 or
21 3 days and averaged over 3 days.

22 Both controlled human exposure and toxicological studies have found O₃-induced
23 increases in the cytokines IL-6 and IL-8 (Section [5.3.3](#), Section [6.2.3.1](#), and
24 Section [6.2.3.3](#)), which are involved in initiating an influx of neutrophils, a hallmark of
25 O₃-induced inflammation (Section [6.2.3.1](#)). Epidemiologic studies conducted in Mexico
26 City had similar findings. [Sienra-Monge et al. \(2004\)](#) found that 8-h max O₃ was
27 associated with increases in nasal lavage levels of IL-6 and IL-8 (placebo group), with
28 larger effects estimated for lag 0-2 avg than for lag 2 or 3 O₃ (

29 Table 6-17). In another cohort of children with asthma, a 30-ppb increase in lag 0 of
30 8-h max O₃ was associated with a 1.61 pg/mL increase (95% CI: 1.4, 1.8) in nasal lavage
31 levels of IL-8 ([Barraza-Villarreal et al., 2008](#)). This study also reported a small
32 O₃-associated decrease in EBC pH (

33 Table 6-17). EBC pH, which is thought to reflect the proton-buffering capacity of
34 ammonium in airways, decreases upon asthma exacerbation, and is negatively correlated
35 with airway levels of pro-inflammatory cytokines ([Carpagnano et al., 2005](#); [Kostikas et](#)
36 [al., 2002](#); [Hunt et al., 2000](#)).

1 Albeit with limited investigation, controlled human exposure studies have found
2 O₃-induced increases in eosinophils in adults with asthma (Section [6.2.3.1](#)). Eosinophils
3 are believed to be the main effector cells that initiate and sustain inflammation in asthma
4 and allergy ([Schmekel et al., 2001](#)). Consistent with these findings, in a cross-sectional
5 study of adults with asthma in Atlanta, GA, a 30-ppb increase in lag 2 of 8-h max O₃ was
6 associated with a 2.4% increase (95% CI: 0.62, 4.2) in blood eosinophils ([Khatri et al.,](#)
7 [2009](#)). Potential confounding by weather was not evaluated in models.

8 The prominent influences demonstrated for ROS and antioxidants in mediating the
9 respiratory effects of O₃ provide biological plausibility for effect modification by
10 antioxidant capacity. Effect modification by antioxidant capacity has been described for
11 O₃-associated lung function in controlled human exposure and epidemiologic studies
12 (Section [6.2.1.1](#) and Section [6.2.1.2](#)). An epidemiologic study conducted in Mexico City
13 also found that vitamin C and E supplements, which potentially increase antioxidant
14 capacity, attenuated O₃-associated inflammation and oxidative stress. Among children
15 with asthma supplemented daily with vitamin C and E, the ratios of the geometric means
16 of nasal lavage IL-6 and IL-8 per 30-ppb increases in lag 0-2 avg of 8-h max O₃ were 1.0,
17 reflecting no change with increases in O₃ concentration (

18 Table 6-17) ([Sierra-Monge et al., 2004](#)). The results did not clearly delineate interactions
19 among O₃ concentrations, endogenous antioxidants, and dietary antioxidants (

20 Table 6-17). Ozone was associated with increases in uric acid in the antioxidant group
21 but decreases in the placebo group across the O₃ lags examined. Associations with
22 glutathione were similar in the two groups. In another cohort, 8-h max O₃ concentrations
23 ≥ 38 ppb enhanced the effects of diets high in antioxidant vitamins and/or omega-3 fatty
24 acids on protecting against O₃-related increases in nasal lavage IL-8 ([Romieu et al.,](#)
25 [2009](#)). Information on the main effects of O₃ or effect modification by diet was not
26 presented.

27 The levels of several biological markers such as eNO, EBC pH, and MDA consistently
28 differ between groups with and without asthma and change during an asthma
29 exacerbation ([Corradi et al., 2003](#); [Hunt et al., 2000](#)); however, the magnitudes of change
30 associated with these overt effects are not well defined. Ozone-associated increases in
31 interleukins and indicators of oxidative stress were small: 1-2% increase for each 30-ppb
32 increase in 8-h max O₃ concentration (

33 Table 6-17). Ozone-associated increases in eNO were larger: 6-36% increase per 30-ppb
34 increase in 8-h max ambient O₃ concentration ([Berhane et al., 2011](#); [Delfino et al., 2010a](#);
35 [Khatri et al., 2009](#); [Barraza-Villarreal et al., 2008](#)). Some studies in populations with
36 asthma found O₃-associated increases in pulmonary inflammation concurrently (at the

1 same lag) with O₃-associated in respiratory symptoms. For example, among adults with
2 asthma in Atlanta, an increase in ambient O₃ concentration was associated with increases
3 in eNO, blood eosinophils, and a decrease in quality of life score, which incorporates
4 indices for symptoms and activity limitations ([Khatri et al., 2009](#)). Also, among children
5 with asthma in Mexico City, O₃ was associated with increases in eNO and nasal lavage
6 IL-8 and concurrently assessed cough but not wheeze ([Barraza-Villarreal et al., 2008](#)).

Children without Asthma

7 In the limited investigation, short-term increases in ambient O₃ concentration (8-h max or
8 avg) were associated with increases in pulmonary inflammation in children without
9 asthma ([Berhane et al., 2011](#); [Barraza-Villarreal et al., 2008](#)) ([Figure 6-10](#) and [Table 6-16](#)
10 and

11 [Table 6-17](#)). The study of children in Mexico City found a larger O₃-associated increase
12 in eNO in the children without asthma than with asthma (13.5% versus 6.2% increase per
13 30-ppb increase in lag 0 of 8-h max O₃) ([Barraza-Villarreal et al., 2008](#)). Ozone was
14 associated with similar magnitudes of change in IL-8 and EBC pH in children with and
15 without asthma. A distinguishing feature of this study was that 72% of children without
16 asthma had allergies. A study conducted in 13 Southern California communities also
17 found that increases in ambient O₃ concentration (8-h avg, 10 a.m.-6 p.m.) were
18 associated with increases in eNO in children with respiratory allergy ([Berhane et al.,](#)
19 [2011](#)). Coherence for these epidemiologic findings is provided by observations of
20 O₃-induced allergic inflammation in animal models of allergy (Section [6.2.3.3](#) and
21 Section [6.2.6](#)).

22 [Berhane et al. \(2011\)](#) found O₃-associated increases in eNO in children without asthma
23 and children without respiratory allergy, providing evidence for effects on pulmonary
24 inflammation in healthy children. This study provided detailed information on differences
25 in association among various lags of 8-h avg (10 a.m.-6 p.m.) O₃. Ozone concentrations
26 averaged over the several hours preceding eNO collection were not significantly
27 associated with eNO. Consistent with other studies examining pulmonary inflammation
28 and oxidative stress, [Berhane et al. \(2011\)](#) found that relatively short lags of O₃, i.e., 1 to
29 5 days, were associated with increases in eNO. However, among several types of lag-
30 based models, including unconstrained lag models, polynomial distributed lag models,
31 spline-based distributed lag models, and cumulative lag models, a 23-day cumulative lag
32 of O₃ best fit the data. Among the studies evaluated in this ISA, [Berhane et al. \(2011\)](#) was
33 unique in evaluating and finding larger respiratory effects for multi-week (e.g., 13-
34 30 days) average O₃ concentrations. The mechanism for the effects of O₃ peaking with a

1 23-day cumulative lag of exposure has not been delineated. Further, with examination of
2 such long lag periods, there is greater potential for residual confounding by weather.

Populations with Increased Outdoor Exposures

3 With limited investigation, increases in ambient O₃ concentration were not consistently
4 associated with pulmonary inflammation in populations engaged in outdoor activity or
5 exercise. Common limitations of these studies were the small numbers of subjects and
6 lack of consideration for potential confounding factors. A study in 16 adolescent long-
7 distance runners near Atlanta, GA was noted for the daily collection of EBC and the
8 likely greater extent to which ambient O₃ concentrations represented ambient exposures
9 because of the analysis of O₃ concentrations measured during outdoor running at a site
10 less than 1 mile from the exercise track ([Ferdinands et al., 2008](#)). Increases in 1-h max O₃
11 (lags 0 to 2) were associated with increases in EBC pH, indicating O₃-associated
12 decreases in pulmonary inflammation. Among 9 adult male runners in Sicily, Italy
13 examined 3 days before and 20 hours after 3 races in fall, winter, and summer, weekly
14 average O₃ concentrations (8-h avg, 7 a.m.-3 p.m.) were positively correlated with
15 apoptosis of neutrophils (Spearman's $r = 0.70$, $p < 0.005$) and bronchial epithelial cell
16 differential counts (Spearman's $r = 0.47$, $p < 0.05$) but not with neutrophil or macrophage
17 cell counts or levels of the pro-inflammatory cytokines TNF- α and IL-8 ([Chimenti et al.,](#)
18 [2009](#)). Associations with O₃ concentrations measured during the races (mean 35 to 89
19 minutes) were not examined. This study provides evidence for new endpoints; however,
20 the implications of findings are limited due to the lack of a rigorous statistical analysis.

21 In a cross-sectional study of children at camps in south Belgium, although lung function
22 was not associated with O₃ measured at camps during outdoor activity, an association
23 was found for eNO ([Nickmilder et al., 2007](#)). Children at camps with lag 0 1-h max O₃
24 concentrations >85.2 ppb had greater increases in intraday eNO compared with children
25 at camps with O₃ concentrations <51 ppb. A benchmark dose analysis indicated that the
26 threshold for an O₃-associated increase of 4.3 ppb eNO (their definition of increased
27 pulmonary inflammation) was 68.6 ppb for 1-h max O₃ and 56.3 ppb for 8-h max O₃.
28 While these results provide additional evidence for O₃-associated increases in pulmonary
29 inflammation in healthy children, they should be interpreted with caution since they were
30 unadjusted for any potential confounding factors and based on camp-level comparisons.

Older Adults

31 The panel studies examining O₃-associated changes in eNO in older adults produced
32 contrasting findings ([Figure 6-10](#) and [Table 6-16](#)). The studies differed with respect to
33 geographic location, inclusion of healthy subjects, exposure assessment method, and lags

1 of O₃ examined. [Delfino et al. \(2010a\)](#) followed 60 older adults with coronary artery
2 disease in the Los Angeles, CA area for 6 weeks each during a warm and cool season; the
3 specific months were not specified. Ambient O₃ was measured at subjects' retirement
4 homes, possibly reducing some exposure measurement error due to spatial variability.
5 Multiday averages of O₃ (3- to 9-day) were associated with increases in eNO, with effect
6 estimates increasing with increasing number of averaging days. In contrast with most
7 other studies, an association was found in the cool season but not warm season (increase
8 in eNO per 20-ppb increase in lag 0-4 avg of 24-h avg O₃: 4.1 ppb [95% CI: 1.3, 6.9] in
9 cool season, -0.01 ppb [95% CI: -2.3, 2.1] in warm season). Despite these unusual
10 findings for the cool season, they were similar to findings from another study of
11 Los Angeles area adults with asthma, which indicated an O₃-associated decrease in
12 indoor activity during the fall season ([Eiswerth et al., 2005](#)).

13 In a cool season (September-December) study conducted in older adults (ages 54-
14 91 years) in Steubenville, OH, [Adamkiewicz et al. \(2004\)](#) found that increases in O₃
15 (1-h avg and 24-h avg before eNO collection) were associated with decreases in eNO,
16 reflecting decreases in pulmonary inflammation ([Figure 6-10](#) and

17 [Table 6-17](#)). The study included healthy adults and those with asthma or COPD. A study
18 in a subset of these adults illustrated why it is difficult to detect effects with central site
19 O₃ concentrations in the cool season by showing that subjects spent ≥ 90% of time
20 indoors and >77% at home and had a mean 24-h avg O₃ personal-ambient ratio of 0.27
21 ([Sarnat et al., 2006a](#)).

Confounding in Epidemiologic Studies of Pulmonary Inflammation and Oxidative Stress

22 Except where noted in the preceding text; epidemiologic studies of pulmonary
23 inflammation and oxidative stress accounted for potential confounding by meteorological
24 factors. Increases in ambient O₃ concentration were associated with pulmonary
25 inflammation or oxidative stress in models that adjusted for temperature and/or humidity
26 ([Delfino et al., 2010a](#); [Barraza-Villarreal et al., 2008](#); [Romieu et al., 2008](#)). Final results
27 from [Sienra-Monge et al. \(2004\)](#) and [Berhane et al. \(2011\)](#) were not adjusted for
28 temperature because associations were not altered by adjustment for temperature. Most
29 studies conducted over multiple seasons adjusted for season or time trend.

30 In evidence limited to a small number of studies conducted in Mexico City, O₃-associated
31 pulmonary inflammation and oxidative stress were not found to be confounded by PM_{2.5}
32 or PM₁₀. These studies, which analyzed 8-hour averages for both O₃ and PM, found
33 robust associations for O₃ ([Barraza-Villarreal et al., 2008](#); [Romieu et al., 2008](#); [Sienra-
34 Monge et al., 2004](#)). Ozone and PM, both measured at central sites located within 5 km of

1 subjects' schools or homes, were moderately correlated ($r = 0.46-0.54$). Weak
2 correlations have been found between personal exposures of O_3 and $PM_{2.5}$
3 (Section 4.3.4.1). Only [Romieu et al. \(2008\)](#) provided quantitative results. Lag 0 of
4 8-h max O_3 was associated with the same magnitude of increase in MDA without and
5 with adjustment for lag 0 of 8-h max $PM_{2.5}$ (ratio of geometric means for a 30-ppb
6 increase: 1.3 [95% CI: 1.0, 1.7]). In comparison, the O_3 -adjusted effect estimate for $PM_{2.5}$
7 was cut in half.

Summary of Epidemiologic Studies of Pulmonary Inflammation and Oxidative Stress

8 Many epidemiologic studies provided evidence that short-term increases in ambient O_3
9 exposure increase pulmonary inflammation and oxidative stress in children with asthma,
10 with evidence primarily provided by studies conducted in Mexico City. By also finding
11 that associations were attenuated with higher antioxidant intake, these studies indicated
12 that inhaled O_3 may be an important source of ROS in airways and/or may increase
13 pulmonary inflammation via oxidative stress-mediated mechanisms. Studies found
14 O_3 -associated increases in pulmonary inflammation in children with allergy ([Berhane et al., 2011](#);
15 [Barraza-Villarreal et al., 2008](#)). The limited available evidence in children and
16 adults with increased outdoor exposures and older adults was inconclusive. Temperature
17 and humidity were not found to confound O_3 associations. Copollutant models were
18 analyzed in a few studies conducted in Mexico City; O_3 effect estimates were robust to
19 adjustment for moderately correlated ($r = 0.46-0.54$) $PM_{2.5}$ or PM_{10} ([Barraza-Villarreal et al., 2008](#);
20 [Romieu et al., 2008](#); [Sienra-Monge et al., 2004](#)).

21 Ozone-associated increases in pulmonary inflammation and oxidative stress were found
22 in studies that used varied exposure assessment methods: measurement on site of
23 subjects' outdoor activity ([Nickmilder et al., 2007](#)), average of concentrations measured
24 at the closest site each hour ([Khatri et al. \(2009\)](#)), measurement at a site within 5 km of
25 subjects' schools or homes ([Barraza-Villarreal et al., 2008](#); [Romieu et al., 2008](#); [Sienra-Monge et al., 2004](#)),
26 and measurement at single site per town ([Berhane et al., 2011](#)).
27 While these methods may differ in the degree of exposure measurement error, in the
28 limited body of evidence, there was not a clear indication that the method of exposure
29 assessment influenced the strength or magnitude of associations.

30 Most studies examined and found associations with 8-h max or daytime 8-h avg O_3
31 concentrations, although associations were found for 1-h max ([Nickmilder et al., 2007](#))
32 and 24-h avg O_3 ([Delfino et al., 2010a](#)). Collectively, studies examined single-day O_3
33 concentrations lagged from 0 to 5 days and concentrations averaged over 2 to 9 days. Lag
34 0 of 8-h max O_3 was most frequently examined and consistently associated with

1 pulmonary inflammation and oxidative stress. However, in the few studies that examined
2 multiple O₃ lags, multiday average 8-h max or 8-h avg concentrations were associated
3 with larger increases in pulmonary inflammation and oxidative stress ([Berhane et al.,
4 2011](#); [Delfino et al., 2010a](#); [Sienra-Monge et al., 2004](#)). These findings for multiday
5 average O₃ concentrations are supported by controlled human exposure (Section [6.2.3.1](#))
6 and animal studies (Section [6.2.3.3](#)) that similarly have found that some markers of
7 pulmonary inflammation remain elevated with O₃ exposures repeated over multiple days.

8 Several epidemiologic studies concurrently examined associations of ambient O₃
9 concentrations with biological markers of pulmonary inflammation and lung function or
10 respiratory symptoms. Whether evaluated at the same or different lags of O₃, associations
11 generally were stronger for biological markers of airway inflammation than for lung
12 function ([Khatri et al., 2009](#); [Barraza-Villarreal et al., 2008](#); [Nickmilder et al., 2007](#)).
13 Controlled human exposure studies also have demonstrated a lack of correlation between
14 inflammatory and spirometric responses induced by O₃ exposure (Section [6.2.3.1](#)).
15 Evidence has suggested that O₃-related respiratory morbidity may occur via multiple
16 mechanisms with varying time courses of action, and the examination of a limited
17 number of O₃ lags in these aforementioned studies may explain some of the
18 inconsistencies in associations of O₃ with measures of pulmonary inflammation and lung
19 function. In contrast, based on examination in a few studies, increases in ambient O₃
20 concentration were associated concurrently (at the same lag) with increases in pulmonary
21 inflammation and increases in respiratory symptoms or activity limitations in the same
22 population of individuals with asthma ([Khatri et al., 2009](#); [Barraza-Villarreal et al.,
23 2008](#)).

6.2.3.3 Toxicology: Inflammation and Injury

24 The 2006 O₃ AQCD states that the “extensive human clinical and animal toxicological
25 evidence, together with the limited available epidemiologic evidence, is clearly indicative
26 of a causal role for O₃ in inflammatory responses in the airways” ([U.S. EPA, 2006b](#)).
27 Airway ciliated epithelial cells and Type 1 cells are the most O₃-sensitive cells and are
28 initial targets of O₃. These cells are damaged by O₃ and produce a number of
29 pro-inflammatory mediators (e.g., interleukins [IL-6, IL-8], PGE₂) capable of initiating a
30 cascade of events leading to PMN influx into the lung, activation of alveolar
31 macrophages, inflammation, and increased permeability across the epithelial barrier. One
32 critical aspect of inflammation is the potential for metaplasia and alterations in
33 pulmonary morphology. Studies have observed increased thickness of the alveolar septa,
34 presumably due to increased cellularity after acute exposure to O₃. Epithelial hyperplasia
35 starts early in exposure and increases in magnitude for several weeks, after which it

1 plateau until exposure ceases. When exposure persists for a month and longer, excess
2 collagen and interstitial fibrosis are observed. This response, discussed in Chapter 7,
3 continues to increase in magnitude throughout exposure and can even continue to
4 increase after exposure ends ([Last et al., 1984](#)). Previously reviewed toxicological studies
5 of the ability of O₃ to cause inflammation, injury, and morphological changes are
6 described in Table 6-5 on page 6-25 ([U.S. EPA, 1996f](#)) and Table 6-10 ([U.S. EPA,](#)
7 [1996k](#)) and Table 6-11 ([U.S. EPA, 1996l](#)) beginning on page 6-61 of the 1996 O₃ AQCD,
8 and Tables AX5-8 ([U.S. EPA, 2006d](#)) and AX5-9 ([U.S. EPA, 2006e](#)), beginning on page
9 AX5-17 of the 2006 O₃ AQCD. Numerous recent in vitro and in vivo studies add to this
10 very large body of evidence for O₃-induced inflammation and injury, and provide new
11 information regarding the underlying mechanisms (see Section 5.3).

12 A number of species, including dogs, rabbits, guinea pigs, rats, and mice have been used
13 as models to study the pulmonary effects of O₃, but the similarity of non-human primates
14 to humans makes them an attractive model in which to study the pulmonary response to
15 O₃. As reviewed in the 1996 and 2006 O₃ AQCDs, several pulmonary effects, including
16 inflammation, changes in morphometry, and airway hyperresponsiveness, have been
17 observed in macaque and rhesus monkeys after acute exposure to O₃ ([Table 6-18](#) presents
18 a highlight of these studies). Increases in inflammatory cells were observed after a single
19 8-h exposure of adult rhesus monkeys to 1 ppm O₃ ([Hyde et al., 1992](#)). Inflammation was
20 linked to morphometric changes, such as increases in necrotic cells, smooth muscle,
21 fibroblasts, and nonciliated bronchiolar cells, which were observed in the trachea,
22 bronchi, or respiratory bronchioles. Effects have also been observed after short-term
23 repeated exposure to O₃ at concentrations that are more relevant to ambient O₃
24 concentrations. Morphometry changes in the lung, nose, and vocal cords were observed
25 after exposure to 0.15 ppm O₃ for 8-h/day for 6 days ([Harkema et al., 1993](#); [Dimitriadis,](#)
26 [1992](#); [Harkema et al., 1987a](#)). Since 2006, however, only one study has been published
27 regarding acute exposure of non-human primates to O₃ (a number of recent chronic
28 studies in non-human primates are described in Chapter 7). In this study, a single 6-hour
29 exposure of adult male cynomolgus monkeys to 1 ppm O₃ induced significant increases
30 in inflammatory and injury markers, including BAL neutrophils, total protein, alkaline
31 phosphatase, IL-6, IL-8, and G-CSF ([Hicks et al., 2010a](#)). Gene expression analysis
32 confirmed the increases in the pro-inflammatory cytokine IL-8, which had been
33 previously described in O₃ exposed rhesus monkeys ([Chang et al., 1998](#)). The
34 anti-inflammatory cytokine IL-10 was also elevated, but the fold changes in IL-10 and
35 G-CSF were relatively low and highly variable. The single exposure also caused necrosis
36 and sloughing of the epithelial lining of the most distal portions of the terminal
37 bronchioles and the respiratory bronchioles. Bronchiolitis, alveolitis, parenchymal and
38 centriacinar inflammation were also observed. A second exposure protocol (two
39 exposures with a 2-week inter-exposure period) resulted in similar inflammatory

1 responses, with the exception of total protein and alkaline phosphatase levels which were
2 attenuated, indicating that attenuation of some but not all lavage parameters occurred
3 upon repeated exposure of non-human primates to O₃ ([Hicks et al., 2010a](#)). This
4 variability in attenuation is similar to the findings of earlier reports in rodents ([Wiester et
5 al., 1996c](#)) and non-human primates ([Tyler et al., 1988](#)).

6 [Table 6-18](#) describes key morphometric studies conducted in non-human primates
7 exposed to O₃. Morphologic observations made by [Dungworth \(1976\)](#); ([1975](#)) indicate
8 that the rat and Bonnet monkey (*Macaca radiata*) are approximately equal in
9 susceptibility to short-term effects of O₃. Mild but discernible lesions were caused in both
10 species by exposure to 0.2 ppm O₃ for 8 h/day for 7 days. The authors stated that
11 detectable morphological effects in the rat occurred at levels as low as 0.1 ppm O₃. In
12 both species, the lesion occurred at the junction of the small airways and the gaseous
13 exchange region. In rats, the prominent features were accumulation of macrophages,
14 replacement of necrotic Type 1 epithelial cells with Type 2 cells, and damage to ciliated
15 and nonciliated Clara cells. The principal site of damage was the alveolar duct. In
16 monkeys, the prominent O₃-induced injury was limited to the small airways. At 0.2 ppm
17 O₃, the lesion was observed at the proximal portion of the respiratory bronchioles. As
18 concentrations of O₃ were increased up to 0.8 ppm, the severity of the lesion increased,
19 and the damage extended distally to involve the proximal portions of the alveolar duct.
20 [Mellick et al. \(1977\)](#) found similar but more pronounced effects when rhesus monkeys (3
21 to 5 years of age) were exposed to 0.5 and 0.8 ppm O₃, 8 hours/day for 7 days. In these
22 experiments, the respiratory bronchioles were the most severely damaged, and more
23 distal parenchymal regions were unaffected. Major effects were hyperplasia and
24 hypertrophy of the nonciliated bronchiolar epithelial cells and the accumulation of
25 macrophages intraluminally. In mice, continuous exposure to 0.5 ppm O₃ caused nodular
26 hyperplasia of Clara cells after 7 days of exposure. Similar findings were reported by
27 [Schwartz \(1976\)](#) and [Schwartz et al. \(1976\)](#), who exposed rats to 0.2, 0.5 or 0.8 ppm O₃
28 for 8 or 24 hours/day for 1 week. Changes observed within the proximal alveoli included
29 infiltration of inflammatory cells and swelling and necrosis of Type 1 cells. In the
30 terminal bronchiole, the changes reported were shortened cilia, clustering of basal bodies
31 in ciliated cells suggesting ciliogenesis, and reduction in height or loss of cytoplasmic
32 luminal projection of the Clara cells. Effects were seen at O₃ concentrations as low as
33 0.2 ppm. A dose-dependent pulmonary response to the three levels of O₃ was evident. No
34 differences were observed in morphologic characteristics of the lesions between rats
35 exposed continuously and those exposed intermittently for 8 hours/day.

Table 6-18 Morphometric observations in non-human primates after acute ozone exposure.

| Reference | O ₃ concentration (ppm) | Exposure duration | Species, Sex, Age | Observation |
|---|------------------------------------|---|---|--|
| Harkema et al. (1993) | 0.15 | 8 h/day for 6 days | <i>Macaca radiata</i> (bonnet macaques) 2-6 years old | Several fold increase in thickness of surface epithelium in respiratory bronchioles; increase in interstitial mass with increase in proportion of cuboidal cells. |
| Harkema et al. (1987a); (1987b) | 0.15 | 8 h/day for 6 days | <i>Macaca radiata</i> , M, F 2-6 years old | Ciliated cell necrosis, shortened cilia, and increased mucous cells in the respiratory epithelium of nose after 0.15 ppm; changes in nonciliated cells, intraepithelial leukocytes, and mucous cells in the transitional epithelium |
| Dungworth (1976) | 0.2 0.5 0.8 | 8 h/day for 7 days for monkey and rat; continuous at 0.5 ppm for 7 days for mouse | Adult Rhesus and bonnet monkeys; S-D rats; Mice | In both rats and monkeys mild but discernible lesions were observed at 0.2 ppm; similar severity between species but different site of lesions – respiratory bronchioles for monkey and damage to ciliated, Clara, and alveolar epithelial cells for rat; Clara cell hyperplasia in mice |
| Leonard et al. (1991) | 0.25 | 8 h/day for 7 days | <i>Macaca radiata</i> age not specified | The O ₃ exposure level is not clear – the abstract states 0.64 ppm, but the text mentions only 0.25 ppm. Morphometric changes in vocal cord mucosa: disruption and hyperplasia of stratified squamous epithelium; epithelial and connective tissue thickness increased |
| Chang et al. (1998) | 0.96 | 8 h | Rhesus, M age not specified | Increase in IL-8 in airway epithelium correlated with PMN influx |
| Hyde et al. (1992) | 0.96 | 8 h | Rhesus, M 2 - 8.5 years old | Increased PMNs; morphometric changes in trachea, conducting airways, respiratory bronchioles including increased smooth muscle in bronchi and RB. |
| Hicks et al. (2010b) | 1.0 | 6 h | Cynomolgus, M 5-7 kg (Adult) | Increase in PMNs and IL-8 in lavage fluid |

1 Exposure of adult BALB/c mice to 0.1 ppm O₃ for 4 hours increased BAL levels of
2 keratinocyte chemoattractant (KC; IL-8 homologue) (~ fold), IL-6 (~12-fold), and TNF- α
3 (~ 2-fold) ([Damera et al., 2010](#)). Additionally, O₃ increased BAL neutrophils by 21%
4 without changes in other cell types. A trend of increased neutrophils with increased O₃
5 concentration (0.12-2 ppm) was observed in BALB/c mice exposed for 3 hours ([Jang et](#)
6 [al., 2005](#)). Although alterations in the epithelium of the airways were not evident in 129J
7 mice after 4 hours of exposure to 0.2 ppm O₃ ([Plopper et al., 2006](#)), detachment of the
8 bronchiolar epithelium was observed in SD rats after 5 days or 60 days of exposure to
9 0.25 ppm O₃ ([Oyarzún et al., 2005](#)). Subacute (65 hours) exposure to 0.3 ppm O₃ induced
10 pulmonary inflammation, cytokine induction, and enhanced vascular permeability in wild
11 type mice of a mixed background (129/Ola and C57BL/6) and these effects were
12 exacerbated in metallothionein I/II knockout mice ([Inoue et al., 2008](#)). Three hours or
13 72 hours of exposure to 0.3 ppm O₃ resulted in similar levels of IL-6 expression in the
14 lungs of C57BL/6 mice ([Johnston et al., 2005b](#)), along with increases in BAL protein,

1 sTNFR1, and sTNFR2. Increased neutrophils were observed only after the 72-hour
2 exposure, and neither exposure resulted in detectable levels of IL-6 or KC protein. Levels
3 of BAL protein, sTNFR1, and sTNFR2 were higher in the 72-hour exposure group than
4 in the 3-hour exposure group. In another study, the same subacute (72 hours) exposure
5 protocol elicited increases in BALF protein, IP-10, sTNFR1, macrophages, neutrophils,
6 and IL-6, IL-1 α , and IL-1 β expression ([Johnston et al., 2007](#)). [Yoon et al. \(2007\)](#) exposed
7 C57BL/6J mice continuously to 0.3 ppm O₃ for 6, 24, 48, or 72 hours, and observed
8 elevated levels of KC, MIP-2, metalloproteinases, and inflammatory cells in the lungs at
9 various time points. A similar exposure protocol using C3H/HeJ and C3H/OuJ mice
10 demonstrated elevations in protein, PMNs, and KC, which were predominantly TLR 4
11 pathway dependent based on their prominence in the TLR 4 sufficient C3H/OuJ strain
12 [Bauer et al. \(2011\)](#). C3H/OuJ mice also had elevated levels of the heat-shock protein
13 HSP70, and further experiments in HSP70 deficient mice indicated a role for this
14 particular pathway in O₃-related injury, discussed in more detail in Chapter 5.

15 As reviewed in the 2006 O₃ AQCD, the time course for changes in BAL depends on the
16 parameters being studied. Similarly, after exposing adult C57BL mice to 0.5 ppm O₃ for
17 3 hours, [Han et al. \(2008\)](#) observed early (5 hours postexposure) increases in BAL TNF- α
18 and IL-1 β , which diminished by 24 hours postexposure. Total BAL protein was elevated
19 at 24 hours, but there were only minimal or negligible changes in LDH, total cells, or
20 PMNs. Ozone increased BAL mucin levels (with statistical significance by 24 hours
21 postexposure), and significantly elevated surfactant protein D at both time points. Prior
22 intratracheal (IT) exposure to multiwalled carbon nanotubes enhanced most of these
23 effects, but the majority of responses to the combined exposure were not greater than
24 those to nanotubes alone. Ozone exposure did not induce markers of oxidative stress in
25 lung tissue, BAL, or serum. Consistent with this study, [Aibo et al. \(2010\)](#) did not detect
26 changes in BAL inflammatory cell numbers in the same mouse strain after a 6-hour
27 exposure to 0.25 or 0.5 ppm. The majority of inflammatory cytokines (pulmonary or
28 circulating) were not significantly changed (as assessed 9 hours post-O₃ exposure).
29 Exposure of C57BL/6 mice to 1 ppm for 3 hours increased BAL total cells, neutrophils,
30 and KC; these responses were greatest at 24 hours postexposure. F2-isoprostane
31 (8-isoprostane), a marker of oxidative stress, was also elevated by O₃, peaking at
32 48 hours postexposure ([Voynow et al., 2009](#)).

33 Atopic asthma appears to be a risk factor for more severe O₃ induced airway
34 inflammation in humans ([Balmes et al., 1997](#); [Scannell et al., 1996](#)), and allergic animal
35 models are often used to investigate the effects of O₃ on this potentially at-risk
36 population. [Farraj et al. \(2010\)](#) exposed allergen-sensitized adult male BALB/c mice to
37 0.5 ppm O₃ for 5 hours once per week for 4 weeks. Ovalbumin-sensitized mice exposed
38 to O₃ had significantly increased BAL eosinophils by 85% and neutrophils by 103%

1 relative to OVA sensitized mice exposed to air, but these changes were not evident upon
2 histopathological evaluation of the lung, and no O₃ induced lesions were evident in the
3 nasal passages. Ozone increased BAL levels of N-acetyl-glucosaminidase (NAG; a
4 marker of injury) and protein. DEP co-exposure (2.0 mg/m³, nose only) inhibited these
5 responses. These pro-inflammatory effects in an allergic mouse model have also been
6 observed in rats. [Wagner et al. \(2007\)](#) exposed the relatively O₃-resistant Brown Norway
7 rat strain to 1 ppm O₃ after sensitizing and challenging with OVA. Rats were exposed for
8 2 days, and airway inflammation was assessed one day later. Filtered air for controls
9 contained less than 0.02 ppm O₃. Histopathology indicated O₃ induced site-specific lung
10 lesions in the centriacinar regions, characterized by wall thickening partly due to
11 inflammatory cells influx. BAL neutrophils were elevated by O₃ in allergic rats, and
12 modestly increased in non-allergic animals (not significant). A slight (but not significant)
13 increase in macrophages was observed, but eosinophil numbers were not affected by O₃.
14 Soluble mediators of inflammation (Cys-LT, MCP-1, and IL-6) were elevated by O₃ in
15 allergic animals but not non-allergic rats. Treatment with γT, which neutralizes oxidized
16 lipid radicals and protects lipids and proteins from nitrosative damage, did not alter the
17 morphologic character or severity of the centriacinar lesions caused by O₃, nor did it
18 reduce neutrophil influx. It did, however, significantly reduce O₃-induced soluble
19 inflammatory mediators in allergic rats. The effects of O₃ in animal models of allergic
20 asthma are discussed in Section [6.2.6](#).

21 In summary, a large number of toxicology studies have demonstrated that acute exposure
22 to O₃ produces injury and inflammation in the mammalian lung, supporting the
23 observations in controlled human exposure studies (Section [6.2.3.1](#)). These acute
24 changes, both in inflammation and morphology, provide a limited amount of evidence for
25 long term sequelae of exposure to O₃. Related alterations resulting from long term
26 exposure, such as fibrotic changes, are discussed in Chapter [7](#).

6.2.4 Respiratory Symptoms and Medication Use

27 Controlled human exposure and toxicological studies have described modes of action
28 through which short-term O₃ exposure may increase respiratory symptoms by
29 demonstrating O₃-induced airway hyperresponsiveness (Section [6.2.2](#)) and pulmonary
30 inflammation (Section [6.2.3.1](#) and Section [6.2.3.3](#)). Epidemiologic studies have not
31 widely examined associations between ambient O₃ concentrations and airway
32 hyperresponsiveness but have found O₃-associated increases in pulmonary inflammation
33 and oxidative stress (Section [6.3.2.2](#)). In addition to lung function decrements, controlled
34 human exposure studies clearly indicate O₃-induced increases in respiratory symptoms
35 including pain on deep inspiration, shortness of breath, and cough. This evidence is

1 detailed in Section [6.2.1.1](#); however, salient observations include an increase in
2 respiratory symptoms with increasing concentration and duration of O₃ exposure and
3 activity level of exposed subjects ([McDonnell et al., 1999b](#)). Further, increases in total
4 subjective respiratory symptoms have been reported following 5.6 and 6.6 hours of
5 exposure to 60 ppb O₃ relative to baseline ([Adams, 2006a](#)). At 70 ppb, [Schelegle et al.](#)
6 ([2009](#)) observed a statistically significant O₃-induced FEV₁ decrement of 6.1% at 6.6
7 hours and a significant increase in total subjective symptoms at 5.6 and 6.6 hours. The
8 findings for O₃-induced respiratory symptoms in controlled human exposure studies and
9 the evidence integrated across disciplines describing underlying modes of action provide
10 biological plausibility for epidemiologic associations observed between short-term
11 increases in ambient O₃ concentration and increases in respiratory symptoms.

12 In epidemiologic studies, respiratory symptom data typically are collected by having
13 subjects (or their parents) record symptoms and medication use in a diary without direct
14 supervision by study staff. Several limitations of symptom reports are well recognized:
15 recall error if not recorded daily, differences among subjects in the interpretation of
16 symptoms, differential reporting by subjects with and without asthma, and occurrence in
17 a smaller percentage of the population compared with changes in lung function and
18 biological markers of pulmonary inflammation. Nonetheless, symptom diaries remain a
19 convenient tool to collect individual-level data from a large number of subjects and allow
20 modeling of associations between daily changes in O₃ concentration and daily changes in
21 respiratory morbidity. Importantly, most of the limitations described above are sources of
22 random measurement error that can bias effect estimates to the null or increase the
23 uncertainty around effect estimates. Furthermore, because respiratory symptoms are
24 associated with limitations in activity and function and are the primary reason for using
25 medication and seeking medical care, the evidence is directly coherent with the consistent
26 associations observed between increases in ambient O₃ concentration and increases in
27 asthma ED visits (Section [6.2.7.3](#)).

28 Most studies were conducted in individuals with asthma, and as was concluded in the
29 2006 O₃ AQCD ([U.S. EPA, 2006b, 1996a](#)), the collective body of epidemiologic
30 evidence indicates that short-term increases in ambient O₃ concentrations are associated
31 with increases in respiratory symptoms in children with asthma. Studies also found
32 O₃-associated increases in the use of asthma medication in children. In a smaller body of
33 studies, increases in ambient O₃ concentration were associated with increases in
34 respiratory symptoms in adults with asthma. Ozone-associated increases in respiratory
35 symptoms in healthy populations were not as clearly indicated.

6.2.4.1 Children with Asthma

Respiratory Symptoms

1 [Table 6-19](#) presents the locations, time periods, and ambient O₃ concentrations for studies
2 examining respiratory symptoms and medication use in children with asthma. The
3 evidence supporting associations between short-term increases in ambient O₃
4 concentration and increases in respiratory symptoms in children with asthma is derived
5 mostly from examination of 1-h max, 8-h max, or 8-h avg O₃ concentrations and strong
6 findings from a large body of single-region or single-city studies ([Figure 6-11](#) and
7 [Table 6-20](#)). The few available U.S. multicity studies produced less consistent
8 associations.

9 Similar to lung function, associations with respiratory symptoms in children with asthma
10 were found with ambient O₃ concentrations assigned to subjects using various methods
11 with potentially different degrees of exposure measurement error. As was discussed for
12 lung function, methods included measurement of O₃ on site of and at the time of outdoor
13 activity ([Thurston et al., 1997](#)), which is associated with higher ambient-personal O₃
14 correlations and ratios (Section [4.3.3](#)); O₃ concentrations measured at sites within 5 km of
15 subjects' home or school ([Escamilla-Nuñez et al., 2008](#); [Romieu et al., 2006](#); [1997](#);
16 [1996](#)); O₃ measured at a single city site ([Gielen et al., 1997](#)); and O₃ concentrations
17 averaged across multiple sites ([Gent et al., 2003](#); [Mortimer et al., 2002](#)). In analyses with
18 O₃ averaged across multiple sites, which were restricted to warm seasons, O₃
19 concentrations within the region were temporally correlated as indicated by high
20 statewide correlations [median r = 0.83 in [Gent et al. \(2003\)](#)] or similar odds ratios for O₃
21 averaged across all within-city monitors and that averaged from the three closest sites
22 ([Mortimer et al., 2002](#)). In these panel studies, the averaged ambient concentrations may
23 have well represented the temporal variability in subjects' ambient O₃ exposures.

Table 6-19 Mean and upper percentile ozone concentrations in epidemiologic studies of respiratory symptoms, medication use, and activity levels in children with asthma.

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|---|--|-------------------------------|--|--|
| Thurston et al. (1997) | CT River Valley, CT | June 1991-1993 | 1-h max | 83.6 ^a | Max: 160 ^a |
| Escamilla-Núñez et al. (2008) | Mexico City, Mexico | July-March 2003-2005 | 1-h max | 86.5 | NR |
| 2006) | Mexico City, Mexico | October 1998-April 2000 | 8-h max 1-h max | 69 102 | Max: 184 Max: 309 |
| 1997) | Southern Mexico City, Mexico | April-July 1991; November 1991-February 1992 | 1-h max | 196 | Max: 390 |
| Romieu et al. (1996) | Northern Mexico City, Mexico | April-July 1991; November 1991-February 1992 | 1-h max | 190 | Max: 370 |
| Gent et al. (2003) | CT, southern MA | April-September 2001 | 8-h rolling avg 1-h max | 51.3, 50.0 (median) 58.6, 55.5 (median) | Max: 99.6 Max: 125.5 |
| Mortimer et al. (2002); (2000) | Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO ; (NCICAS) | June-August 1993 | 8-h avg (10 a.m.-6 p.m.) | 48 | NR |
| Gielen et al. (1997) | Amsterdam, Netherlands | April-July 1995 | 8-h max | 34.2 ^b | Max: 56.5 ^b |
| Delfino et al. (2003) | Los Angeles, CA | November 1999-January 2000 | 8-h max 1-h max | 17.1 25.4 | 90th: 26.1, Max: 37 90th: 38.0, Max: 52 |
| Rabinovitch et al. (2004) | Denver, CO | November-March 1999-2002 | 1-h max | 28.2 | 75th: 60, Max: 70.0 |
| Schildcrout et al. (2006) | Albuquerque, NM; Baltimore, MD; Boston, MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; Toronto, ON, Canada (CAMP) | May-September 1994-1995 | 1-h max | Range in medians across cities: 43.0-65.8 | Range in 90th across cities: 61.5-94.7 |
| Jalaludin et al. (2004) | Sydney, Australia | February-December 1994 | 15-h avg (6 a.m.-9 p.m.) | 12 | Max: 43 |

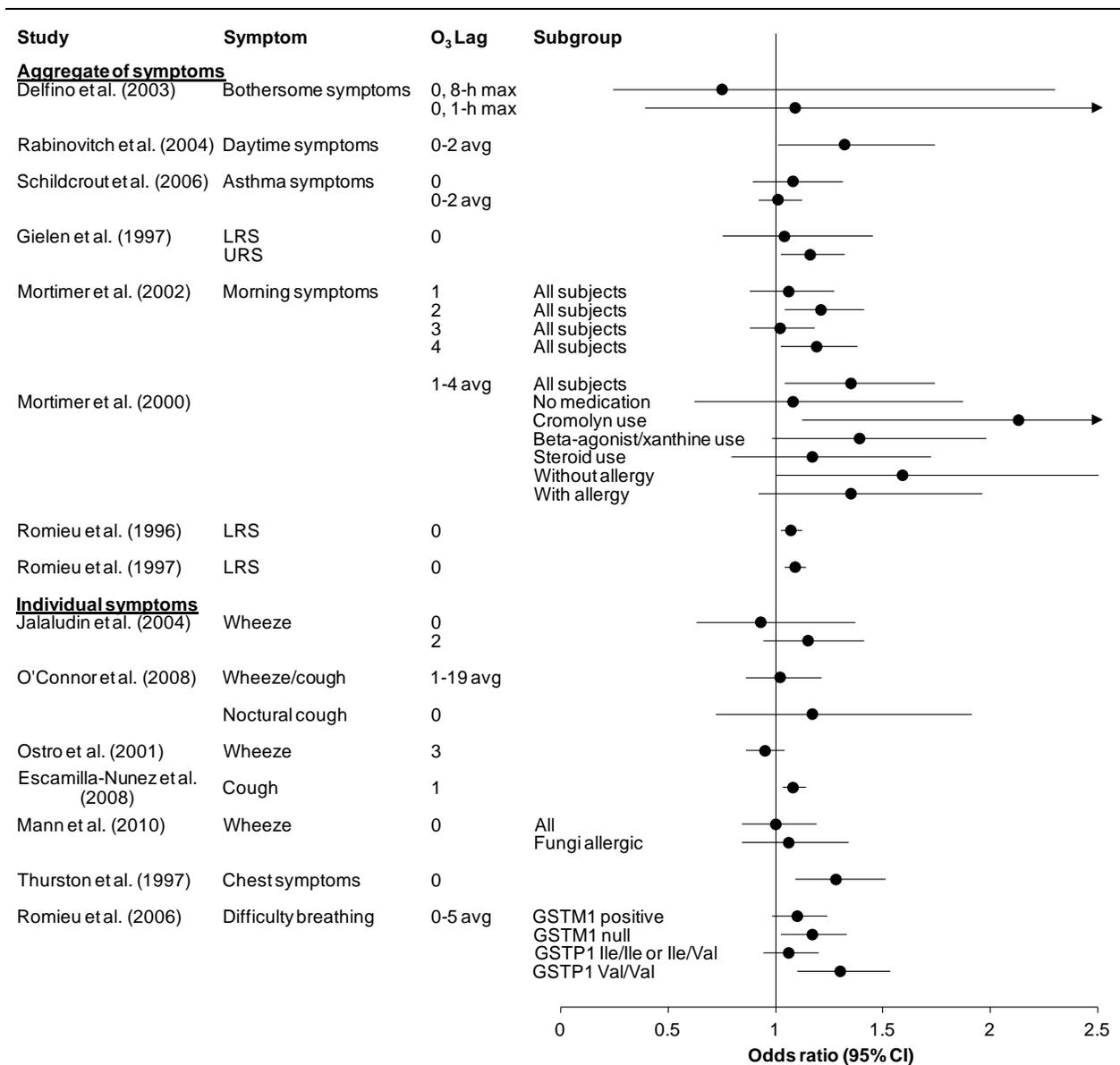
| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|--|---------------------------------|-------------------------------|-------------------------------------|---------------------------------------|
| O'Connor et al. (2008) | Boston, MA; Bronx, Manhattan NY; Chicago, IL; Dallas, TX, Seattle, WA; Tucson, AZ (ICAS) | August 1998- July 2001 | 24-h avg | NR | NR |
| Ostro et al. (2001) | Los Angeles, CA | August- October 1993 | 1-h max | Los Angeles: 59.5 Pasadena: 95.8 | Max: 130 Max: 220 |
| Mann et al. (2010) | Fresno/Clovis, California | Winter- Summer 2000- 2005 | 8-h max | 49.4 (median) | 75th: 69.5, Max: 120.0 |
| Just et al. (2002) | Paris, France | April-June 1996 | 24-h avg | 30.0 ^b | Max: 61.7 ^b |

* Note: Studies presented in order of first appearance in the text of this section.

NCICAS = National Cooperative Inner-City Asthma Study, NR = Not Reported, ICAS = Inner City Asthma Study, CAMP = Childhood Asthma Management Program.

^aMeasured on site of subjects' outdoor activity.

^bConcentrations converted from $\mu\text{g}/\text{m}^3$ to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).



Note: Results are presented first for aggregate indices of symptoms then for individual symptoms. Within each category, results generally are organized in order of increasing mean ambient O₃ concentration. LRS = lower respiratory symptoms, URS = upper respiratory symptoms. Odds ratios are from single-pollutant models and are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max (or 8-h avg or 15-h avg), and 24-h avg O₃ concentrations, respectively.

Figure 6-11 Associations between ambient ozone concentrations and respiratory symptoms in children with asthma.

Table 6-20 Additional characteristics and quantitative data for studies presented in Figure 6-11.

| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Symptom | Subgroup | Standardized OR (95% CI) ^a |
|---|--|-------------------------------|--------------------|---------------------|------------------------|---------------------------------------|
| Studies examining aggregates of symptoms | | | | | | |
| Delfino et al. (2003) | Los Angeles, CA | 8-h max | 0 | Bothersome symptoms | | 0.75 (0.24, 2.30) |
| | 22 children with asthma, ages 10-16 yr | 1-h max | | | 1.09 (0.39, 3.03) | |
| Rabinovitch et al. (2004) | Denver, CO 86 children with asthma, ages 6-12 yr | 1-h max | 0-2 avg | Daytime symptoms | | 1.32 (1.01, 1.74) |
| Schildcrout et al. (2006) | Albuquerque, NM; Baltimore, MD; Boston, MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; Toronto, ON, Canada 990 children with asthma, ages 5-12 yr | 1-h max | 0 | Asthma symptoms | | 1.08 (0.89, 1.31) |
| | | | 0-2 avg | | 1.01 (0.92, 1.12) | |
| Gielen et al. (1997) | Amsterdam, Netherlands 61 children with asthma, ages 7-13 yr | 8-h max | 0 | LRS | | 1.04 (0.75, 1.45) |
| | | | | URS | | 1.16 (1.02, 1.32) |
| (2002); Mortimer et al. (2000) | Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO 846 children with asthma, ages 4-9 yr | 8-h avg (10 a.m.-6 p.m.) | 1 | Morning symptoms | All subjects | 1.06 (0.88, 1.27) |
| | | | | | All subjects | 1.21 (1.04, 1.41) |
| | | | | | All subjects | 1.02 (0.88, 1.18) |
| | | | | | All subjects | 1.19 (1.02, 1.38) |
| | | | | | All subjects | 1.35 (1.04, 1.74) |
| | | | | | No medication use | 1.08 (0.62, 1.87) |
| | | | | | Cromolyn use | 2.13 (1.12, 4.04) |
| | | | | | β-agonist/xanthine use | 1.39 (0.98, 1.98) |
| | | | | | 1.17 (0.79, 1.72) | |
| | | | | | 1.59 (1.00, 2.52) | |
| Steroid use | 1.35 (0.92, 1.96) | | | | | |
| Without allergy | | | | | | |
| With allergy | | | | | | |
| Romieu et al. (1996) | northern Mexico City, Mexico 71 children with asthma, ages 5-7 yr | 1-h max | 0 | LRS | | 1.07 (1.02, 1.12) |
| Romieu et al. (1997) | southern Mexico City, Mexico 65 children with asthma, ages 5-13 yr | 1-h max | 0 | LRS | | 1.09 (1.04, 1.14) |
| Studies examining individual symptoms | | | | | | |
| Jalaludin et al. (2004) | Sydney, Australia 125 children with asthma, mean age 9.6 yr | 15-h avg (6 a.m.-9 p.m.) | 0 | Wheeze | | 0.93 (0.63, 1.37) |
| | | | | | 2 | 1.15 (0.94, 1.41) |
| O'Connor et al. (2008) | Boston, MA; Bronx, Manhattan NY; Chicago, IL; Dallas, TX, Seattle, WA; Tucson, AZ 861 children with asthma, mean (SD) age 7.7 (2.0) yr | 24-h avg | 1-19 avg | Wheeze/cough | | 1.02 (0.86, 1.21) |

| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Symptom | Subgroup | Standardized OR (95% CI) ^a |
|--|---|-------------------------------|--------------------|---------------------------|------------------------------|---------------------------------------|
| Just et al. (2002) | Paris, France 82 children with asthma, mean (SD) age 10.9 (2.5) yr | 24-h avg | 0 | Nocturnal cough incidence | | 1.17 (0.72, 1.91) |
| Ostro et al. (2001) | Los Angeles, CA 138 children with asthma, ages 6-13 yr | 1-h max | 3 | Wheeze | | 0.95 (0.86, 1.04) |
| Escamilla-Nuñez et al. (2008) | Mexico City, Mexico 147 children with asthma, mean age 9.6 yr | 1-h max | 1 | Wheeze | | 1.08 (1.03, 1.14) |
| Mann et al. (2010) | Fresno/Clovia, California 280 children with asthma, ages 6-11 yr | 8-h max | 0 | Wheeze | All | 1.00 (0.84, 1.19) |
| | | | | | Fungi allergic | 1.06 (0.84, 1.34) |
| Thurston et al. (1997) | CT River Valley, CT 166 children with asthma, ages 7-13 yr | 1-h max | 0 | Chest symptoms | | 1.28 (1.09, 1.51) |
| Romieu et al. (2006) | Mexico City, Mexico 151 children with asthma, mean age 9 yr | 1-h max | 0-5 avg | Difficulty breathing | GSTM1 positive | 1.10 (0.98, 1.24) |
| | | | | | GSTM1 null | 1.17 (1.02, 1.33) |
| | | | | | GSTP1 Ile/Ile or Ile/Val | 1.06 (0.94, 1.20) |
| | | | | | GSTP1 Val/Val | 1.30 (1.10, 1.53) |
| Gent et al. (2003)^b | CT, southern MA 130 children with asthma on maintenance medication | 1-h max | 0 | Wheeze | O ₃ <43.2 ppb | 1.00 (reference) |
| | | | | | O ₃ 43.2-51.5 ppb | 1.04 (0.89, 1.21) |
| | | | | | O ₃ 51.6-58.8 ppb | 1.16 (1.00, 1.35) |
| | | | | | O ₃ 58.9-72.6 ppb | 1.16 (1.00, 1.35) |
| | | | | | O ₃ ≥ 72.7 ppb | 1.22 (0.97, 1.53) |
| | | | | Chest tightness | O ₃ <43.2 ppb | 1.00 (reference) |
| | | | | | O ₃ 43.2-51.5 ppb | 1.11 (0.91, 1.36) |
| | | | | | O ₃ 51.6-58.8 ppb | 1.01 (0.83, 1.23) |
| | | | | | O ₃ 58.9-72.6 ppb | 1.16 (0.97, 1.39) |
| | | | | | O ₃ ≥ 72.7 ppb | 1.31 (0.97, 1.77) |

*Includes studies for [Figure 6-11](#), plus others.

LRS = Lower respiratory symptoms, URS = Upper respiratory symptoms.

^aEffect estimates are standardized to a 40, 30, and 20 ppb increase for 1-h max, 8-h max (or 8-h avg or 15-h avg), and 24-h avg O₃, respectively.

^bResults not included in [Figure 6-11](#) because results presented per quintile of ambient O₃ concentration.

1 Among U.S. multicity studies of children with asthma, each of which examined a
2 different O₃ averaging time, O₃ was not consistently associated with increases in
3 respiratory symptoms ([O'Connor et al., 2008](#); [Schildcrout et al., 2006](#); [Mortimer et al.,
4 2002](#)). In the NCICAS cohort (described in Section [6.2.1.2](#)), increases in most evaluated
5 lags of O₃ (1 to 4 and 1-4 avg) were associated with increases in asthma symptoms. A
6 30-ppb increase in lag 1-4 avg, of 8-h avg (10 a.m.-6 p.m.), O₃ was associated with an
7 increase in morning asthma symptoms with an OR of 1.35 (95% CI: 1.04, 1.69)
8 ([Mortimer et al., 2002](#)). The OR was similar in an analysis restricted to O₃ concentrations
9 <80 ppb. Associations were similarly strong for lags 2 and 4 of O₃ but weaker for lags 1

1 and 3 ([Figure 6-11](#) and [Table 6-20](#)). In the ICAS cohort (described in Section [6.2.1.2](#)),
2 associations of 19-day avg of 24-h avg O₃ with wheeze and nighttime asthma were
3 positive and negative, respectively ([O'Connor et al., 2008](#)). NCICAS collected symptom
4 data daily ([Mortimer et al., 2002; 2000](#)), whereas in ICAS, every 2 months, parents
5 reported the number of days with symptoms over the previous 2 weeks ([O'Connor et al.,](#)
6 [2008](#)). Thus, ICAS was precluded from examining associations with single-day O₃
7 concentrations and shorter lag periods.

8 Like NCICAS, the U.S. multicity Childhood Asthma Management Program (CAMP,
9 with cities in common with NCICAS and ICAS, [Table 6-19](#)) collected daily symptom
10 data, analyzed data collected between May and September, and evaluated multiple lags of
11 O₃ ([Schilderout et al., 2006](#)). However, associations in CAMP were weaker for all
12 evaluated lags of O₃. In meta-analyses that combined city-specific estimates, a 40-ppb
13 increase in lag 0 of 1-h max O₃ was associated with asthma symptoms with an OR of
14 1.08 (95% CI: 0.89, 1.31). Odds ratios for lags 1 and 2 and the 3-day sum of O₃ were
15 between 1.0 and 1.03. In this study, data available from an average of 12 subjects per day
16 per city were used to produce city-specific ORs. These city-specific ORs then were
17 combined in meta-analyses to produce study-wide ORs. Because O₃ analyses were
18 restricted to warm seasons, there likely was less power to detect associations with O₃ than
19 with other pollutants, which were analyzed using year-round data.

20 Several longitudinal studies conducted in different cohorts of children with asthma in
21 Mexico City, Mexico examined and found increases in respiratory symptoms in
22 association with 1-h max O₃ concentrations ([Escamilla-Núñez et al., 2008; Romieu et al.,](#)
23 [2006; 1997; 1996](#)).[1997](#)); ([1996](#)) [Romieu et al. \(1997\); \(1996\)](#) found larger increases in
24 symptoms in association with increases in 1-h max O₃ at lag 0, than at lag 1 or 2. Recent
25 studies expanded on earlier evidence by indicating associations with multiday averages of
26 O₃ concentrations. [Romieu et al. \(2006\)](#) and [Escamilla-Núñez et al. \(2008\)](#) found that
27 ORs for associations of ambient 1-h max O₃ concentrations with respiratory symptoms
28 and medication use increased as the number of averaging days increased (up to lag 0-5
29 avg).

30 Studies of children with asthma examined factors that may modify symptom responses to
31 ambient O₃ exposure but did not produce conclusive evidence. Larger O₃-associated
32 (8-h avg [10 a.m.-6 p.m.] or 8-h max) increases in symptoms were found in children
33 taking asthma medication, although the specific medications examined differed between
34 studies. As with results for PEF, in the NCICAS multicity cohort, O₃-associated increases
35 in morning symptoms were larger in children taking cromolyn (used to treat asthma with
36 allergy) or beta-agonists/xanthines than in children taking no medication. Odds ratios
37 were similar in children taking steroids and children taking no medication ([Figure 6-11](#)

1 and [Table 6-20](#)) ([Mortimer et al., 2000](#)). Among children with asthma in Southern New
2 England, O₃-associated increases in symptoms were limited mostly to children taking
3 steroids, cromolyn, or leukotriene inhibitors for maintenance ([Gent et al., 2003](#)).

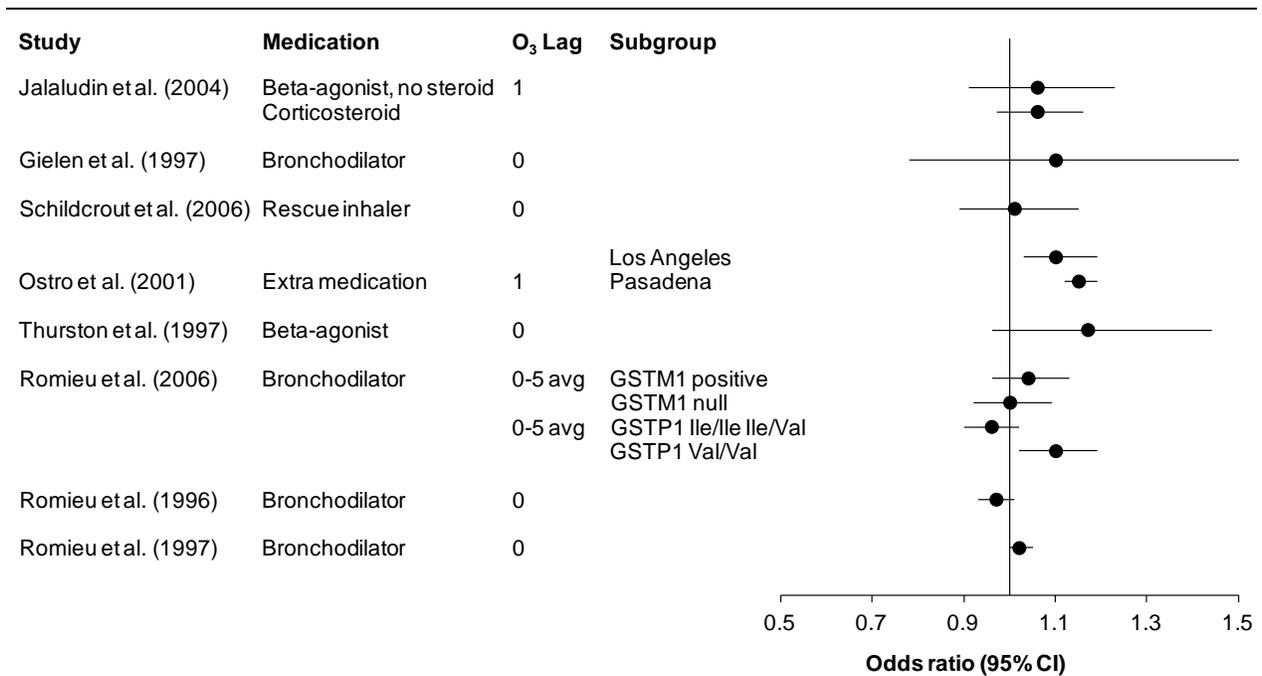
4 In most studies of children with asthma, a majority of subjects (52 to 100%) had atopy as
5 determined by sensitization to any examined allergen. While studies found O₃-associated
6 increases in pulmonary inflammation in children with atopy (Section [6.2.3.2](#)) and in
7 animal models of allergy (Section [6.2.3.3](#)), studies did not indicate that the risk of
8 O₃-associated respiratory symptoms differed in children with asthma with and without
9 atopy. In NCICAS, [Mortimer et al. \(2000\)](#) found that an increase in 8-h avg (10 a.m.-6
10 p.m.) O₃ was associated with a similar increased incidence of asthma symptoms among
11 the 79% of subjects with atopy and the 21% of subjects without atopy ([Figure 6-11](#) and
12 [Table 6-20](#)). Odds ratios for O₃ did not differ by residential allergen levels. Among
13 children with asthma in Fresno, CA, most associations of single- and multiday lags of
14 8-h max O₃ concentrations (0-14 days) with wheeze were near or below 1.0 among all
15 subjects. Among the various O₃ lags examined, increases in O₃ were not consistently
16 associated with increases in wheeze in subjects with cat or fungi allergy either ([Mann et](#)
17 [al., 2010](#)).

18 [Romieu et al. \(2006\)](#) found differences in O₃-associated respiratory symptoms by genetic
19 variants in GST enzymes, particularly, GSTP1 and less so for GSTM1. Compared with
20 GSTP1 Ile/Ile or Ile/Val subjects, larger effects were estimated for GSTP1 Val/Val
21 subjects ([Figure 6-11](#) and [Table 6-20](#)). The largest OR was found for difficulty breathing
22 in children with asthma who had both GSTM1 null and GSTP1 Val/Val genotypes (OR:
23 1.49 [95% CI: 1.14, 1.93] per 30-ppb increase in lag 0-5 avg of 8-h max O₃). While these
24 results are consistent with those described for antioxidant capacity modifying
25 O₃-associated changes in lung function (Section [6.2.1.2](#)) and pulmonary inflammation
26 [Section [6.2.3.2](#) for results in the same cohort ([Sienra-Monge et al., 2004](#))], it is important
27 to note that effect modification by GSTP1 variants has not been consistent. ([Romieu et](#)
28 [al., 2006](#)) found an O₃-associated decrease in FEV₁ only in children with GSTP1 Ile/Ile
29 or Ile/Val genotype. Among children in southern California, GSTP1 Ile/Ile was
30 associated with greater risk of asthma onset (Section [7.2.1](#)). Asthma prevalence has not
31 been consistently associated with a particular GSTP1 genotype either ([Tamer et al., 2004](#);
32 [Mapp et al., 2002](#); [Hemmingsen et al., 2001](#)).

Asthma Medication Use

33 Although recent studies contributed mixed evidence, the collective body of evidence
34 supports associations between increases in ambient O₃ concentration and increased
35 asthma medication use in children ([Figure 6-12](#) and [Table 6-21](#)). Most studies examined

1 and found associations with lags 0 or 1 of 1-h max O₃ concentrations; however,
 2 associations also were found for multiday average O₃ concentrations (lag 0-5 avg in
 3 [Romieu et al. \(2006\)](#) and lags 0-2 avg and 0-4 avg in [Just et al. \(2002\)](#)). Within several
 4 studies, associations were consistent between respiratory symptoms and asthma
 5 medication use ([Escamilla-Nuñez et al., 2008](#); [Romieu et al., 2006](#); [Schildcrout et al.,](#)
 6 [2006](#); [Jalaludin et al., 2004](#); [Romieu et al., 1997](#); [Thurston et al., 1997](#)). As an exception,
 7 [Romieu et al. \(1996\)](#) found that O₃ was associated with an increase in respiratory
 8 symptoms but not bronchodilator use, and [Rabinovitch et al. \(2004\)](#) indicated statistically
 9 significant associations with symptoms but not bronchodilator use (OR not reported). A
 10 few studies found higher odds of O₃-associated increases in asthma medication use than
 11 in respiratory symptoms ([Just et al., 2002](#); [Ostro et al., 2001](#)).



Note: CS = corticosteroid. Results generally are presented in order of increasing mean ambient O₃ concentration. Odds ratios are from single-pollutant models and are standardized to a 40- ppb for 1-h max O₃ and a 30-ppb increase for 8-h max or 15-h avg O₃.

Figure 6-12 Associations between ambient ozone concentrations and asthma medication use.

Table 6-21 Additional characteristics and quantitative data for studies presented in Figure 6-12.

| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Medication | Subgroup | Standardized OR (95% CI) ^a |
|--|---|-------------------------------|--------------------|------------------------------------|-----------------------------|---------------------------------------|
| Jalaludin et al. (2004) | Sydney, Australia 125 children with asthma, mean age 9.6 yr | 15-h avg (6 a.m.-9 p.m.) | 1 | Beta-agonist, no corticosteroid | | 1.06 (0.91, 1.23) |
| | | | | | Inhaled corticosteroid | 1.06 (0.97, 1.16) |
| Gielen et al. (1997) | Amsterdam, Netherlands 61 children with asthma, ages 7-13 yr | 8-h max | 0 | Bronchodilator | | 1.10 (0.78, 1.55) |
| Schildcrouet et al. (2006) | Albuquerque, NM; Baltimore, MD; Boston, MA; Denver, CO; San Diego, CA; Seattle, WA; St. Louis, MO; Toronto, ON, Canada 990 children with asthma, ages 5-12 yr | 1-h max | 0 | Rescue inhaler | | 1.01 (0.89, 1.15) |
| Ostro et al. (2001) | Los Angeles, CA 138 children with moderate/severe asthma, ages 6-13 yr | 1-h max | 1 | Any extra medication | Pasadena | 1.15 (1.12, 1.19) |
| | | | | | Los Angeles | 1.10 (1.03, 1.19) |
| Thurston et al. (1997) | CT River Valley, CT 166 children with asthma, ages 7-13 yr | 1-h max | 0 | Beta-agonist | | 1.17 (0.96, 1.44) |
| Romieu et al. (2006) | Mexico City, Mexico 151 children with asthma, mean age 9 yr | 1-h max | 0-5 avg | Bronchodilator | GSTM1 positive | 1.04 (0.96, 1.13) |
| | | | | | GSTM1 null | 1.00 (0.92, 1.09) |
| | | | | | GSTP1 Ile/Ile or Ile/Val | 0.96 (0.90, 1.02) |
| | | | | | GSTP1 Val/Val | 1.10 (1.02, 1.19) |
| Romieu et al. (1996) | northern Mexico City, Mexico 71 children with asthma, ages 5-7 yr | 1-h max | 0 | Bronchodilator | | 0.97 (0.93, 1.01) |
| Romieu et al. (1997) | southern Mexico City, Mexico 65 children with asthma, ages 5-13 yr | 1-h max | 0 | Bronchodilator | | 1.02 (1.00, 1.05) |

| Study* | Location/Population | O ₃ Averaging Time | O ₃ Lag | Medication | Subgroup | Standardized OR (95% CI) ^a |
|---|--|-------------------------------|--------------------|-----------------------------|----------------------------------|---------------------------------------|
| Just et al. (2002) ^b | Paris, France 82 Children with asthma, mean (SD) age 10.9 (2.5) yr | 24-h avg | 0 | Beta-agonist, no steroid | | 3.95 (1.22, 12.9) |
| Gent et al. (2003) ^b | CT, southern MA 130 children with asthma on maintenance medication | 1-h max | 0 | Bronchodilator | O ₃ <43.2 ppb | 1.00 (reference) |
| | | | | | O ₃ 43.2- 51.5 ppb | 1.00 (0.96, 1.05) |
| | | | | | O ₃ 51.6- 58.8 ppb | 1.04 (1.00, 1.09) |
| | | | | | O ₃ 58.9- 72.6 ppb | 1.02 (0.98, 1.07) |
| | | | | | O ₃ ≥ 72.7 ppb | 1.05 (0.97, 1.13) |

*Includes studies in [Figure 6-12](#), plus others.

^aEffect estimates are standardized to a 40-ppb increase for 1-h max O₃, a 30-ppb increase for 8-h max or 15-h avg O₃, and a 20-ppb increase for 24-h avg O₃.

^bResults not included in [Figure 6-12](#). Results from [Just et al. \(2002\)](#) were out of range of other estimates, and results from [Gent et al. \(2003\)](#) were presented per quintile of ambient O₃ concentration.

Changes in Activity

1 While investigation has been limited, evidence does not consistently demonstrate O₃-
2 associated diminished activity in children with asthma ([O'Connor et al., 2008](#); [Delfino et](#)
3 [al., 2003](#)). These studies examined different O₃ averaging times and lags. In the multicity
4 ICAS cohort, [O'Connor et al. \(2008\)](#) found that a 20-ppb increase in lag 1-19 avg of
5 24-hour O₃ was associated with a 10% lower odds (95% CI: -26, 10) of slow play. In a
6 small (n = 22) panel study conducted in children with asthma in Los Angeles CA,
7 [Delfino et al. \(2003\)](#) found that a 40-ppb increase in lag 0 of 1-h max O₃ was associated
8 with an increase in symptoms that interfered with daily activity with an OR of 7.41
9 (95% CI: 1.18, 43.2). Several studies reported increases in school absenteeism in children
10 with asthma in association with increases in ambient O₃ concentration with long lag
11 periods (14-day and 30-day distributed lags, 19-day avg) ([O'Connor et al., 2008](#); [Gilliland](#)
12 [et al., 2001](#); [Chen et al., 2000](#)). Whereas [Chen et al. \(2000\)](#) and [O'Connor et al. \(2008\)](#)
13 examined absences for any reason, [Gilliland et al. \(2001\)](#) found associations with
14 absences for respiratory illnesses. Despite this evidence, several limitations are notable,
15 including the lack of a well-characterized mode of action for long lag periods of O₃
16 exposure and the potential for residual seasonal confounding with examination of long
17 lag periods. In analyses of single-day lags, [Gilliland et al. \(2001\)](#) found associations with
18 O₃ lagged 1 to 5 days, indicating respiratory absences may be affected by O₃ exposures
19 with shorter lag periods.

6.2.4.2 Adults with Respiratory Disease

1 Within a small body of studies, several found that increases in ambient O₃ concentration
2 (8-hour or 1-h max) were associated with increases in respiratory symptoms in adults
3 with asthma ([Khatri et al., 2009](#); [Feo Brito et al., 2007](#); [Ross et al., 2002](#)). Details from
4 studies of respiratory symptoms in adults with respiratory disease regarding location,
5 time period, and ambient O₃ concentrations are presented in [Table 6-22](#). These studies
6 used different exposure assessment methods: concentrations averaged from sites closest
7 to subjects' location each hour ([Khatri et al., 2009](#)) or concentrations measured at one
8 ([Ross et al., 2002](#)) or multiple ([Feo Brito et al., 2007](#)) city sites. [Park et al. \(2005a\)](#) found
9 inconsistent associations for 24-h avg O₃ measured at 10 city sites among the various
10 symptoms and medication use examined in adults with asthma in Korea during a period
11 of dust storms. In a study of adults with COPD in London, England, increases in lag 1 of
12 8-h max O₃ (at a single city site) were associated with higher odds of dyspnea and sputum
13 changes but lower odds of nasal discharge, wheeze, or upper respiratory symptoms
14 ([Peacock et al., 2011](#)).

Table 6-22 Mean and upper percentile ozone concentrations in epidemiologic studies of respiratory symptoms and medication use in adults with respiratory disease .

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|---|------------------------------------|--------------------------------|-------------------------------|--|---|
| Khatri et al. (2009) | Atlanta, GA | May-September 2003, 2005, 2006 | 8-h max | 61 ^a | 75th: 74 ^a |
| Feo Brito et al. (2007) | Ciudad Real and Puertollano, Spain | May-June 2000-2001 | 1-h max | 65.9 (Ciudad Real) ^b 56.8 (Puertollano) ^b | Max: 101.5 ^b (Ciudad Real); 138.2 ^b (Puertollano) |
| Eiswerth et al. (2005) | Glendora, CA | October-November 1983 | 1-h max | NR | NR |
| Ross et al. (2002) | East Moline, IL | April-October 1994 | 8-h avg | 41.5 | Max: 78.3 |
| Peacock et al. (2011) | London, England | All-year 1995-1997 | 8-h max | 15.5 | Autumn/Winter Max: 32 Spring/Summer Max: 74 |
| Park et al. (2005a) | Incheon, Korea | March-June 2002 | 24-h avg | Dust event days: 23.6 Control days: 25.1 | NR |
| Wiwatanadate and Liwsrisakun (2011) | Chiang Mai, Thailand | August 2005-June 2006 | 24-h avg | 17.5 | 90th: 26.82, Max: 34.65 |

* Note: Studies presented in order of first appearance in the text of this section.

NR = Not Reported

^aIndividual-level estimates were derived based on time spent in the vicinity of various O₃ monitors.

^bConcentrations converted from µg/m³ to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

1 Some studies that included adults with asthma examined populations with a high
2 prevalence of atopy. In a study of children and adults with asthma (at least 53% with
3 atopy), [Ross et al. \(2002\)](#) found that an increase in lag 1-3 avg of 8-h max O₃ was
4 associated with an increase in symptom score and asthma medication use. [Feo Brito et al.](#)
5 [\(2007\)](#) followed 137 adults with asthma in two central Spain cities. All subjects had
6 pollen allergy and were examined during pollen season. In Puertollano, O₃ concentrations
7 were obtained from four city monitors, and a 40-ppb increase in lag 3 of 1-h max O₃ was
8 associated with a 14.3% increase (95% CI: 3.6, 26.0) in the number of subjects reporting
9 respiratory symptoms, adjusting only for time trend. The association was much weaker in
10 Ciudad Real (2.3% increase [95% CI: -14, 21%] per 40-ppb increase in lag 4 of 1-h max
11 O₃), a city characterized by lower ambient air pollution levels and a narrower range of
12 ambient O₃ concentrations as measured at a single site established by investigators.

13 Cross-sectional studies reported ambient O₃-associated decreases in activity in adults
14 with asthma; however, due to various limitations in the collective body of evidence, firm
15 conclusions are not warranted. Although conducted over single seasons, studies did not
16 consider confounding by meteorological factors. In a warm season study in Atlanta, GA
17 (described in Section [6.2.1.2](#)), [Khatri et al. \(2009\)](#) found that a 30-ppb increase in lag 2 of

1 8-h max O₃ was associated with a 0.69-point decrease (95% CI: -1.28, -0.11) in the
2 Juniper quality of life score, which incorporates indices for symptoms, mood, and activity
3 limitations (7-point scale). In a fall study conducted in the Los Angeles, CA area in
4 individuals with asthma (age 16 years and older), [Eiswerth et al. \(2005\)](#) found that a
5 40-ppb increase in 1-h max O₃ was associated with a 0.24% (95% CI: 0.08, 0.40%) lower
6 probability of indoor activity but higher probability of outdoor activity. The authors
7 acknowledged that their findings were unexpected and may have been influenced by lack
8 of control for potential confounders but interpreted the decrease in indoor activities as
9 rest replacing chores. In contrast with the aforementioned studies, a panel study of
10 individuals with asthma (ages 13-78 years) in Thailand found that a 20-ppb increase in
11 lag 4 of 24-h avg O₃ was associated with a 26% (95% CI: 4, 43) lower odds of symptoms
12 that interfered with activities ([Wiwatanadate and Liwsrisakun, 2011](#)).

6.2.4.3 Populations not Restricted to Individuals with Asthma

13 Locations, time periods, and ambient O₃ concentrations for studies of symptoms in
14 populations not restricted to individuals with asthma are presented in [Table 6-23](#). Most
15 studies examined children, and in contrast with lung function results (Section [6.2.1.2](#)),
16 short-term increases in ambient O₃ concentration were not consistently associated with
17 increases in respiratory symptoms in children in the general population ([Figure 6-13](#) and
18 [Table 6-24](#)). Because examination of adults was limited, conclusions cannot be drawn.

Table 6-23 Mean and upper percentile ozone concentrations in epidemiologic studies of respiratory symptoms in populations not restricted to individuals with asthma.

| Study* | Location | Study Period | O ₃ Averaging Time | Mean/Median Concentration (ppb) | Upper Percentile Concentrations (ppb) |
|--|-----------------------------------|------------------------------|---|--|---|
| Neas et al. (1995) | Uniontown, PA | June-August 1990 | 12-h avg (8 a.m.-8 p.m.) | 37.2 | Max: 87.5 |
| Linn et al. (1996) | Rubidoux, Upland, Torrence, CA | September-June 1992-1994 | 24-h avg personal 24-h avg ambient | 5 23 | Max: 16 Max: 53 |
| Hoek and Brunekreef (1995) | Deurne and Enkhuizen, Netherlands | March-July 1989 | 1-h max | Deurne: 57 Enkhuizen: 59 | Max: 107 Max: 114 |
| Rodriguez et al. (2007) | Perth, Australia | All-year, 1996-2003 | 24-h avg 1-h max | 28 33 | Max: 74 Max: 95 |
| Moon et al. (2009) | 4 cities, South Korea | April-May 2003 | 8-h avg (10 a.m.-6 p.m.) | NR | NR |
| Ward et al. (2002) | Birmingham and Sandwell, England | January-March, May-July 1997 | 24-h avg | Winter median: 13.0 Summer median: 22.0 | Winter Max: 33 Summer Max: 41 |
| Triche et al. (2006) | Southwestern VA | June-August 1995-1996 | 24-h avg 8-h max 1-h max | 35.2 54.5 60.8 | 75th: 40.6, Max: 56.6 75th: 64.1, Max: 87.6 75th: 70.0, Max: 95.0 |
| Gold et al. (1999) | Mexico City, Mexico | January-November 1991 | 24-h avg | 52.0 ^a | Max: 103 ^a |
| Apte et al. (2008) | Multiple U.S. cities (NR) | Winter or summer 1994-1998 | Workday avg (8 a.m. - 5 p.m.) 24-h avg | 34.2 ^b 25.5 ^b | Max: 86.2 ^b Max: 67.3 ^b |

* Note: Studies presented in order of first appearance in the text of this section.

NR = Not Reported.

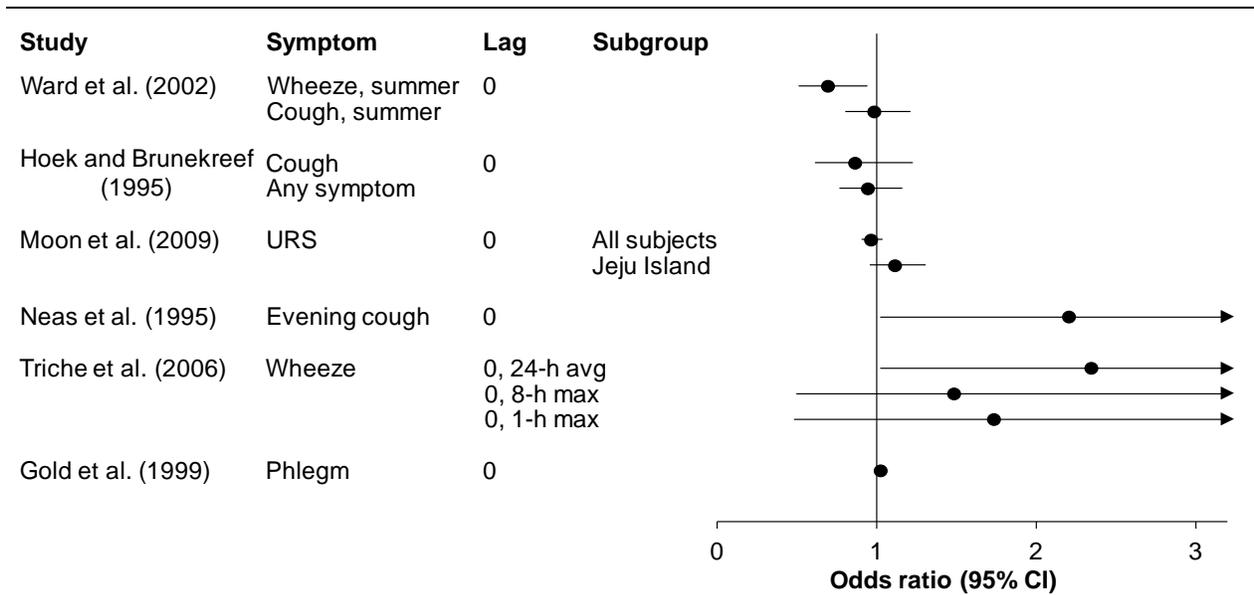
^aMeasured at subject's schools.

^bConcentrations converted from µg/m³ to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

Children

1 Although evidence of O₃-associated increases in respiratory symptoms in children was
2 inconsistent, it did not appear to be attributable to the differences in exposure assessment
3 method among studies [e.g., O₃ measured at a single site ([Linn et al., 1996](#); [Hoek and](#)
4 [Brunekreef, 1995](#)), O₃ averaged across multiple city sites ([Rodriguez et al., 2007](#)), O₃
5 measured at sites near schools ([Moon et al., 2009](#); [Ward et al., 2002](#))]. Some studies that
6 found weak or inconsistent associations between ambient O₃ concentrations and
7 respiratory symptoms found O₃-associated decrements in lung function ([Ward et al.,](#)
8 [2002](#); [Linn et al., 1996](#)). In their study of healthy children in Uniontown, PA, [Neas et al.](#)
9 [\(1995\)](#) found differences in association with respiratory symptoms between two estimates
10 of O₃ exposure. Ambient O₃ concentrations were measured at one central site in town.

1 Subjects spent a mean 5.4 hours outdoors during the 12-hour period (8 a.m.-8 p.m.) over
 2 which O₃ concentrations were averaged and symptoms were reported. Evening cough
 3 was more strongly associated with O₃ concentrations weighted by time spent outdoors
 4 (OR: 2.20 [95% CI: 1.02, 4.75] per 30-ppb increase in lag 0 of 12-h avg O₃) than with
 5 unweighted O₃ concentrations (OR: 1.36 [95% CI: 0.86, 2.13]). Time spent outdoors has
 6 been shown to influence O₃ personal-ambient ratios and correlations (Section 4.3.3), thus
 7 the weighted O₃ concentrations may have represented personal O₃ exposures better.



Note: Results generally are presented in increasing order of mean ambient O₃ concentration. URS = Upper respiratory symptoms. Odds ratios are from single-pollutant models and are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max (or 12-h avg), and 24-h avg O₃ concentrations, respectively.

Figure 6-13 Associations between ambient ozone concentrations and respiratory symptoms in children in the general population.

Table 6-24 Additional characteristics and quantitative data for studies represented in Figure 6-13.

| Study* | Location/ Population | O ₃ Lag | O ₃ Averaging Time | Symptom | Subgroup | Standardized OR (95% CI) ^a |
|--|--|--------------------|--------------------------------|---------------------------------|-----------------------------|---|
| Ward et al. (2002) | Birmingham and Sandwell, England 162 children, age 9 yr | 0-6 avg | 24-h avg | Wheeze, summer Cough, summer | | 0.69 (0.51, 0.94) 0.98 (0.80, 1.21) |
| Hoek and Brunekreef (1995) | Enkhuizen, Netherlands 300 children, ages 7 - 11 yr | 0 | 1-h max | Cough Any symptom | | 0.86 (0.61, 1.22) 0.94 (0.76, 1.16) |
| Moon et al. (2009) | 4 cities, South Korea 696 children, ages <13 yr | 0 | 8-h avg (10 a.m.-6 p.m.) | URS | All subjects Jeju Island | 0.96 (0.90, 1.03) 1.11 (0.95, 1.30) |
| Neas et al. (1995) | Uniontown, PA 83 healthy children, 4th and 5th grades | 0 | 12-h avg (8 a.m.-8 p.m.) | Evening cough | | 2.20 (1.02, 4.75) ^b |
| Triche et al. (2006) | Southwestern VA 691 infants of mothers with asthma, age <1 yr | 0 | 24-h avg 8-h max 1-h max | Wheeze | | 2.34 (1.02, 5.37) 1.48 (0.49, 4.41) 1.73 (0.48, 6.22) |
| Gold et al. (1999) | Mexico City, Mexico 40 children, ages 8-11 yr | 1 | 24-h avg | Phlegm | | 1.02 (1.00, 1.04) |
| Linn et al. (1996)^c | Rubidoux, Upland, Torrence, CA 269 children, 4th and 5th grades | 0 | 24-h avg | Evening symptom score | | -0.96 (-2.2, 0.26) |

*Includes studies in [Figure 6-13](#), plus others.

URS = Upper respiratory symptoms

^aEffect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max (or 8-h avg or 12-h avg), and 24-h avg O₃, respectively.

^bO₃ concentrations were weighted by the proportion of time spent outdoors.

^cResults not presented in [Figure 6-13](#) because outcome is a continuous variable indicating intensity of symptoms (negative indicates improvement in symptoms).

1 Several other panel studies of children, in which asthma prevalence ranged from 0 to
 2 50%, reported null or negative associations between various averaging times and lags of
 3 ambient O₃ concentration and respiratory symptoms ([Moon et al., 2009](#); [Rodriguez et al.,](#)
 4 [2007](#); [Ward et al., 2002](#); [Linn et al., 1996](#); [Hoek and Brunekreef, 1995](#)) ([Figure 6-13](#) and
 5 [Table 6-24](#)). Among children in Mexico City, [Gold et al. \(1999\)](#) reported an increase in
 6 phlegm in association with an increase in lag 1 of 24-h avg O₃ concentration measured at
 7 schools; however, investigators acknowledged being unable to distinguish between the
 8 effects of O₃ and PM₁₀ due to their high correlation (r = 0.75).

9 Unlike other studies that examined ambient O₃ concentrations from a single monitoring
 10 site, [Triche et al. \(2006\)](#) found respiratory symptoms to be associated with O₃ measured

1 at a site that for some subjects was located >100 miles away from home ([Figure 6-13](#) and
2 [Table 6-24](#)). Subjects included infants in Southwestern VA. Odds ratios were 46-73%
3 larger in the group who had mothers with asthma than among all infants ([Triche et al.,](#)
4 [2006](#)). Larger ORs were found for 24-h avg than 1-hour or 8-h max O₃ concentrations,
5 particularly for wheeze but less so for difficulty breathing. While these results suggested
6 that children with mothers with asthma may be at increased risk of O₃-related respiratory
7 morbidity, the authors acknowledged that mothers with asthma may be more likely to
8 report symptoms in their children. Additionally, transient wheeze, which is common in
9 infants, may not predict respiratory morbidity later in life. In another cohort of children
10 with parental history of asthma that was followed to an older age (5 years), increases in
11 ambient O₃ concentration (increment of effect estimate not reported) were not associated
12 with increases in respiratory symptoms ([Rodriguez et al., 2007](#)).

Adults

13 A cross-sectional study of 4,200 adult workers from 100 office buildings across the U.S.
14 found that multiple ambient O₃ metrics, including the 24-h, workday (8 a.m.-5 p.m.), and
15 late workday (3-6 p.m.) average, were associated with similar magnitudes of increase in
16 building-related symptoms ([Apte et al., 2008](#)). It should be noted that office workers
17 likely have a low personal-ambient O₃ correlation and ratio, thus the implications of these
18 findings compared to those of the other respiratory symptom studies are limited.

6.2.4.4 Confounding in Epidemiologic Studies of Respiratory Symptoms and Medication Use

19 Epidemiologic evidence does not indicate that confounding by meteorological factors or
20 copollutant exposures fully accounts for associations observed between short-term
21 increases in ambient O₃ concentration and respiratory symptoms and medication use.
22 Except where specified in the text, studies found O₃-associated increases in respiratory
23 symptoms or medication in statistical models that adjusted for temperature. [Thurston et](#)
24 [al. \(1997\)](#) found no independent association between temperature and respiratory
25 symptoms among children with asthma at summer camps. A few studies additionally
26 included humidity in models ([Triche et al., 2006](#); [Ross et al., 2002](#)).

27 Several studies that examined populations with a high prevalence of atopy found
28 O₃-associated increases in respiratory symptoms and asthma medication use with
29 adjustment for daily pollen counts ([Just et al., 2002](#); [Ross et al., 2002](#); [Gielen et al.,](#)
30 [1997](#)). [Gielen et al. \(1997\)](#) and [Ross et al. \(2002\)](#) examined populations with a high
31 prevalence of grass pollen allergy (52% and 38%, respectively). In a study conducted

1 over multiple seasons, [Ross et al. \(2002\)](#) found a similar magnitude of association
2 between O₃ and morning symptoms and medication use with adjustment for pollen
3 counts. [Feo Brito et al. \(2007\)](#) followed adults in central Spain specifically with asthma
4 and pollen allergy. In one city, O₃ was associated with an increase in the number of
5 subjects reporting symptoms. A smaller increase was estimated for pollen. Conversely, in
6 another city, pollen was associated with an increased reporting of respiratory symptoms,
7 whereas O₃ was not. The results suggested that O₃ and pollen may have independent
8 effects that vary by location, depending on the mix of ambient pollutants.

9 Results from copollutant models did not indicate strong confounding by copollutants
10 such as PM_{2.5}, PM₁₀, sulfate, SO₂, or NO₂ ([Table 6-25](#)). Notably, studies examined
11 different averaging times for O₃ (1-h max or 8-h avg) and copollutants (3-hour to
12 24-h avg) and reported a range of correlations between O₃ and copollutants, which may
13 complicate interpretation of copollutant model results. Information on potential
14 copollutant confounding of asthma medication use results was limited. The association
15 between O₃ and bronchodilator use did not change with adjustment for PM_{2.5} in [Gent et](#)
16 [al. \(2003\)](#) but decreased in magnitude with adjustment for 12-h avg sulfate in [Thurston et](#)
17 [al. \(1997\)](#). In [Thurston et al. \(1997\)](#) and [Gent et al. \(2003\)](#), 1-h max O₃ was highly
18 correlated with 12-h avg sulfate (r = 0.74) and 24-h avg PM_{2.5} (r = 0.77), respectively,
19 making it difficult to distinguish the independent effects of O₃. Studies conducted
20 concurrently in two areas of Mexico City examined 1-h max O₃ and 24-h avg PM₁₀ or
21 PM_{2.5} and found robust ORs for respiratory symptoms for both O₃ and PM ([Romieu et al.,](#)
22 [1997](#); [Romieu et al., 1996](#)). [Romieu et al. \(1997\)](#) reported a moderate correlation between
23 1-h max O₃ and 24-h avg PM₁₀ (r = 0.47). Associations between O₃ and respiratory
24 symptoms were observed in NCICAS in copollutant models with SO₂, NO₂, or PM₁₀,
25 which were examined with different averaging times and lags than was O₃ ([Mortimer et](#)
26 [al., 2002](#)) ([Table 6-25](#)). Also difficult are interpretations of the O₃-associated increases in
27 respiratory symptoms found with adjustment for two copollutants in the same model
28 (i.e., PM_{2.5} plus NO₂ or PM_{10-2.5}) ([Escamilla-Núñez et al., 2008](#); [Triche et al., 2006](#)).

Table 6-25 Associations between ambient ozone concentrations and respiratory symptoms in single- and co-pollutant models.

| Study | Location/Population | O ₃ Metrics | Symptom | OR for O ₃ in Single-Pollutant Model (95% CI) ^a | OR for O ₃ in Copollutant Model (95% CI) ^a |
|--|--|--------------------------|----------------------------|---|--|
| Mortimer et al. (2002) | Bronx, East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI, Cleveland, OH; Chicago, IL; St. Louis, MO 846 children with asthma, ages 4-9 yr | 8-h avg (10 a.m.-6 p.m.) | Morning symptoms | 8 cities with SO ₂ data 1.35 (1.04, 1.74) | With lag 1-2 avg, 3-h avg SO ₂ 1.23 (0.94, 1.61) |
| | | Lag 1-4 avg | | 7 cities with NO ₂ data 1.25 (0.94, 1.67) | With lag 1-6 avg, 24-h avg NO ₂ 1.14 (0.85, 1.55) |
| | | | | 3 cities with PM ₁₀ data 1.21 (0.61, 2.41) | With lag 1-2 avg, 24-h avg PM ₁₀ 1.08 (0.49, 2.39) |
| Thurston et al. (1997) | CT River Valley 166 children with asthma, ages 7-13 yr | 1-h max | Chest symptoms | 1.21 (1.12, 1.31) ^b | With lag 0, 12-h avg sulfate 1.19 (1.06, 1.35) ^b |
| | | Lag 0 | Beta-agonist use | 1.20 (1.09, 1.32) ^b | With lag 0, 12-h avg sulfate 1.07 (0.92, 1.24) ^b |
| Romieu et al. (1996) | Mexico City, Mexico 71 children with asthma, ages 5-7 yr | 1-h max Lag 0 | Lower respiratory symptoms | 1.07 (1.02, 1.12) | With lag 0, 24-h avg PM _{2.5} 1.06 (1.02, 1.10) |
| Romieu et al. (1997) | Mexico City, Mexico 65 children with asthma, ages 5-13 yr | 1-h max Lag 0 | Lower respiratory symptoms | 1.09 (1.04, 1.14) | With lag 0, 24-h avg PM ₁₀ 1.09 (1.01, 1.19) |

Results generally are presented in order of increasing mean ambient O₃ concentration.

^aORs are standardized to a 40- and 30-ppb increase for 1-h max and 8-h avg O₃, respectively.

^bTemperature not included in models.

6.2.4.5 Summary of Epidemiologic Studies of Respiratory Symptoms and Asthma Medication Use

1 Comprising a majority of available evidence, single-city and -region epidemiologic
2 studies provide consistent evidence for the effects of short-term increases in ambient O₃
3 exposure on increasing respiratory symptoms and asthma medication use in children with
4 asthma ([Figure 6-11](#) and [Figure 6-12](#) and [Table 6-20](#) and [Table 6-21](#)). Evidence from the
5 few available U.S. multicity studies is less consistent ([O'Connor et al., 2008](#); [Schildcrout](#)
6 [et al., 2006](#); [Mortimer et al., 2002](#)). Findings from a small body of studies indicate
7 O₃-associated increases in respiratory symptoms in adults with asthma. Associations
8 between short-term increases in ambient O₃ concentration and reduced activity in
9 children or adults with asthma are not clearly demonstrated. While O₃-associated
10 increases in school absenteeism were found in children with asthma, evidence for
11 respiratory-related absences and for O₃ exposure lag periods shorter than 14 days is
12 sparse. Short-term increases in ambient O₃ concentration were not consistently associated

1 with increases in respiratory symptoms in groups comprising children with and without
2 asthma.

3 Increases in respiratory symptoms and medication use were associated with increases in
4 ambient O₃ concentration assigned to subjects using various methods. Associations were
5 found with methods likely to represent better ambient exposures, including O₃ measured
6 on site and at the time of children's outdoor activity ([Thurston et al., 1997](#)) and
7 concentrations weighted by time spent outdoors ([Neas et al., 1995](#)). However,
8 associations also were found with methods that varied in their representation of ambient
9 exposures and spatial variability in ambient concentrations, i.e., concentrations averaged
10 among subjects' locations each hour ([Khatri et al., 2009](#)), measured within 5 km of
11 schools or homes ([Escamilla-Nuñez et al., 2008](#); [Romieu et al., 2006](#); [1997](#); [1996](#)),
12 averaged across multiple sites ([Feo Brito et al., 2007](#); [Gent et al., 2003](#); [Mortimer et al.,](#)
13 [2002](#)), and measured at a single site ([Ross et al., 2002](#); [Gielen et al., 1997](#)).

14 Associations with respiratory symptoms were demonstrated most frequently for 1-h max
15 and 8-h max or avg O₃, and within-study comparisons indicated similar ORs for 1-h max
16 and 8-h max O₃ ([Delfino et al., 2003](#); [Gent et al., 2003](#)). Respiratory symptoms also were
17 associated with 12-hour and 24-h avg O₃ ([Jalaludin et al., 2004](#); [Gold et al., 1999](#); [Neas et](#)
18 [al., 1995](#)). Epidemiologic studies examined respiratory symptoms associated with O₃
19 concentrations lagged 0 to 5 days and those averaged over 2 to 19 days. While O₃ at lags
20 0 or 1 were consistently associated with respiratory symptoms, several studies found
21 larger ORs for multiday averages (3- to 6-day) of O₃ ([Escamilla-Nuñez et al., 2008](#);
22 [Romieu et al., 2006](#); [Just et al., 2002](#); [Mortimer et al., 2002](#); [Ross et al., 2002](#)).

23 Epidemiologic findings for lagged or multiday average O₃ are supported by evidence that
24 O₃ sensitizes bronchial smooth muscle to hyperreactivity and thus acts as a primer for
25 subsequent exposure to antigens such as allergens (Section [5.3.5](#)). Many studies
26 examined populations with asthma with a high prevalence of atopy (52-100%). In these
27 populations, sensitization of airways provides a biologically plausible mode of action by
28 which increases in respiratory symptoms result from increases in O₃ exposure after a lag
29 or accumulated over several days. Further support is provided by findings that airway
30 hyperresponsiveness (Section [6.2.2.1](#)) and some indicators of inflammation
31 (Section [6.2.3.1](#)) remained elevated following repeated O₃ exposures in controlled human
32 exposure studies and by observations from epidemiologic studies that increases in
33 pulmonary inflammation were associated with multiday average O₃ concentrations
34 (Section [6.2.3.2](#)).

35 There is not strong evidence that O₃-associated increases in respiratory symptoms are
36 confounded by temperature, pollen, or copollutants. In limited analysis, ambient O₃ was
37 associated with respiratory symptoms with adjustment for copollutants, primarily PM.

1 However, identifying the independent effects of O₃ in some studies was complicated due
2 to the high correlations observed between O₃ and PM or different lags and averaging
3 times examined for copollutants. Nonetheless, the consistency of associations among
4 individuals with asthma with and without adjustment for ambient copollutant
5 concentrations combined with findings from controlled human exposure studies for the
6 direct effect of O₃ exposure provide substantial evidence for the independent effects of
7 short-term ambient O₃ exposure on increasing respiratory symptoms.

6.2.5 Lung Host Defenses

8 The mammalian respiratory tract has a number of closely integrated defense mechanisms
9 that, when functioning normally, provide protection from the potential health effects
10 attributed to exposure to a wide variety of inhaled particles and microbes. For simplicity,
11 these interrelated defenses can be divided into two major parts: (1) nonspecific (transport,
12 phagocytosis, and bactericidal activity) and (2) specific (immunologic) defense
13 mechanisms. A variety of sensitive and reliable methods have been used to assess the
14 effects of O₃ on these components of the lung's defense system to provide a better
15 understanding of the health effects associated with the inhalation of this pollutant. The
16 previous O₃ AQCD stated that animal toxicological studies provide extensive evidence
17 that acute O₃ exposures as low as 0.08 to 0.5 ppm can cause increases in susceptibility to
18 infectious diseases due to modulation of lung host defenses. Table 6-6 through Table 6-9
19 ([U.S. EPA, 1996g, h, i, j](#)) beginning on page 6-41 of the 1996 O₃ AQCD ([U.S. EPA,
20 1996a](#)), and Table AX5-7 ([U.S. EPA, 2006c](#)), beginning on page AX5-8 of the 2006 O₃
21 AQCD ([U.S. EPA, 2006b](#)), present studies on the effects of O₃ on host defense
22 mechanisms. This section discusses the various components of host defenses, such as the
23 mucociliary escalator, the phagocytic, bactericidal, and regulatory role of the alveolar
24 macrophages (AMs), the adaptive immune system, and integrated mechanisms that are
25 studied by investigating the host's response to experimental pulmonary infections.

6.2.5.1 Mucociliary Clearance

26 The mucociliary system is one of the lung's primary defense mechanisms. It protects the
27 conducting airways by trapping and quickly removing material that has been deposited or
28 is being cleared from the alveolar region by migrating alveolar macrophages. Ciliary
29 movement directs particles trapped on the overlying mucous layer toward the pharynx,
30 where the mucus is swallowed or expectorated.

1 The effectiveness of mucociliary clearance can be determined by measuring such
2 biological activities as the rate of transport of deposited particles; the frequency of ciliary
3 beating; structural integrity of the ciliated cells; and the size, number, and distribution of
4 mucus-secreting cells. Once this defense mechanism has been altered, a buildup of both
5 viable and nonviable inhaled substances can occur on the epithelium and may jeopardize
6 the health of the host, depending on the nature of the uncleared substance. Impaired
7 mucociliary clearance can result in an unwanted accumulation of cellular secretions,
8 increased infections, chronic bronchitis, and complications associated with COPD. A
9 number of previous studies with various animal species have examined the effect of O₃
10 exposure on mucociliary clearance and reported morphological damage to the cells of the
11 tracheobronchial tree from acute and sub-chronic exposure to O₃ 0.2 ppm and higher. The
12 cilia were either completely absent or had become noticeably shorter or blunt. After
13 placing these animals in a clean-air environment, the structurally damaged cilia
14 regenerated and appeared normal ([U.S. EPA, 1986](#)). Based on such morphological
15 observations, related effects such as ciliostasis, increased mucus secretions, and a slowing
16 of mucociliary transport rates might be expected. However, no measurable changes in
17 ciliary beating activity have been reported due to O₃ exposure alone. Essentially no data
18 are available on the effects of prolonged exposure to O₃ on ciliary functional activity or
19 on mucociliary transport rates measured in the intact animal. In general, functional
20 studies of mucociliary transport have observed a delay in particle clearance soon after
21 acute exposure. Decreased clearance is more evident at higher doses (1 ppm), and there is
22 some evidence of attenuation of these effects ([U.S. EPA, 1986](#)). However, no recent
23 studies have evaluated the effects of O₃ on mucociliary clearance.

6.2.5.2 Alveolobronchiolar Transport Mechanism

24 In addition to the transport of particles deposited on the mucous surface layer of the
25 conducting airways, particles deposited in the deep lung may be removed either up the
26 respiratory tract or through interstitial pathways to the lymphatic system. The pivotal
27 mechanism of alveolobronchiolar transport involves the movement of AMs with
28 phagocytized particles to the bottom of the mucociliary escalator. Failure of the AMs to
29 phagocytize and sequester the deposited particles from the vulnerable respiratory
30 membrane can lead to particle entry into the interstitial spaces. Once lodged in the
31 interstitium, particle removal is more difficult and, depending on the toxic or infectious
32 nature of the particle, its interstitial location may allow the particle to set up a focus for
33 pathologic processes. Although some studies show reduced early (tracheobronchial)
34 clearance after O₃ exposure, late (alveolar) clearance of deposited material is accelerated,

1 presumably due to macrophage influx (which in itself can be damaging due to proteases
2 and oxidative reactions in these cells).

6.2.5.3 Alveolar Macrophages

3 Within the gaseous exchange region of the lung, the first line of defense against
4 microorganisms and nonviable particles that reach the alveolar surface is the AM. This
5 resident phagocyte is responsible for a variety of activities, including the detoxification
6 and removal of inhaled particles, maintenance of pulmonary sterility via destruction of
7 microorganisms, and interaction with lymphocytes for immunologic protection. Under
8 normal conditions, AMs seek out particles deposited on the alveolar surface and ingest
9 them, thereby sequestering the particles from the vulnerable respiratory membrane. To
10 adequately fulfill their defense function, the AMs must maintain active mobility, a high
11 degree of phagocytic activity, and an optimally functioning biochemical and enzyme
12 system for bactericidal activity and degradation of ingested material. As discussed in
13 previous AQCDs, short periods of O₃ exposure can cause a reduction in the number of
14 free AMs available for pulmonary defense, and these AMs are more fragile, less
15 phagocytic, and have decreased lysosomal enzyme activities required for killing
16 pathogens. For example, in results from earlier work in rabbits, a 2-hour exposure to
17 0.1 ppm O₃ inhibited phagocytosis and a 3-hour exposure to 0.25 ppm decreased
18 lysosomal enzyme activities ([Driscoll et al., 1987](#); [Hurst et al., 1970](#)). Similarly, AMs
19 from rats exposed to 0.1 ppm O₃ for 1 or 3 weeks exhibited reduced hydrogen peroxide
20 production ([Cohen et al., 2002](#)). A controlled human exposure study reported decrements
21 in the ability of alveolar macrophages to phagocytize yeast following exposure of healthy
22 volunteers to 80 to 100 ppb O₃ for 6.6-hour during moderate exercise ([Devlin et al.,](#)
23 [1991](#)). Although the percentage of phagocytosis-capable macrophages was unchanged by
24 O₃ exposure, the number of yeast engulfed was reduced when phagocytosis was
25 complement-dependent. However, there was no difference in the ability of macrophages
26 to produce superoxide anion after O₃ exposure. These results are consistent with those
27 from another controlled human exposure study in which no changes in the level of
28 lysosomal enzymes or superoxide anion production were observed in macrophages
29 lavaged from healthy human subjects exposed to 400 ppb O₃ for 2 hours with heavy
30 intermittent exercise ([Koren et al., 1989](#)). More recently, [Lay et al. \(2007\)](#) observed no
31 difference in phagocytic activity or oxidative burst capacity in macrophages or
32 monocytes from sputum or blood collected from healthy volunteers after a 2-hour
33 exposure to 400 ppb O₃ with moderate intermittent exercise. However, another study
34 found that oxidative burst and phagocytic activity in macrophages increased in GSTM1
35 null subjects compared to GSTM1 positive subjects, who had relatively unchanged

1 macrophage function parameters after an O₃ exposure identical to that of Lay et al.
2 described above ([Alexis et al., 2009](#)). Collectively, these studies demonstrate that O₃ can
3 affect multiple steps or aspects required for proper macrophage function, but any C-R
4 relationship appears complex and genotype may be a consideration. A few other recent
5 studies have evaluated the effects of O₃ on macrophage function, but these are of
6 questionable relevance due to the use of in vitro exposure systems and amphibian animal
7 models ([Mikerov et al., 2008c](#); [Dohm et al., 2005](#); [Klestadt et al., 2005](#)).

6.2.5.4 Infection and Adaptive Immunity

General Effects on the Immune System

8 The effects of O₃ on the immune system are complex and dependent on the exposure
9 regimen and the observation period. According to toxicological studies it appears that the
10 T-cell-dependent functions of the immune system are more affected than B-cell-
11 dependent functions ([U.S. EPA, 2006b](#)). Generally, there is an early immunosuppressive
12 effect that subsides with continued O₃ exposure, resulting in either a return to normal
13 responses or an enhancement of immune responses. However, this is not always the case
14 as Aranyi et al. [Aranyi et al. \(1983\)](#) showed decreased T-cell mitogen reactions in mice
15 after subchronic (90-day) exposure to 0.1 ppm O₃. Earlier studies report changes in cell
16 populations in lymphatic tissues ([U.S. EPA, 2006b](#)). A more recent study in mice
17 demonstrated that numbers of certain T-cell subsets in the spleen were reduced after
18 exposure to 0.6 ppm O₃ (10h/day x 15d) ([Feng et al., 2006](#)).

19 The inflammatory effects of O₃ involve the innate immune system, and as such, O₃ can
20 affect adaptive (or acquired) immunity via alterations in antigen presentation and
21 costimulation by innate immune cells such as macrophages and dendritic cells. Several
22 recent controlled human exposure studies demonstrate increased expression of molecules
23 involved in antigen presentation or costimulation. [Lay et al. \(2007\)](#) collected sputum
24 monocytes from healthy volunteers exposed to 400 ppb O₃ for 2 hours with moderate
25 intermittent exercise and detected increases in HLA-DR, used to present antigen to
26 T-cells, and CD86, a costimulatory marker necessary for T-cell activation. Upregulation
27 of HLA-DR was also observed by [Alexis et al. \(2009\)](#) in sputum dendritic cells and
28 macrophages from GSTM1 null subjects exposed to 400 ppb O₃ for 2 hours with
29 moderate intermittent exercise. On airway monocytes from healthy volunteers 24 hours
30 after exposure to 80 ppb O₃ for 6.6 hours with moderate intermittent exercise, HLA-DR,
31 CD86, and CD14 (a molecule involved in bacterial endotoxin reactivity) were increased,
32 whereas CD80, a costimulatory molecule of more heterogeneous function, was decreased
33 ([Alexis et al., 2010](#)). Patterns of expression on macrophages were similar, except that

1 HLA-DR was found to be significantly decreased after O₃ exposure and CD86 was not
2 significantly altered. An increase in IL-12p70, a macrophage and dendritic cell product
3 that activates T-cells, was correlated with increased numbers of dendritic cells. It should
4 be noted that these results are reported as comparisons to baseline as there was no clean
5 air control ([Alexis et al., 2010](#); [Alexis et al., 2009](#)). Another controlled human exposure
6 study reported no increase in IL-12p70 in sputum from healthy, atopic, or atopic
7 asthmatic subjects following a 2-hour exposure to 400 ppb O₃ with intermittent moderate
8 exercise ([Hernandez et al., 2010](#)). Levels of HLA-DR, CD14 and CD86 were not
9 increased on macrophages collected from any of these subjects. It is difficult to compare
10 these results to those of [Lay et al. \(2007\)](#) and [Alexis et al. \(2010\)](#) due to differences in O₃
11 concentration, cell type examined, and timing of postexposure analysis.

12 Although no controlled human exposure studies have examined the effects of O₃ on the
13 ability to mount antigen-specific responses, upregulation of markers associated with
14 innate immune activation and antigen presentation could potentially enhance adaptive
15 immunity and increase immunologic responses to antigen. While this may bolster
16 defenses against infection, it also may enhance allergic responses (Section [6.2.6](#)).

17 In animal models, O₃ has been found to alter responses to antigenic stimulation. For
18 example, antibody responses to a T-cell-dependent antigen were suppressed after a
19 56-day exposure of mice to 0.8 ppm O₃, and a 14-day exposure to 0.5 ppm O₃ decreased
20 the antiviral antibody response following influenza virus infection ([Jakab and Hmieleski,
21 1988](#)); the latter impairment may pave the way for lowered resistance to re-infection. The
22 immune response is highly influenced by the temporal relationship between O₃ exposure
23 and antigenic stimulation. When O₃ exposure preceded *Listeria* infection, there were no
24 effects on delayed-type hypersensitivity or splenic lymphoproliferative responses;
25 however, when O₃ exposure occurred during or after *Listeria* infection was initiated,
26 these immune responses were suppressed ([Van Loveren et al., 1988](#)). In another study, a
27 reduction in mitogen activated T-cell proliferation was observed after exposure to
28 0.6 ppm O₃ for 15 days that could be ameliorated by antioxidant supplementation.
29 Antigen-specific proliferation decreased by 60%, indicating attenuation of the acquired
30 immunity needed for subsequent memory responses ([Feng et al., 2006](#)). O₃ exposure also
31 skewed the ex-vivo cytokine responses elicited by non-specific stimulation toward
32 inflammation, decreasing IL-2 and increasing IFN- γ . Modest decreases in immune
33 function assessed in the offspring of O₃-exposed dams (mice) were observed by [Sharkhuu
34 et al. \(2011\)](#). The ability to mount delayed-type hypersensitivity responses was
35 significantly suppressed in 42 day-old offspring when dams were exposed to 0.8 or
36 1.2 ppm O₃, but not 0.4 ppm, from gestational day 9-18. Humoral responses to
37 immunization with sheep red blood cells were unaffected, as were other immune
38 parameters such as splenic populations of CD45+ T-cells, iNKT-cells, and levels of IFN-

1 γ , IL-4, and IL-17 in the BALF. Generally, continuous exposure to O₃ impairs immune
2 responses for the first several days of exposure, followed by an adaptation to O₃ that
3 allows a return of normal immune responses. Most species show little effect of O₃
4 exposures prior to immunization, but show a suppression of responses to antigen in O₃
5 exposures post-immunization.

Microbial Infection

Bacterial infection

6 A relatively large body of evidence shows that O₃ increases susceptibility to bacterial
7 infections. The majority of studies in this area were conducted before the 1996 O₃ AQCD
8 was published and many are included in Table 6-9 ([U.S. EPA, 1996j](#)) on page 6-53 of
9 that document. Known contributing factors are impaired mucociliary streaming, altered
10 chemotaxis/motility, defective phagocytosis of bacteria, decreased production of
11 lysosomal enzymes or superoxide radicals by alveolar macrophages, and decreased IFN- γ
12 levels. In animal models of bacterial infection, exposure to 0.08 ppm O₃ increases
13 streptococcus-induced mortality, regardless of whether O₃ exposure precedes or follows
14 infection ([Miller et al., 1978](#); [Coffin and Gardner, 1972](#); [Coffin et al., 1967](#)). Increases in
15 mortality are due to the infectious agent, thereby reflecting functional impairment of host
16 defenses. Exercise and copollutants can enhance the effects of O₃ in infectivity models.
17 Although both mice and rats exhibit impaired bactericidal macrophage activity after O₃
18 exposure, mortality due to infection is only observed in mice. Additionally, although
19 mice and humans share many host defense mechanisms, there is little compelling
20 evidence from epidemiologic studies to suggest an association between O₃ exposure and
21 decreased resistance to bacterial infection, and the etiology of respiratory infections is not
22 easily identified via ICD codes (Section [6.2.7.3](#)).

Viral infection

23 Only a few studies, described in previous AQCDs, have examined the effects of O₃
24 exposure on the outcome of viral respiratory infection [see Table 6-9 on page 6-53 of the
25 1996 O₃ AQCD ([U.S. EPA, 1996j](#))]. Some studies show increased mortality, while others
26 show diminished severity and increased survival time. There is little to no evidence from
27 studies of animals or humans to suggest that O₃ increases the incidence of respiratory
28 viral infection in humans. In human volunteers infected with rhinovirus prior to O₃
29 exposure (0.3 ppm for 5 consecutive days), no effect on viral titers, IFN- γ production, or
30 blood lymphocyte proliferative responses to viral antigen was observed ([Henderson et al.,
31 1988](#)). In vitro cell culture studies of human bronchial epithelial cells indicate O₃-induced
32 exacerbation of human rhinovirus infection ([Spannhake et al., 2002](#)), but this is of limited
33 relevance. More recent studies on the interactions of O₃ and viral infections have not been

1 published. Natural killer (NK) cells, which destroy virally infected cells and tumors in the
2 lung, appear to be inhibited by higher concentrations of O₃ and either unaffected or
3 stimulated at lower concentrations. Several studies show decreases in NK cell activity
4 following acute exposures ranging from 0.8 to 1 ppm ([Gilmour and Jakab, 1991](#); [Van
5 Loveren et al., 1990](#); [Burlleson et al., 1989](#)). However, [Van Loveren et al. \(1990\)](#) showed
6 that a 1-week exposure to 0.2 or 0.4 ppm O₃ increased NK cell activity, and an urban
7 pattern of exposure (base of 0.06 ppm with peaks of 0.25 ppm) had no effect on NK cell
8 activity after 1, 3, 13, 52, or 78 weeks of exposure ([Selgrade et al., 1990](#)). A more recent
9 study demonstrated a 35% reduction in NK cell activity after exposure of mice to
10 0.6 ppm O₃ (10h/day x 15d) ([Feng et al., 2006](#)). The defective IL-2 production
11 demonstrated in this study may impair NK cell activation. Alternatively, NK cell surface
12 charge may be altered by ROS, decreasing their adherence to target cells ([Nakamura and
13 Matsunaga, 1998](#)).

6.2.5.5 Summary of Lung Host Defenses

14 Taken as a whole, the data clearly indicate that an acute O₃ exposure impairs the host
15 defense capability of animals, primarily by depressing AM function and perhaps also by
16 decreasing mucociliary clearance of inhaled particles and microorganisms. Coupled with
17 limited evidence from controlled human exposure studies, this suggests that humans
18 exposed to O₃ could be predisposed to bacterial infections in the lower respiratory tract.
19 The seriousness of such infections may depend on how quickly bacteria develop
20 virulence factors and how rapidly PMNs are mobilized to compensate for the deficit in
21 AM function. It remains unclear how O₃ might affect antigen presentation and the
22 costimulation required for T-cell activation, given the mixed results from controlled
23 human exposure studies, but there is toxicological evidence for suppression of T-cell-
24 dependent functions by O₃, including reductions in antigen-specific proliferation and
25 antibody production, indicating the potential for impaired acquired immunity and
26 memory responses. To date, a limited number of epidemiologic studies have examined
27 associations between O₃ exposure and hospital admissions or ED visits for respiratory
28 infection, pneumonia, or influenza. Results have been mixed, and in some cases
29 conflicting (see Section [6.2.7.2](#) and Section [6.2.7.3](#)). With the exception of influenza, it is
30 difficult to ascertain whether cases of respiratory infection or pneumonia are of viral or
31 bacterial etiology. A study that examined the association between O₃ exposure and
32 respiratory hospital admissions in response to an increase in influenza intensity did
33 observe an increase in respiratory hospital admissions ([Wong et al., 2009](#)), but
34 information from toxicological studies of O₃ and viral infections is ambiguous.

6.2.6 Allergic and Asthma-Related Responses

1 Effects resulting from combined exposures to O₃ and allergens have been studied in a
2 variety of animal species, generally as models of experimental asthma. Pulmonary
3 function and airways hyperresponsiveness in animal models of asthma are discussed in
4 Section [6.2.1.3](#) and Section [6.2.2.2](#). Previous evidence indicates that O₃ exposure skews
5 immune responses toward an allergic phenotype. For example, [Gershwin et al. \(1981\)](#)
6 reported that O₃ (0.8 and 0.5 ppm for 4 days) exposure caused a 34-fold increase in the
7 number of IgE (allergic antibody)-containing cells in the lungs of mice. In general, the
8 number of IgE-containing cells correlated positively with levels of anaphylactic
9 sensitivity. In humans, allergic rhinoconjunctivitis symptoms are associated with
10 increases in ambient O₃ concentrations ([Riediker et al., 2001](#)). Recent controlled human
11 exposure studies have observed O₃-induced changes indicating allergic skewing. Airway
12 eosinophils, which participate in allergic disease and inflammation, were observed to
13 increase in atopic, mildly asthmatic volunteers 18 hours following a 7.6-hour exposure to
14 160 ppb O₃ with light intermittent exercise ([Peden et al., 1997](#)). No increase in airway
15 eosinophils was observed 4 hours after exposure of healthy, atopic, or atopic asthmatic
16 subjects to 400 ppb O₃ for 2 hours with moderate intermittent exercise ([Hernandez et al.,
17 2010](#)). However, atopic subjects did exhibit increased IL-5, a cytokine involved in
18 eosinophil recruitment and activation, suggesting that perhaps these two studies observed
19 the same effect at different time points. Epidemiologic studies discussed in Section [7.2.5](#)
20 describe an association between eosinophils and long-term O₃ exposure, consistent with
21 chronic exposure studies in non-human primates. [Hernandez et al. \(2010\)](#) also observed
22 increased expression of high and low affinity IgE receptors on sputum macrophages from
23 atopic asthmatics, which may enhance IgE-dependent inflammation. Sputum levels of
24 IL-4 and IL-13, both pro-allergic cytokines that aid in the production of IgE, were
25 unaltered in all groups. The lack of increase in IL-4 levels in sputum reported by
26 [Hernandez et al. \(2010\)](#), along with increased IL-5, is consistent with results from [Bosson
27 et al. \(2003\)](#), in which IL-5 (but not IL-4 levels) increased in bronchial epithelial biopsy
28 specimens following exposure of mild atopic asthmatics to 200 ppb O₃ for 2 hours with
29 moderate intermittent exercise. IL-5 was not elevated in specimens obtained from healthy
30 (non-asthmatic) O₃-exposed subjects. Collectively, findings from these studies suggest
31 that O₃ can induce or enhance certain components of allergic inflammation in atopic and
32 atopic asthmatic individuals.

33 Ozone enhances inflammatory and allergic responses to allergen challenge in sensitized
34 animals. Short-term exposure (2 days) to 1 ppm O₃ exacerbated allergic rhinitis and lower
35 airway allergic inflammation in Brown Norway rats, a rat strain that is comparatively less
36 sensitive to O₃ than other rats or humans ([Wagner et al., 2009; 2007](#)). OVA-sensitized
37 rats were intranasally challenged with OVA on days 1 and 2, and exposed to 0 or 1 ppm

1 O₃ (8 h/day) on days 4 and 5. Analysis at day 6 indicated that O₃ exposure enhanced
2 intraepithelial mucosubstances in the nose and airways, induced cys-LTs, MCP-1, and
3 IL-6 production in BALF, and upregulated expression of the proallergic cytokines IL-5
4 and IL-13. These changes were not evident in non-allergic controls. All of these
5 responses were blunted by gamma-tocopherol (γ T; vitamin E) therapy. γ T neutralizes
6 oxidized lipid radicals, and protects lipids and proteins from nitrosative damage from
7 NO-derived metabolites. [Farraj et al. \(2010\)](#) exposed allergen-sensitized adult male
8 BALB/c mice to 0.5 ppm O₃ for 5 hours once per week for 4 weeks. Ozone exposure and
9 O₃/DEP (2.0 mg/m³) co-exposure of OVA-sensitized mice elicited significantly greater
10 serum IgE levels than in DEP-exposed OVA-sensitized mice (98% and 89% increases,
11 respectively). Ozone slightly enhanced levels of BAL IL-5, but despite increases in IgE,
12 caused a significant decrease in BAL IL-4 levels. IL-10, IL-13, and IFN- γ levels were
13 unaffected. Lung resistance and elastance were unaffected in allergen sensitized mice
14 exposed solely to 0.5 ppm O₃ once a week for 4 weeks ([Farraj et al., 2010](#)). However,
15 co-exposure to O₃ and diesel exhaust particles increased lung resistance.

16 In addition to exacerbating existing allergic responses, O₃ can also act as an adjuvant to
17 produce sensitization in the respiratory tract. In a model of murine asthma, using OVA
18 free of detectable endotoxin, inclusion of 1 ppm O₃ during the initial exposures to OVA
19 (2 h, days 1 and 6) enhanced the inflammatory and allergic responses to subsequent
20 allergen challenge ([Hollingsworth et al., 2010](#)). Compared to air exposed animals,
21 O₃-exposed mice exhibited significantly higher levels of total cells, macrophages,
22 eosinophils, and PMNs in BALF, and increased total serum IgE. Pro-allergic cytokines
23 IL-4, and IL-5 were also significantly elevated, along with pleiotropic Th2 cytokine IL-9
24 (associated with bronchial hyperresponsiveness) and pro-inflammatory IL-17, produced
25 by activated T-cells. Based on lower inflammatory, IgE, and cytokine responses in
26 Toll-like receptor 4 deficient mice, the effects of O₃ seem to be dependent on TLR 4
27 signaling, as are a number of other biological responses to O₃ according to studies by
28 [Hollingsworth et al. \(2004\)](#), [Kleeberger et al. \(2000\)](#) and [Garantziotis et al. \(2010\)](#). The
29 involvement of TLR 4, along with its endogenous ligand, hyaluronan, in O₃-induced
30 responses described in these studies has been corroborated by a controlled human
31 exposure study by [Hernandez et al. \(2010\)](#), who found increased TLR 4 expression and
32 elevated levels of hyaluronic acid in atopic and atopic asthmatic volunteers exposed to
33 400 ppb O₃. This pathway is discussed in more detail in Chapter 5. Examination of
34 dendritic cells (DCs) from the draining thoracic lymph nodes indicated that O₃ did not
35 enhance the migration of DCs from the lungs to the lymph nodes, nor did it alter the
36 expression of functional DC markers such as CD40, MHC class II, or CD83. However,
37 O₃ did increase expression of CD86, which is generally associated with Th2 responses
38 and is detected at higher levels on DCs from allergic asthmatics compared to those from
39 healthy donors [Chen et al. \(2006b\)](#). Increased CD86 has also been observed on airway

1 cells collected from human subjects following exposure to O₃ in studies by [Lay et al.](#)
2 [\(2007\)](#) and [Alexis et al. \(2009\)](#), but not [Hernandez et al. \(2010\)](#) (study details described
3 in Section [6.2.5.4](#)).

4 Ozone exposure during gestation has modest effects on allergy and asthma related
5 endpoints in adult offspring. When dams were exposed to 1.2 ppm O₃ (but not 0.8 ppm)
6 from gestational day 9-18, some allergic and inflammatory responses to OVA
7 sensitization and challenge were reduced compared to air exposed controls. This included
8 IgE levels and eosinophils, and was only true of mice that were immunized early in life
9 (PND 3) as opposed to later (PND 42), perhaps due to the proximity of O₃ and antigen
10 exposure. The effects of gestational O₃ exposure on immune function have not been
11 widely studied, and although reductions in allergic endpoints are not generally observed
12 in association with O₃, other parameters of immune function were found to be reduced, so
13 a more global immunosuppression may underlie these effects.

14 In addition to pro-allergic effects, O₃ could also make airborne allergens more allergenic.
15 When combined with NO₂, O₃ has been shown to enhance nitration of common protein
16 allergens, which may increase their allergenicity [Franze et al. \(2005\)](#).

6.2.7 Hospital Admissions, Emergency Department Visits, and Physicians Visits

6.2.7.1 Summary of Findings from 2006 Ozone AQCD

17 The 2006 O₃ AQCD evaluated numerous respiratory ED visits and hospital admissions
18 studies, which consisted primarily of time-series studies conducted in the U.S., Canada,
19 Europe, South America, Australia and Asia. Upon collectively evaluating the scientific
20 evidence, the 2006 O₃ AQCD concluded that “the overall evidence supports a causal
21 relationship between acute ambient O₃ exposures and increased respiratory morbidity
22 resulting in increased ED visits and [hospital admissions] during the warm season” [U.S.](#)
23 [EPA \(2006b\)](#). This conclusion was “strongly supported by the human clinical, animal
24 toxicologic[al], and epidemiologic evidence for [O₃-induced] lung function decrements,
25 increased respiratory symptoms, airway inflammation, and airway hyperreactivity” [U.S.](#)
26 [EPA \(2006b\)](#).

27 Since the completion of the 2006 O₃ AQCD, relatively fewer studies conducted in the
28 U.S., Canada, and Europe have examined the association between short-term exposure to
29 ambient O₃ and respiratory hospital admissions and ED visits with a growing number of
30 studies having been conducted in Asia. This section focuses primarily on multicity

1 studies because they examine the effect of O₃ on respiratory-related hospital admissions
2 and ED visits over a large geographic area using a consistent statistical methodology.
3 Single-city studies that encompass a large number of hospital admissions or ED visits, or
4 included a long study-duration were also evaluated because these studies have more
5 power to detect whether an association exists between short-term O₃ exposure and
6 respiratory hospital admissions and ED visits compared to smaller single-city studies.
7 Additional single-city studies were also evaluated within this section, if they were
8 conducted in locations not represented by the larger single-city and multicity studies, or
9 examined population-specific characteristics not included in the larger studies that may
10 modify the association between short-term O₃ exposure and respiratory-related hospital
11 admissions or ED visits. The remaining single-city studies identified were not evaluated
12 in this section due to factors such as inadequate study design or insufficient sample size.

13 It should be mentioned that when examining the association between short-term O₃
14 exposure and respiratory health effects that require medical attention, it is important to
15 distinguish between hospital admissions and ED visits. This is because it is likely that a
16 small percentage of respiratory ED visits will be admitted to the hospital; therefore,
17 respiratory ED visits may represent potentially less serious, but more common outcomes.
18 As a result, in the following sections respiratory hospital admission and ED visit studies
19 are evaluated individually. Additionally, within each section, results are presented as
20 either a collection of respiratory diagnoses or as individual diseases (e.g., asthma, COPD,
21 pneumonia and other respiratory infections) in order to evaluate the potential effect of
22 short-term O₃ exposure on each respiratory-related outcome. The ICD codes (i.e., ICD-9
23 or ICD-10) that encompass each of these endpoints are presented in [Table 6-26](#) along
24 with the air quality characteristics of the city, or across all cities, included in each study
25 evaluated in this section.

Table 6-26 Mean and upper percentile concentrations of respiratory-related hospital admission and emergency department (ED) visit studies evaluated

| Study | Location | Type of Visit (ICD9/10) | Averaging Time | Mean Concentration (ppb) ^a | Upper Percentile Concentrations (ppb) ^a |
|--|---|--|----------------------|---|--|
| Katsouyanni et al. (2009) ^{b,c} | 90 U.S. cities (NMMAPS) ^d 32 European cities (APHEA) ^d 12 Canadian cities | Hospital Admissions: NMMAPS: All respiratory (460-519) APHEA: All respiratory (460-519) 12 Canadian cities: All respiratory (460-519) ^e | 1-h max | NMMAPS: 50th: 34.9-60.0 APHEA: 50th: 11.0-38.1 12 Canadian cities: 50th: 6.7-8.3 | NMMAPS: 75th: 46.8-68.8 APHEA: 75th: 15.3-49.4 12 Canadian cities: 75th: 8.4-12.4 |
| Cakmak et al. (2006b) | 10 Canadian cities | Hospital Admissions: All respiratory (466, 480-486, 490, 491, 492, 493, 494, 496) | 24-h avg | 17.4 | Max: 38.0-79.0 |
| Biggeri et al. (2005) ^c | 4 Italian cities ^f | Hospital Admissions: All respiratory (460-519) | 8-h max | Warm season (May-September): 5.7-60.0 | 95th: 86.1-90.0 Max: 107.5-115.1 |
| Dales et al. (2006) | 11 Canadian cities | Hospital Admissions: Respiratory disorders (486, 768.9, 769, 770.8, 786, 799.0, 799.1) | 24-h avg | 17.0 | 95th: 24.9-46.0 |
| Lin et al. (2008a) | 11 New York regions | Hospital Admissions: Respiratory diseases (466, 490-493, 496) | 8-h max ^g | 44.1 | 75th: 54.0 Max: 217.0 |
| Wong et al. (2009) ^c | Hong Kong | Hospital Admissions: All respiratory (460-519) COPD (490-496) | 8-h max ^g | 18.8 | 75th: 25.9 Max: 100.3 |
| Medina-Ramon et al. (2006) ^h | 36 U.S. cities | Hospital Admissions: COPD (490-496, excluding 493) Pneumonia (480-487) | 8-h max | Warm (May-September): 45.8 Cool (October-April): 27.6 | NR |
| Yang et al. (2005b) | Vancouver, Canada | Hospital Admissions: COPD (490-492, 494, 496) | 24-h avg | All year: 14.1 Winter (January-March): 13.2 Spring (April-June): 19.4 Summer (July-September): 13.8 Fall (October-December): 10.0 | Max: 38.6 |
| Zanobetti and Schwartz (2006) ^b | Boston, MA | Hospital Admissions: Pneumonia (480-487) | 24-h avg | 22.4 | 75th: 31.0 95th: 47.6 |
| Silverman and Ito (2010) ^b | New York, NY | Hospital Admissions: Asthma (493) | 8-h max | Warm (April-August): 41.0 | 75th: 53 90th: 68 |

| Study | Location | Type of Visit (ICD9/10) | Averaging Time | Mean Concentration (ppb) ^a | Upper Percentile Concentrations (ppb) ^a |
|--|-------------------|---|----------------|--|---|
| Stieb et al. (2009) | 7 Canadian cities | ED Visits: Asthma (493) COPD (490-492, 494-496) Respiratory infection (464, 466, 480-487) | 24-h avg | 18.4 | 75th: 19.3-28.6 |
| Tolbert et al. (2007) | Atlanta, GA | ED Visits: All respiratory (460-465, 460.0, 466.1, 466.11, 466.19, 477, 480-486, 491, 492, 493, 496, 786.07, 786.09) | 8-h max | Warm: 53.0 | 75th: 67.0 90th: 82.1 Max: 147.5 |
| Darrow et al. (2011a) | Atlanta, GA | ED Visits: All respiratory (460-466, 477, 480-486, 491, 492, 493, 496, 786.09) | 8-h max | Warm (March-October): 8-h max: 53 | 8-h max :75th: 67 8-h max :Max: 148 |
| | | | 1-h max | Warm (March-October): 1-h max: 62 | 1-h max :75th: 76 1-h max :Max: 180 |
| | | | 24-h avg | Warm (March-October): 24-h avg: 30 | 24-h avg :75th: 37 24-h avg :Max: 81 |
| | | | Commute | Warm (March-October): Commute: 35 ⁱ | Commute :75th: 45 Commute :Max: 106 |
| | | | Day-time | Warm (March-October): Day-time: 45 ⁱ | Day-time :75th: 58 Day-time :Max: 123 |
| | | | Night-time | Warm (March-October): Night-time: 14 ⁱ | Night-time :75th: 22 Night-time :Max: 64 |
| Villeneuve et al. (2007)^b | Alberta, CAN | ED Visits: Asthma (493) | 8-h max | Summer (April-September): 38.0 Winter (October-March): 24.3 | Summer: 75th: 46.0 Winter: 75th: 31.5 |
| Ito et al. (2007b) | New York, NY | ED Visits: Asthma (493) | 8-h max | All year: 30.4 Warm (April-September): 42.7 Cold (October-March): 18.0 | All year: 95th: 68.0 Warm months: 95th: 77.0 Cold months: 95th: 33.0 |
| Strickland et al. (2010) | Atlanta, GA | ED Visits: Asthma (493) Wheeze (786.07 after 10/1/98, 786.09 before 10/1/98) | 8-h max | All year: 45.4 ⁱ Warm (May-October): 55.2 ^j Cold (November-April): 34.5 ^j | NR |
| Mar and Koenig (2009) | Seattle, WA | ED Visits: Asthma (493-493.9) | 1-h max | Warm (May-October): | 75th: |
| | | | 8-h max | 1-h max: 38.6 8-h max: 32.2 | 1-h max: 45.5 8-h max: 39.2 |
| Arbex et al. (2009) | Sao Paulo, Brazil | ED Visits: COPD (J40-44) | 1-h max | 48.8 | 75th: 61.0 Max: 143.8 |

| Study | Location | Type of Visit (ICD9/10) | Averaging Time | Mean Concentration (ppb) ^a | Upper Percentile Concentrations (ppb) ^a |
|--|--------------------|---|----------------------|---|--|
| Orazzo et al. (2009)^c | 6 Italian cities | ED Visits: Wheezing | 8-h max ^k | Summer (April-September): 21.1-44.3 Winter (October-March): 11.5-27.9 | NR |
| Burra et al. (2009) | Toronto, Canada | Physician Visits: ED Asthma (493) | 1-h max | 33.3 | 95th: 66 Max: 121 |
| Villeneuve et al. (2006b) | Toronto, Canada | Physician Visits: Allergic rhinitis (177) | 8-h max | 30.0 | Max: 98.7 |
| Sinclair et al. (2010)^j | Atlanta, GA | Physician Visits: Asthma Upper respiratory infection Lower respiratory infection | 8-h max | Total Study Period: All-year: 44.0 25 mo Period: All-year: 47.9 Warm: 61.2 Cold: 27.8 28 mo Period: All-year: 40.7 Warm: 51.8 Cold: 26.0 | NR |

^aSome studies did not present an overall value for the mean, middle and/or upper percentiles of the O₃ distribution; as a result, the range of the mean, middle, and/or upper percentiles across all of the cities included in the study are presented.

^bStudy only presented median concentrations.

^cStudy presented concentrations as µg/m³. Concentration was converted to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

^dA subset of the European and U.S. cities included in the mortality analyses were used in the hospital admissions analyses: 8 of the 32 European cities and 14 of 90 U.S. cities.

^eHospital admission data was coded using three classifications (ICD-10-CA, ICD-9, and ICD-9-CM). Attempts were made by the original investigators to convert diagnosis from ICD-10-CA back to ICD-9.

^fOnly 4 of the 8 cities included in the study collected O₃ data.

^gO₃ measured from 10:00 a.m. to 6:00 p.m.

^hOnly 35 of the 36 cities included in the analysis had O₃ data.

ⁱCommute (7:00 a.m. to 10:00 a.m., 4:00 p.m. to 7:00 p.m.); day-time (8:00 a.m. to 7:00 p.m.); Night-time (12:00 a.m. to 6:00 a.m.).

^jMeans represent population-weighted O₃ concentrations.

^kO₃ measured from 8:00 a.m. to 4:00 p.m.

^lThis study did not report the ICD codes used for the conditions examined. The 25-month period represents August 1998-August 2000, and the 28-month period represents September 2000-December 2002. This study defined the warm months as April – October and the cold months as November-March.

6.2.7.2 Hospital Admission Studies

Respiratory Diseases

1 The association between exposure to an air pollutant, such as O₃, and daily respiratory-
2 related hospital admissions has primarily been examined using all respiratory-related
3 hospital admissions within the range of ICD-9 codes 460-519. Recent studies published
4 since the 2006 AQCD ([U.S. EPA, 2006b](#)) attempt to further examine the effect of O₃
5 exposure on respiratory-related hospital admissions through a multicity design that
6 examines O₃ effects across countries using a standardized methodology; multicity studies

1 that examine effects within one country; and multi- and single-city studies that attempt to
2 examine potential modifiers of the O₃-respiratory-related hospital admission relationship.

3 The Air Pollution and Health: A European and North American Approach (APHENA)
4 study combined data from existing multicity study databases from Canada, Europe
5 (APHEA2) ([Katsouyanni et al., 2001](#)), and the U.S. (NMMAPS) ([Samet et al., 2000](#)) in
6 order to “develop more reliable estimates of the potential acute effects of air pollution on
7 human health [and] provide a common basis for [the] comparison of risks across
8 geographic areas” ([Katsouyanni et al., 2009](#)). In an attempt to address both of these
9 issues, the investigators conducted extensive sensitivity analyses to evaluate the
10 robustness of the results to different model specifications (e.g., penalized splines [PS]
11 versus natural splines [NS]) and the extent of smoothing to control for seasonal and
12 temporal trends. The trend analyses consisted of subjecting the models to varying extent
13 of smoothing selected either a priori (i.e., 3 df/year, 8 df/year, and 12 df/year), which was
14 selected through exploratory analyses using between 2 and 20 df, or by using the absolute
15 sum of the residuals of the partial autocorrelation function (PACF). Although the
16 investigators did not identify the model they deemed to be the most appropriate for
17 comparing the results across study locations, they did specify that “overall effect
18 estimates (i.e., estimates pooled over several cities) tended to stabilize at high degrees of
19 freedom” ([Katsouyanni et al., 2009](#)). Therefore, in discussion of the results across the
20 three study locations below, the 8 df/year results are presented for both the PS and NS
21 models because: (1) 8 df/year is most consistent with the extent of temporal adjustment
22 used in previous and recent large multicity studies in the U.S. (e.g., NMMAPS); (2) the
23 risk estimates for 8 df/year and 12 df/year are comparable for all three locations; (3) the
24 models that used the PACF method did not report the actual degrees of freedom chosen;
25 and (4) the 3 df/year and the PACF method resulted in negative O₃ risk estimates, which
26 is inconsistent with the results obtained using more aggressive seasonal adjustments and
27 suggests inadequate control for seasonality. Additionally, in comparisons of results across
28 studies in figures, only the results from one of the spline models (i.e., NS) are presented
29 because it has been previously demonstrated that alternative spline models result in
30 relatively similar effect estimates ([HEL, 2003](#)). This observation is consistent with the
31 results of the APHENA analysis that was conducted with a higher number of degrees of
32 freedom (e.g., ≥ 8 df/year) to account for temporal trends.

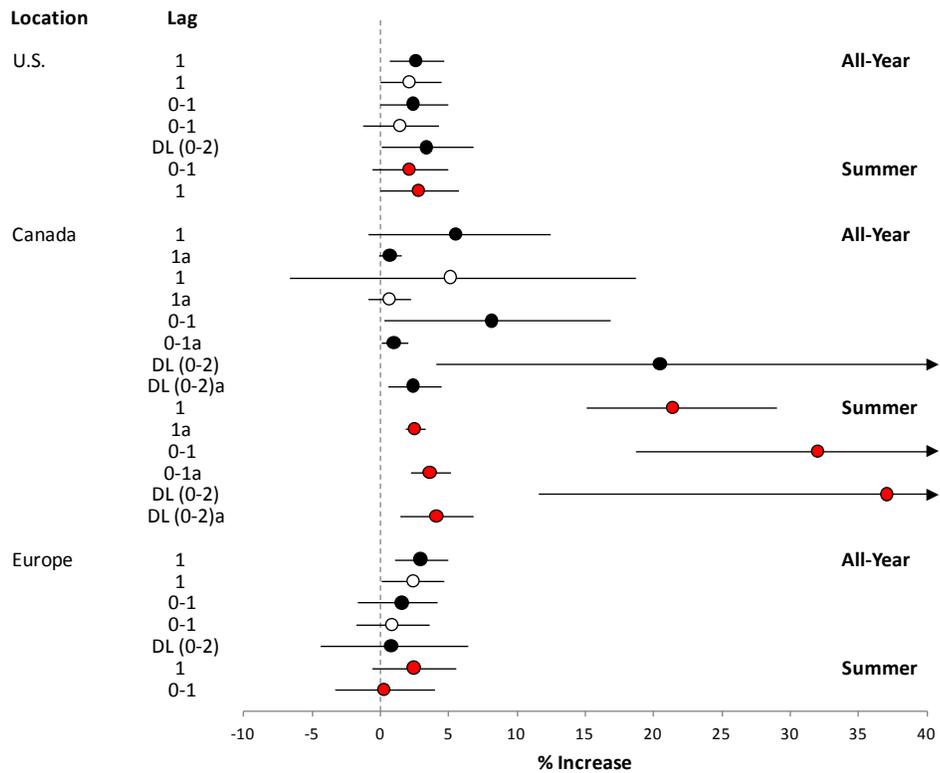
33 [Katsouyanni et al. \(2009\)](#) examined respiratory hospital admissions for people aged
34 65 years and older using 1-h max O₃ data. The extent of hospital admission and O₃ data
35 varied across the 3 datasets: Canadian dataset included 12 cities with data for 3 years
36 (1993-1996) per city; European dataset included 8 cities with each city having data for
37 between 2 and 8 years from 1988-1997; and the U.S. dataset included 14 cities with each
38 city having data for 4 to 10 years from 1985-1994 and 7 cities having only summer O₃

1 data. The investigators used a three-stage hierarchical model to account for within-city,
2 within region, and between region variability. Results were presented individually for
3 each region ([Figure 6-14](#); [Table 6-27](#)). Ozone and PM₁₀ concentrations were weakly
4 correlated in all locations in the summer ($r = 0.27-0.40$), but not in the winter.

5 In the Canadian cities, using all-year data, a 40 ppb increase in 1-h max O₃
6 concentrations at lag 0-1 was associated with an increase in respiratory hospital
7 admissions of 8.9% (95% CI: 0.79, 16.8%) in a PS model and 8.1% (95% CI: 0.24,
8 16.8%) in a NS model ([Katsouyanni et al., 2009](#)). The results were somewhat sensitive to
9 the lag day selected, reduced when using a single-day lag (e.g., lag 1) (PS: 6.0%; NS:
10 5.5%) and increased when using a distributed lag model (PS: 18.6%; NS: 20.4%). When
11 adjusting for PM₁₀, the magnitude of the effect estimate was attenuated, but remained
12 positive with it being slightly larger in the NS model (5.1% [95% CI: -6.6, 18.6%])
13 compared to the PS model (3.1% [95% CI: -8.3, 15.9%]). However, in the Canadian
14 dataset the copollutant analysis was only conducted using a 1-day lag. The large
15 confidence intervals for both models could be attributed to the reduction in days included
16 in the copollutant analyses as a result of the every-6th-day PM sampling schedule. When
17 the analysis was restricted to the summer months, stronger associations were observed
18 between O₃ and respiratory hospital admissions across the lags examined, ranging from
19 ~22 to 37% (the study does not specify whether these effect estimates are from a NS or
20 PS model). Because O₃ concentrations across the cities included in the Canadian dataset
21 are low (median concentrations ranging from 6.7-8.3 ppb [[Table 6-26](#)]), the standardized
22 increment of 40 ppb for a 1-h max increase in O₃ concentrations represents an unrealistic
23 increase in O₃ concentrations in Canada and increases the magnitude, not direction, of the
24 observed risk estimate. As a result, calculating the O₃ risk estimate using the standardized
25 increment does not accurately reflect the observed risk of O₃-related respiratory hospital
26 admissions. Although this increment adequately characterizes the distribution of 1-h max
27 O₃ concentrations across the U.S. and European datasets, it misrepresents the observed O₃
28 concentrations in the Canadian dataset. As a result in summary figures, for comparability,
29 effect estimates from the Canadian dataset are presented for both a 5.1 ppb increase in
30 1-h max O₃ concentrations (i.e., an approximate interquartile range [IQR] increase in O₃
31 concentrations across the Canadian cities) as well as the standardized increment used
32 throughout the ISA.

33 In Europe, weaker but positive associations were also observed in year round analyses;
34 2.9% (95% CI: 0.63, 5.0%) in the PS model and 1.6% (95% CI: -1.7, 4.2%) in the NS
35 model at lag 0-1 for a 40 ppb increase in 1-h max O₃ concentrations ([Katsouyanni et al.,](#)
36 [2009](#)). Additionally, at lag 1, associations between O₃ and respiratory hospital admissions
37 were also reduced, but in contrast to the lag 0-1 analysis, greater effects were observed in
38 the NS model (2.9% [95% CI: 1.0, 4.9%]) compared to the PS model (1.5% [95% CI:

1 -2.2, 5.4]). Unlike the Canadian analysis, a distributed lag model provided limited
2 evidence of an association between O₃ and respiratory hospital admissions. To compare
3 with the Canadian results, with adjustment for PM₁₀ at lag 1, O₃ effect estimates were
4 increased in the PS model (2.5% [95% CI: 0.39-4.8%]) and remained robust in the NS
5 model (2.4% [95% CI: 0.08, 4.6%]). However, the European analysis also examined the
6 effect of adjusting for PM₁₀ at lag 0-1 and found results were attenuated, but remained
7 positive in both models (PS: 0.8% [95% CI: -2.3, 4.0%]; NS: 0.8% [95% CI: -1.8,
8 3.6%]). Unlike the Canadian and U.S. datasets, the European dataset consisted of daily
9 PM data. The investigators did not observe stronger associations in the summer-only
10 analyses for the European cities at lag 0-1 (PS: 0.4% [95% CI: -3.2, 4.0%]; NS: 0.2%
11 [95% CI: -3.3, 3.9%]), but did observe some evidence for larger effects during the
12 summer, an ~2.5% increase, at lag 1 in both models (the study does not present the extent
13 of temporal smoothing used for these models).



Note: Black circles = all-year results; open circles = all-year results in copollutant model with PM₁₀; and red circles = summer only results. For Canada, lag days with an "a" next to them represent the risk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations.

Figure 6-14 Percent increase in respiratory hospital admissions from natural spline models with 8 df/yr for a 40 ppb increase in 1-h max ozone concentrations for each location of the APHENA study.

Table 6-27 Corresponding effect estimates for Figure 6-14.

| Location* | Season | Lag ^a | Copollutant | % Increase (95% CI) ^b | | |
|----------------------|----------------------|------------------|--------------------------------|----------------------------------|--------------------------------|---------------------------------|
| U.S. | All-year | 1 | | 2.62 (0.63, 4.64) | | |
| | | 1 | PM ₁₀ | 2.14 (-0.08, 4.40) | | |
| | | 0-1 | | 2.38 (0.00, 4.89) | | |
| | | 0-1 | PM ₁₀ | 1.42 (-1.33, 4.23) | | |
| | | DL(0-2) | | 3.34 (0.02-6.78) | | |
| | Summer | 0-1 | | 2.14 (-0.63, 4.97) | | |
| | | 1 | | 2.78 (-0.02, 5.71) | | |
| | | Canada | All-year | 1 | | 5.54 (-0.94, 12.4) |
| | | | | 1a | | 0.69 (-0.12, 1.50) ^a |
| | | | | 1 | PM ₁₀ | 5.13 (-6.62, 18.6) |
| 1a | PM ₁₀ | | | 0.64 (-0.87, 2.20) ^a | | |
| 0-1 | | | | 8.12 (0.24, 16.8) | | |
| 0-1a | | | | 1.00 (0.03, 2.00) ^a | | |
| DL(0-2) | | | | 20.4 (4.07, 40.2) | | |
| DL(0-2) ^a | | | | 2.4 (0.51, 4.40) ^a | | |
| Summer | 1 | | | | 21.4 (15.0, 29.0) | |
| | 1a | | | | 2.50 (1.80, 3.30) ^a | |
| | 0-1 | | 32.0 (18.6, 47.7) | | | |
| | 0-1 ^a | | 3.60 (2.20, 5.10) ^a | | | |
| | DL(0-2) | | 37.1 (11.5, 67.5) | | | |
| | DL(0-2) ^a | | 4.1 (1.40, 6.80) ^a | | | |
| | Europe | All-year | 1 | | 2.94 (1.02, 4.89) | |
| 1 | | | PM ₁₀ | 2.38 (0.08, 4.64) | | |
| 0-1 | | | | 1.58 (-1.71, 4.15) | | |
| 0-1 | | | PM ₁₀ | 0.87 (-1.79, 3.58) | | |
| DL(0-2) | | | | 0.79 (-4.46, 6.37) | | |
| Summer | | 1 | | 2.46 (-0.63, 5.54) | | |
| | | 0-1 | | 0.24 (-3.32, 3.91) | | |

*For effect estimates in [Figure 6-14](#).

^aFor Canada, lag days with an “a” next to them represent the risk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations.

^bUnless noted, risk estimates standardized to 40 ppb for a 1-h max increase in O₃ concentrations.

- 1 For the U.S. in year round analyses, the investigators reported a 1.4% (95% CI: -0.9,
- 2 3.9%) increase in the PS model and 2.4% (95% CI: 0.0, 4.9%) increase in the NS model
- 3 in respiratory hospital admissions at lag 0-1 for a 40 ppb increase in 1-h max O₃
- 4 concentrations with similar results for both models at lag 1 ([Katsouyanni et al., 2009](#)).
- 5 The distributed lag model provided results similar to those observed in the European

1 dataset with the PS model (1.1% [95% CI: -3.0, 5.3%]), but larger effects in the NS
2 model (3.3% [95% CI: 0.02, 6.8%]), which is consistent with the Canadian results. With
3 adjustment for PM₁₀ using the U.S. data (i.e., every-6th-day PM data), results were
4 attenuated, but remained positive at lag 0-1 (PS: 0.6% [95% CI: -2.0, 3.3%]; NS: 1.4%
5 [95% CI: -1.3, 4.2%]) which is consistent with the results presented for the European
6 dataset. However, at lag 1, U.S. risk estimates remained robust to the inclusion of PM₁₀ in
7 copollutant models as was observed in the Canadian and European datasets. Compared to
8 the all-year analyses, the investigators did not observe stronger associations in the
9 summer-only analysis at either lag 0-1 (~2.2%) or lag 1 (~2.8%) in both the PS and NS
10 models (the study does not present the extent of temporal smoothing used for these
11 models).

12 Several additional multicity studies examined respiratory disease hospital admissions in
13 Canada and Europe. [Cakmak et al. \(2006b\)](#) evaluated the association between ambient O₃
14 concentrations and respiratory hospital admissions for all ages in 10 Canadian cities from
15 April 1993 to March 2000. The primary objective of this study was to examine the
16 potential modification of the effect of ambient air pollution on daily respiratory hospital
17 admissions by education and income using a time-series analysis conducted at the city-
18 level. The authors calculated a pooled estimate across cities for each pollutant using a
19 random effects model by first selecting the lag day with the strongest association from the
20 city-specific models. For O₃, the mean lag day across cities that provided the strongest
21 association and for which the pooled effect estimate was calculated was 1.2 days. In this
22 study, all-year O₃ concentrations were used in the analysis, and additional seasonal
23 analyses were not conducted. [Cakmak et al. \(2006b\)](#) reported a 4.4% increase (95% CI:
24 2.2, 6.5%) in respiratory hospital admissions for a 20 ppb increase in 24-hour average O₃
25 concentrations. The investigators only examined the potential effect of confounding by
26 other pollutants through the use of a multipollutant model (i.e., two or more additional
27 pollutants included in the model), which is difficult to interpret due to the potential
28 multicollinearity between pollutants. [Cakmak et al. \(2006b\)](#) also conducted an extensive
29 analysis of potential modifiers, specifically sex, educational attainment, and family
30 income, on the association between air pollution and respiratory hospital admissions.
31 When stratifying by sex, the increase in respiratory hospital admissions due to short-term
32 O₃ exposure were similar in males (5.2% [95% CI: 3.0, 7.3%]) and females (4.2%
33 [95% CI: 1.8, 6.6%]). In addition, the examination of effect modification by income
34 found no consistent trend across the quartiles of family income. However, there was
35 evidence that individuals with an education level less than the 9th grade were
36 disproportionately affected by O₃ exposure (4.6% [95% CI: 1.8, 7.5%]) compared to
37 individuals that completed grades 9-13 (1.7% [95% CI: -1.9, 5.3%]), some university or
38 trade school (1.4% [95% CI: -2.0, 5.1%]), or have a university diploma (0.66% [95% CI:
39 -3.3, 4.7%]). The association between O₃ and respiratory hospital admissions in

1 individuals with an education level less than the 9th grade was the strongest association
2 across all of the pollutants examined.

3 A multicity study conducted in Europe by [Biggeri et al. \(2005\)](#) examined the association
4 between short-term O₃ exposure and respiratory hospital admissions for all ages in four
5 Italian cities from 1990 to 1999. In this study, O₃ was only measured during the warm
6 season (May-September). The authors examined associations between daily respiratory
7 hospital admissions and short-term O₃ exposure at the city-level using a time-series
8 analysis. Pooled estimates were calculated by combining city-specific estimates using
9 fixed and random effects models. The investigators found no evidence of an association
10 between O₃ exposure and respiratory hospital admissions in the warm season in both the
11 random (0.1% [95% CI: -5.2, 5.7%]; distributed lag 0-3) and fixed effects (0.1%
12 [95% CI: -5.2, 5.7%]; distributed lag 0-3) models for a 30 ppb increase in 8-h max O₃
13 concentrations.

14 Additional studies examined associations between short-term O₃ exposure and respiratory
15 hospital admissions specifically in children. In a multicity study conducted in Canada,
16 [Dales et al. \(2006\)](#) examined the association between all-year ambient O₃ concentrations
17 and neonatal (ages 0-27 days) respiratory hospital admissions in 11 Canadian cities from
18 1986 to 2000. The investigators used a statistical analysis approach similar to [Cakmak et
19 al. \(2006b\)](#) (i.e., time-series analysis to examine city-specific associations, and then a
20 random effects model to pool estimates across cities). The authors reported that for O₃,
21 the mean lag day across cities that provided the strongest association was 2 days. The
22 authors reported a 5.4% (95% CI: 2.9, 8.0%) increase in neonatal respiratory hospital
23 admissions for a 20 ppb increase in 24-h avg O₃ concentrations at lag-2 days. The results
24 from [Dales et al. \(2006\)](#) provide support for the associations observed in a smaller scale
25 study that examined O₃ exposure and pediatric respiratory hospital admissions in
26 New York state ([Lin et al., 2008a](#)). [Lin et al. \(2008a\)](#), when examining single-day lags of
27 0 to 3 days, observed a positive association between O₃ and pediatric (i.e., <18 years)
28 respiratory admissions at lag 2 (results not presented quantitatively) in a two-stage
29 Bayesian hierarchical model analysis of 11 geographic regions of New York state from
30 1991 to 2001. Additionally, in copollutant models with PM₁₀, collected every-6th day, the
31 authors found region-specific O₃ associations with respiratory hospital admissions
32 remained relatively robust.

33 Overall, the evidence from epidemiologic studies continues to support an association
34 between short-term O₃ exposure and respiratory-related hospital admissions, but it
35 remains unclear whether certain factors (individual- or population-level) modify this
36 association. [Wong et al. \(2009\)](#) examined the potential modification of the relationship
37 between ambient O₃ (along with NO₂, SO₂, and PM₁₀) and respiratory hospital

1 admissions by influenza intensity in Hong Kong for the period 1996 – 2002. In this study
2 air pollution concentrations were estimated by centering non-missing daily air pollution
3 data on the annual mean for each monitor and then an overall daily concentration was
4 calculated by taking the average of the daily centered mean across all monitors. Influenza
5 intensity was defined as a continuous variable using the proportion of weekly specimens
6 positive for influenza A or B instead of defining influenza epidemics. This approach was
7 used to avoid any potential bias associated with the unpredictable seasonality of influenza
8 in Hong Kong where there are traditionally two seasonal peaks, which is in contrast to the
9 single peaking influenza season in the U.S. ([Wong et al., 2009](#)). In models that examined
10 the baseline effect (i.e., without taking into consideration influenza intensity) of short-
11 term O₃ exposure, the authors found a 3.6% (95% CI: 1.9, 5.3%) and 3.2% (95% CI: 1.0,
12 5.4%) increase in respiratory hospital admissions at lag 0-1 for a 30 ppb increase in
13 8-h max O₃ concentrations for the all age and ≥ 65 age groups, respectively. When
14 examining influenza intensity, [Wong et al. \(2009\)](#) reported that the association between
15 short-term exposure to O₃ and respiratory hospital admissions was stronger with higher
16 levels of influenza intensity: additional increase in respiratory hospital admissions above
17 baseline of 1.4% (95% CI: 0.24, 2.6%) for all age groups and 2.4% (95% CI: 0.94, 3.8%)
18 for those 65 and older when influenza activity increased from 0% to 10%. No difference
19 in effects was observed when stratifying by sex.

Cause-Specific Respiratory Outcomes

20 In the 2006 O₃ AQCD a limited number of studies were identified that examined the
21 effect of short-term O₃ exposure on cause-specific respiratory hospital admissions. The
22 limited evidence “reported positive O₃ associations with... asthma and COPD,
23 especially... during the summer or warm season” ([U.S. EPA, 2006b](#)). Of the studies
24 evaluated since the completion of the 2006 O₃ AQCD, more have focused on identifying
25 whether O₃ exposure is associated with specific respiratory-related hospital admissions,
26 including COPD, pneumonia, and asthma, but the overall body of evidence remains
27 small.

Chronic Obstructive Pulmonary Disease

28 [Medina-Ramon et al. \(2006\)](#) examined the association between short-term exposure to
29 ambient O₃ and PM₁₀ concentrations and Medicare hospital admissions among
30 individuals ≥ 65 years of age for COPD in 35 cities in the U.S. for the years 1986-1999.
31 The cities included in this analysis were selected because they monitored PM₁₀ on a daily
32 basis. In this study, city-specific results were obtained using a monthly time-stratified
33 case-crossover analysis. A meta-analysis was then conducted using random effects
34 models to combine the city-specific results. All cities measured O₃ from May through

1 September, while only 16 of the cities had year-round measurements. The authors
2 reported a 1.6% increase (95% CI: 0.48, 2.9%) in COPD admissions for lag 0-1 in the
3 warm season for a 30 ppb increase in 8-h max O₃ concentrations. When examining
4 single-day lags, stronger associations were observed for lag 1 (2.9% [95% CI: 1.8, 4.0%])
5 compared to lag 0 (-1.5% [95% CI: -2.7, -0.24%]). The authors found no evidence of
6 associations in cool season (-1.9% [95% CI: -3.6, -0.06%]; lag 0-1) or year round (0.24%
7 [95% CI: -0.78, 1.2%]; lag 0-1) analyses. In a copollutant model restricted to days in
8 which PM₁₀ was available, the association between O₃ and COPD hospital admissions
9 remained robust. Of note, the frequency of PM₁₀ measurements varied across cities with
10 measurements collected either every 2, 3, or 6 days. The authors conducted additional
11 analyses to examine potential modification of the warm season estimates for O₃ and
12 COPD admissions by several city-level characteristics: percentage living in poverty,
13 emphysema mortality rate (as an indication of smoking), daily summer apparent
14 temperature, and percentage of households using central air conditioning. Of the city-
15 level characteristics examined, stronger associations were only reported for cities with a
16 smaller variability in daily apparent summer temperature.

17 In a single-city study conducted in Vancouver from 1994-1998, a location with low
18 ambient O₃ concentrations ([Table 6-26](#)), [Yang et al. \(2005b\)](#) examined the association
19 between O₃ and COPD. Ozone was moderately inversely correlated with CO (r = -0.56),
20 NO₂ (r = -0.32), and SO₂ (r = -0.34), and weakly inversely correlated with PM₁₀
21 (r = -0.09), suggesting that the observed O₃ effect is likely not only due to a positive
22 correlation with other pollutants. [Yang et al. \(2005b\)](#) examined 1- to 7-day (e.g., (0-
23 6 days) lagged moving averages and observed an 8.8% (95% CI: -12.5, 32.6%) increase
24 in COPD admissions for lag 0-3 per 20 ppb increase in 24-h avg O₃ concentrations. In
25 two-pollutant models with every-day data for NO₂, SO₂, and PM₁₀ at lag 0-3, O₃ risk
26 estimates remained robust, but were increased slightly when CO was added to the model
27 ([Figure 6-19](#); [Table 6-29](#)).

28 In the study discussed above, [Wong et al. \(2009\)](#) also examined the potential
29 modification of the relationship between ambient O₃ and COPD hospital admissions by
30 influenza intensity. The authors also found evidence of an additional increase in COPD
31 admissions above baseline when influenza activity increased from 0% to 10% of 1.0%
32 (95% CI: -0.82, 2.9%) for all age groups and 2.4% (95% CI: 0.41, 4.4%) for those 65 and
33 older. The baseline increase in COPD hospital admissions at lag 0-1 for a 30 ppb increase
34 in 8-h max O₃ concentrations was 8.5% (95% CI: 5.6, 11.4%) for the all age and 4.2%
35 (95% CI: 1.1, 7.3%) ≥ 65 age groups.

Pneumonia

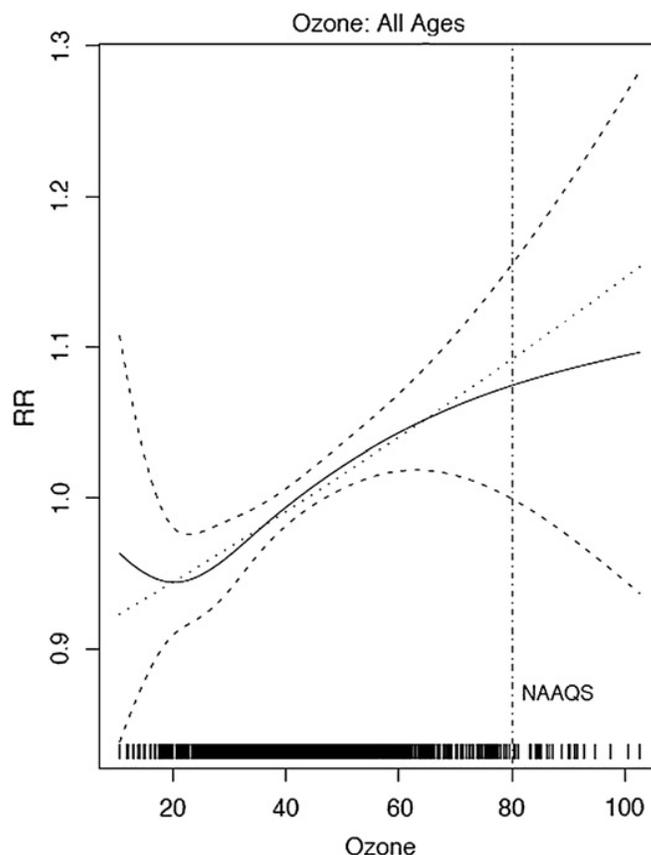
1 In addition to COPD, [Medina-Ramon et al. \(2006\)](#) examined the association between
2 short-term exposure to ambient O₃ and PM₁₀ concentrations and Medicare hospital
3 admissions among individuals ≥ 65 years of age for pneumonia (ICD-9: 480-487). The
4 authors reported an increase in pneumonia-hospital admissions in the warm season (2.5%
5 [95% CI: 1.6, 3.5%] for a 30 ppb increase in 8-h max O₃ concentrations; lag 0-1). Similar
6 to the results observed for COPD hospital admissions, pneumonia-hospital admissions
7 associations were stronger at lag 1 (2.6% [95% CI: 1.8, 3.4%]) compared to lag 0 (0.06%
8 [95% CI: -0.72, 0.78%]), and no evidence of an association was observed in the cool
9 season or year round. In two-pollutant models restricted to days for which PM₁₀ data was
10 available, as discussed above, the association between O₃ exposure and pneumonia-
11 hospital admissions remained robust (results not presented quantitatively). The authors
12 also examined potential effect modification of the warm season estimates for O₃-related
13 pneumonia-hospital admissions, as was done for COPD, by several city-level
14 characteristics. Stronger associations were reported in cities with a lower percentage of
15 central air conditioning use. Across the cities examined, the percentage of households
16 having central air conditioning ranged from 6 to 93%. The authors found no evidence of
17 effect modification of the O₃-pneumonia-hospital admission relationship when examining
18 the other city-level characteristics.

19 Results from a single-city study conducted in Boston did not support the results presented
20 by [Medina-Ramon et al. \(2006\)](#). [Zanobetti and Schwartz \(2006\)](#) examined the association
21 of O₃ and pneumonia Medicare hospital admissions for the period 1995-1999. Ozone was
22 weakly positively correlated with PM_{2.5} (r = 0.20) and weakly inversely correlated with
23 black carbon, NO₂, and CO (-0.25, -0.14, and -0.30, respectively). In an all-year analysis,
24 the investigators reported a 3.8% (95% CI: -7.9, -0.1%) decrease in pneumonia
25 admissions for a 20 ppb increase in 24-hour average O₃ concentrations at lag 0 and a
26 6.0% (95% CI: -11.1, -1.4%) decrease for the average of lags 0 and 1. It should be noted
27 that the mean daily counts of pneumonia admissions was low for this study, ~14
28 admissions per day compared to ~271 admissions per day for [Medina-Ramon et al.](#)
29 [\(2006\)](#). However, in analyses with other pollutants [Zanobetti and Schwartz \(2006\)](#) did
30 observe positive associations with pneumonia-hospital admissions, indicating that the low
31 number of daily hospital admission counts probably did not influence the O₃ pneumonia-
32 hospital admissions association in this study.

Asthma

33 There are relatively fewer studies that examined the association between short-term
34 exposure to O₃ and asthma hospital admissions, presumably due to the limited power
35 given the relative rarity of asthma hospital admissions compared to ED or physician

1 visits. A study from New York City examined the association of 8-h max O₃
2 concentrations with severe acute asthma admissions (i.e., those admitted to the Intensive
3 Care Unit [ICU]) during the warm season in the years 1999 through 2006 ([Silverman and](#)
4 [Ito, 2010](#)). In this study, O₃ was moderately correlated with PM₁₀ (r = 0.59). When
5 stratifying by age, the investigators reported positive associations with ICU asthma
6 admissions for the 6- to 18-year age group (26.8% [95% CI: 1.4, 58.2%] for a 30 ppb
7 increase in maximum 8-h avg O₃ concentrations at lag 0-1), but little evidence of
8 associations for the other age groups examined (<6 years, 19-49, 50+, and all ages).
9 However, positive associations were observed for each age-stratified group and all ages
10 for non-ICU asthma admissions, but again the strongest association was reported for the
11 6- to 18-years age group (28.2% [95% CI: 15.3, 41.5%]; lag 0-1). In two-pollutant
12 models, O₃ effect estimates for both non-ICU and ICU hospital admissions remained
13 robust to adjustment for PM_{2.5}. In an additional analysis, using a smooth function, the
14 authors examined whether the shape of the C-R curve for O₃ and asthma hospital
15 admissions (i.e., both general and ICU for all ages) is linear. To account for the potential
16 confounding effects of PM_{2.5}, [Silverman and Ito \(2010\)](#) also included a smooth function
17 of PM_{2.5} lag 0-1. When comparing the curve to a linear fit line the authors found that the
18 linear fit is a reasonable approximation of the C-R relationship between O₃ and asthma
19 hospital admissions around and below the level of the 1997 O₃ NAAQS ([Figure 6-15](#)).



Note: The average of 0-day and 1-day lagged 8-hour O_3 was used in a two-pollutant model with $PM_{2.5}$ lag 0-1, adjusting for temporal trends, day of the week, and immediate and delayed weather effects. The solid lines are smoothed fit data, with long broken lines indicating 95% confidence bands. The density of lines at the bottom of the figure indicates sample size.

Source: Reprinted with permission of the American Academy of Allergy, Asthma & Immunology ([Silverman and Ito, 2010](#)).

Figure 6-15 Estimated relative risks (RRs) of asthma hospital admissions for 8-h max ozone concentrations at lag 0-1 allowing for possible nonlinear relationships using natural splines.

Averting Behavior

1 The studies discussed above have found consistent positive associations between short-
 2 term O_3 exposure and respiratory-related hospital admissions, however, the strength of
 3 these associations may be underestimated due to the studies not accounting for averting
 4 behavior. As discussed in Section 4.6.5, a recent study ([Neidell and Kinney, 2010](#);
 5 [Neidell, 2009](#)) conducted in Southern California demonstrate that controlling for
 6 avoidance behavior increases O_3 effect estimates for respiratory hospital admissions,
 7 specifically for children and older adults. These studies show that on days where no
 8 public alert was issued warning of high O_3 concentrations there was an increase in asthma
 9 hospital admissions. Although only one study has examined averting behavior and this

1 study is limited to the outcome of asthma hospital admissions in one location (i.e., Los
2 Angeles, CA) for the years 1989-1997, it does provide preliminary evidence indicating
3 that epidemiologic studies may underestimate associations between O₃ exposure and
4 health effects by not accounting for behavioral modification when public health alerts are
5 issued.

6.2.7.3 Emergency Department Visit Studies

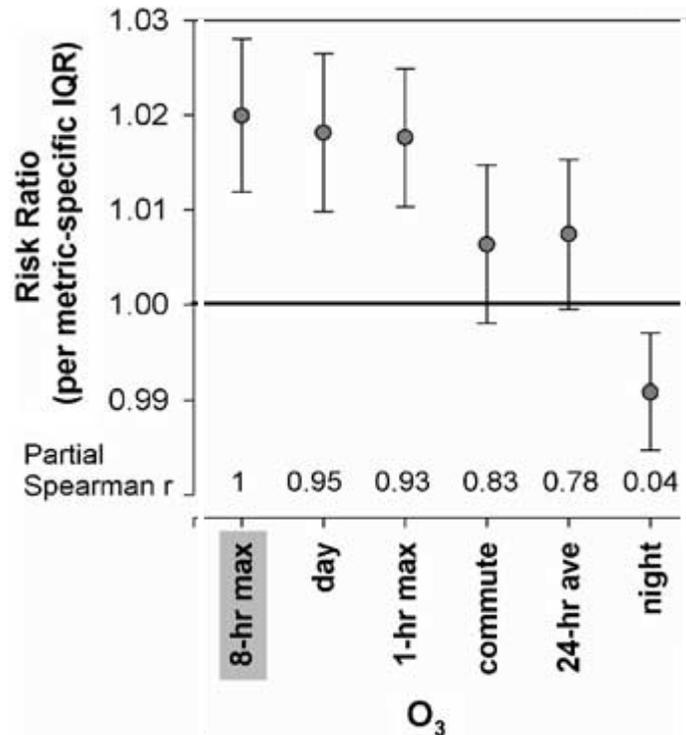
6 Overall, relatively fewer studies have examined the association between short-term O₃
7 exposure and respiratory-related ED visits, compared to hospital admissions. In the 2006
8 O₃ AQCD, positive, but inconsistent, associations were observed between O₃ and
9 respiratory-related ED visits with effects generally occurring during the warm season.
10 Since the completion of the previous AQCD, larger studies have been conducted, in
11 terms of sample size, study duration, and in some cases multiple cities, to examine the
12 association between O₃ and ED visits for all respiratory diseases, COPD, and asthma.

Respiratory Disease

13 A large single-city study conducted in Atlanta, by [Tolbert et al. \(2007\)](#), and subsequently
14 re analyzed by [Darrow et al. \(2011a\)](#) using different air quality data, provides evidence
15 for an association between short-term exposures to ambient O₃ concentrations and
16 respiratory ED visits. [Tolbert et al. \(2007\)](#) examined the association between air
17 pollution, both gaseous pollutants and PM and its components, and respiratory disease
18 ED visits in all ages from 1993 to 2004. The correlations between O₃ and the other
19 pollutants examined ranged from 0.2 for CO and SO₂ to 0.5-0.6 for the PM measures.
20 Using an a priori average of lags 0-2 for each air pollutant examined, the authors reported
21 a 3.9% (95% CI: 2.7, 5.2%) increase in respiratory ED visits for a 30 ppb increase in
22 8-h max O₃ concentrations during the warm season [defined as March-October in [Darrow
23 et al. \(2011a\)](#)]. In copollutant models, limited to days in which data for all pollutants were
24 available, O₃ respiratory ED visits associations with CO, NO₂, and PM₁₀, were attenuated,
25 but remained positive (results not presented quantitatively).

26 [Darrow et al. \(2011a\)](#) examined the same health data as [Tolbert et al. \(2007\)](#), but used air
27 quality data from one centrally located monitor instead of the average of multiple
28 monitors. This study primarily focused on exploring whether differences exist in the
29 association between O₃ exposure and respiratory-related ED visits depending on the
30 exposure metric used (i.e., 8-h max, 1-h max, 24-hour average, commuting period [7:00
31 a.m. to 10:00 a.m.; 4:00 p.m. to 7:00 p.m.], day-time [8:00 a.m. to 7:00 p.m.] and night-
32 time [12:00 a.m. to 6:00 a.m.]). An ancillary analysis of the spatial variability of each
33 exposure metric conducted by [Darrow et al. \(2011a\)](#) found a rather homogenous spatial

1 distribution of O₃ concentrations ($r \sim > 0.8$) as the distance from the central monitor
2 increased from 10 km to 60 km for all exposure durations, except the night-time metric.
3 The relatively high spatial correlation gives confidence in the use of a single monitor and
4 the resulting risk estimates. To examine the association between the various O₃ exposure
5 metrics and respiratory ED visits, the authors conceptually used a time-stratified case-
6 crossover framework where control days were selected as those days within the same
7 calendar month and maximum temperature as the case day. However, instead of
8 conducting a traditional case-crossover analysis, the authors used a Poisson model with
9 indicator variables for each of the strata (i.e., parameters of the control days). [Darrow et](#)
10 [al. \(2011a\)](#) found using an a prior lag of 1 day, the results were somewhat variable across
11 exposure metrics. The strongest associations with respiratory ED visits were found when
12 using the 8-h max, 1-h max, and day-time exposure metrics with weaker associations
13 using the 24-h avg and commuting period exposure metrics; a negative association was
14 observed when using the night-time exposure metric ([Figure 6-16](#)). These results indicate
15 that using the 24-h avg exposure metric may lead to smaller O₃-respiratory ED visits risk
16 estimates due to: (1) the dilution of relevant O₃ concentrations by averaging over hours
17 (i.e., nighttime hours) during which O₃ concentrations are known to be low and (2)
18 potential negative confounding by other pollutants (e.g., CO, NO₂) during the nighttime
19 hours ([Darrow et al., 2011a](#)).



Source: Reprinted with permission of Nature Publishing Group ([Darrow et al., 2011a](#)).

Figure 6-16 Risk ratio for respiratory ED visits and different ozone exposure metrics in Atlanta from 1993-2004.

1 In an additional study conducted in 6 Italian cities, [Orazzo et al. \(2009\)](#) examined
 2 respiratory ED visits for ages 0-2 years in 6 Italian cities from 1996 to 2000. However,
 3 instead of identifying respiratory ED visits using the traditional approach of selecting
 4 ICD codes as was done by [Tolbert et al. \(2007\)](#) and [Darrow et al. \(2011a\)](#), [Orazzo et al.](#)
 5 [\(2009\)](#) used data on wheeze extracted from medical records as an indicator of lower
 6 respiratory disease. This study examined daily counts of wheeze in relation to air
 7 pollution using a time-stratified case-crossover approach in which control days were
 8 matched on day of week in the same month and year as the case day. The authors found
 9 no evidence of an association between 8-h max O₃ concentrations and respiratory ED
 10 visits in children aged 0-2 years in models that examined both single-day lags and
 11 moving averages of lags from 0-6 days in year-round and seasonal analyses (i.e., warm
 12 and cool seasons). In all-year analyses, the percent increase in total wheeze ranged from -
 13 1.4% to -3.3% for a 0-1 to 0-6 day lag, respectively.

COPD

1 [Stieb et al. \(2009\)](#) also examined the association between short-term O₃ exposure and
2 COPD ED visits in 7 Canadian cities. Across cities, in an all-year analysis, O₃ was found
3 to be positively associated with COPD ED visits (2.4% [95% CI: -1.9, 6.9%] at lag 1 and
4 4.0% [95% CI: -0.54, 8.6%] at lag 2 for a 20 ppb increase in 24-h avg O₃ concentrations).
5 In seasonal analyses, larger effects were observed between O₃ and COPD ED visits
6 during the warm season (i.e., April-September) 6.8% [95% CI: 0.11, 13.9%] (lag day not
7 specified); with no associations observed in the winter season. [Stieb et al. \(2009\)](#) also
8 examined associations between respiratory-related ED visits, including COPD, and air
9 pollution at sub-daily time scales (i.e., 3-h avg of ED visits versus 3-h avg pollutant
10 concentrations) and found no evidence of consistent associations between any pollutant
11 and any respiratory outcome.

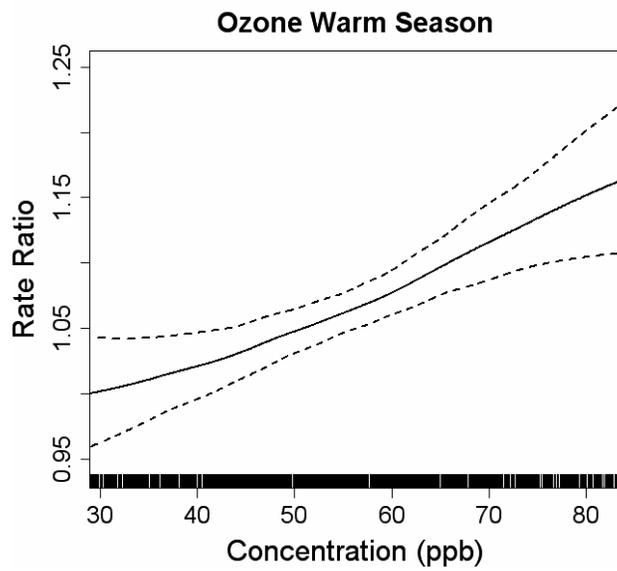
12 In a single-city study, [Arbex et al. \(2009\)](#) examined the association between COPD and
13 several ambient air pollutants, including O₃, in Sao Paulo, Brazil for the years 2001-2003
14 for individuals over the age of 40. Associations between O₃ exposure and COPD ED
15 visits were examined in both single-day lag (0-6 days) and polynomial distributed lag
16 models (0-6 days). In all-year analyses, O₃ was not found to be associated with an
17 increase in COPD ED visits (results not presented quantitatively). The authors also
18 conducted stratified analyses to examine the potential modification of the air pollutant-
19 COPD ED visits relationship by age (e.g., 40-64, >64) and sex. In these analyses O₃ was
20 found to have an increase in COPD ED visits for women, but not for men or either of the
21 age groups examined.

Asthma

22 In a study of 7 Canadian cities, [Stieb et al. \(2009\)](#) also examined the association between
23 exposure to air pollution (i.e., CO, NO₂, O₃, SO₂, PM₁₀, PM_{2.5}, and O₃) and asthma ED
24 visits. Associations between short-term O₃ exposure and asthma ED visits were examined
25 at the city level and then pooled using either fixed or random effects models depending
26 on whether heterogeneity among effect estimates was found to be statistically significant.
27 Across cities, in an all-year analysis, the authors found that short-term O₃ exposure was
28 associated with an increase (4.7% [95% CI: -1.4, 11.1%] at lag 1 and 3.5% [95% CI:
29 0.33, 6.8%] at lag 2 for a 20 ppb increase in 24-h avg O₃ concentrations) in asthma ED
30 visits. The authors did not present the results from seasonal analyses for asthma, but
31 stated that no associations were observed between any pollutant and respiratory ED visits
32 in the winter season. As stated previously, in analyses of 3-h avg O₃ concentrations, the
33 authors observed no evidence of consistent associations between any pollutant and any
34 respiratory outcome, including asthma. A single-city study conducted in Alberta, Canada
35 [Villeneuve et al. \(2007\)](#) from 1992-2002 among individuals two years of age and older

1 provides additional support for the findings from [Stieb et al. \(2009\)](#), but also attempts to
2 identify those lifestages (i.e., 2-4, 5-14, 15-44, 45-64, 65-74, or 75+) at greatest risk to
3 O₃-induced asthma ED visits. In a time-referent case-crossover analysis, Villeneuve et al.
4 found an increase in asthma ED visits in an all-year analysis across all ages (12.0%
5 [95% CI: 6.8, 17.2] for a 30 ppb increase in max 8-h avg O₃ concentrations at lag 0-2)
6 with associations being stronger during the warmer months (19.0% [95% CI: 11.9, 28.1]).
7 When stratified by age, the strongest associations were observed in the warm season for
8 individuals 5-14 (28.1% [95% CI: 11.9, 45.1]; lag 0-2) and 15-44 (19.0% [95% CI: 8.5,
9 31.8]; lag 0-2). These associations were not found to be confounded by the inclusion of
10 aeroallergens in age-specific models.

11 Several additional single-city studies have also provided evidence of an association
12 between asthma ED visits and ambient O₃ concentrations. [Ito et al. \(2007b\)](#) examined the
13 association between short-term exposure to air pollution and asthma ED visits for all ages
14 in New York City from 1999 to 2002. Similar to [Darrow et al. \(2011a\)](#), when examining
15 the spatial distribution of O₃ concentrations, [Ito et al. \(2007b\)](#) found a rather homogenous
16 distribution ($r \geq 0.80$) when examining monitor-to-monitor correlations at distances up to
17 20 miles. [Ito et al. \(2007b\)](#) used three different weather models with varying extent of
18 smoothing to account for temporal relationships and multicollinearity among pollutants
19 and meteorological variables (i.e., temperature and dew point) to examine the effect of
20 model selection on the air pollutant-asthma ED visit relationship. When examining O₃,
21 the authors reported a positive association with asthma ED visits, during the warm season
22 across the models (ranging from 8.6 to 16.9%) and an inverse association in the cool
23 season (ranging from -23.4 to -25.1%), at lag 0-1 for a 30 ppb increase in 8-h max O₃
24 concentrations. [Ito et al. \(2007b\)](#) conducted copollutant models using a simplified version
25 of the weather model used in NMMAPS analyses (i.e., terms for same-day temperature
26 and 1-3 day average temperature). The authors found that O₃ risk estimates were not
27 substantially changed in copollutant models that used every-day data for PM_{2.5}, NO₂,
28 SO₂, and CO during the warm season ([Figure 6-19](#); [Table 6-29](#)).



Note: The reference for the rate ratio is the estimated rate at the 5th percentile of the pollutant concentration. Estimates are presented for the 5th percentile through the 95th percentile of pollutant concentrations due to instability in the C-R estimates at the distribution tails.

Source: Reprinted with permission of American Thoracic Society ([Strickland et al., 2010](#)).

Figure 6-17 Loess C-R estimates and twice-standard error estimates from generalized additive models for associations between 8-h max 3-day average ozone concentrations and ED visits for pediatric asthma.

1 [Strickland et al. \(2010\)](#) examined the association between O₃ exposure and pediatric
 2 asthma ED visits (ages 5-17 years) in Atlanta between 1993 and 2004 using air quality
 3 data over the same years as [Darrow et al. \(2011a\)](#) and [Tolbert et al. \(2007\)](#). However,
 4 unlike [Darrow et al. \(2011a\)](#) and [Tolbert et al. \(2007\)](#), which used single centrally located
 5 monitors or an average of monitors, respectively, [Strickland et al. \(2010\)](#) used
 6 population-weighting to combine daily pollutant concentrations across monitors. In this
 7 study, the authors developed a statistical model using hospital-specific time-series data
 8 that is essentially equivalent to a time-stratified case-crossover analysis (i.e., using
 9 interaction terms between year, month, and day-of-week to mimic the approach of
 10 selecting referent days within the same month and year as the case day). The authors
 11 observed a 6.4% (95% CI: 3.2, 9.6%) increase in ED visits for a 30 ppb increase in
 12 8-h max O₃ concentrations at lag 0-2 in an all-year analysis. In seasonal analyses,
 13 stronger associations were observed during the warm season (i.e., May-October) (8.4%
 14 [95% CI: 4.4, 12.7%]; lag 0-2) than the cold season (4.5% [95% CI: -0.82, 10.0%]; lag 0-
 15 2). [Strickland et al. \(2011\)](#) confirmed these findings in an additional analysis using the
 16 same dataset, and found that the exposure assignment approach used (i.e., centrally

1 located monitor, unweighted average across monitors, and population-weighted average
2 across monitors) did not influence pediatric asthma ED visit risk estimates for spatially
3 homogeneous pollutants such as O₃.

4 In copollutant analyses conducted over the entire dataset for the gaseous pollutants
5 (i.e., (CO, NO₂), and limited to a subset of years (i.e., 1998-2004) for which daily PM
6 data (i.e., PM_{2.5} elemental carbon, PM_{2.5} sulfate) were available, [Strickland et al. \(2010\)](#)
7 found that O₃ risk estimates were not substantially changed when controlling for other
8 pollutants (results not presented quantitatively). The authors also examined the C-R
9 relationship between O₃ exposure and pediatric asthma ED visits and found that both
10 quintile and loess C-R analyses ([Figure 6-17](#)) suggest that there are elevated associations
11 with O₃ at 8-h max concentrations as low as 30 ppb. These C-R analyses do not provide
12 evidence of a threshold level.

13 In a single-city study conducted on the West coast, [Mar and Koenig \(2009\)](#) examined the
14 association between O₃ exposure and asthma ED visits (ICD-9 codes: 493-493.9) for
15 children (<18) and adults (≥ 18) in Seattle, WA from 1998 to 2002. Of the total number
16 of visits over the study duration, 64% of visits in the age group <18 comprised boys, and
17 70% of visits in the ≥ 18 age group comprised females. [Mar and Koenig \(2009\)](#)
18 conducted a time-series analysis using both 1-h max and max 8-h avg O₃ concentrations.
19 A similar magnitude and pattern of associations was observed at each lag examined using
20 both metrics. [Mar and Koenig \(2009\)](#) presented results for single day lags of 0 to 5 days,
21 but found consistent positive associations across individual lag days which supports the
22 findings from the studies discussed above that examined multi-day exposures. For
23 children, consistent positive associations were observed across all lags, ranging from a
24 19.1-36.8% increase in asthma ED visits for a 30 ppb increase in 8-h max O₃
25 concentrations with the strongest associations observed at lag 0 (33.1% [95% CI: 3.0,
26 68.5]) and lag 3 (36.8% [95% CI: 6.1, 77.2]). O₃ was also found to be positively
27 associated with asthma ED visits for adults at all lags, ranging from 9.3-26.0%, except at
28 lag 0. The slightly different lag times for children and adults suggest that children may be
29 more immediately responsive to O₃ exposures than adults [Mar and Koenig \(2009\)](#).

Respiratory Infection

30 Although an increasing number of studies have examined the association between O₃
31 exposure and cause-specific respiratory ED visits this trend has not included an extensive
32 examination of the association between O₃ exposure and respiratory infection ED visits.
33 [Stieb et al. \(2009\)](#) also examined the association between short-term O₃ exposure and
34 respiratory infection ED visits in 7 Canadian cities. In an all-year analysis, there was no
35 evidence of an association between O₃ exposure and respiratory infection ED visits at any
36 lag examined (i.e., 0, 1, and 2). Across cities, respiratory infections comprised the single

1 largest diagnostic category, approximately 32%, of all the ED visits examined, which
2 also included myocardial infarction, heart failure, dysrhythmia, asthma, and COPD.

6.2.7.4 Outpatient and Physician Visit Studies

3 Several studies have examined the association between ambient O₃ concentrations and
4 physician or outpatient (non-hospital, non-eD) visits for acute conditions in various
5 geographic locations. [Burra et al. \(2009\)](#) examined asthma physician visits among
6 patients aged 1-17 and 18-64 years in Toronto, Canada from 1992 to 2001. The authors
7 found little or no evidence of an association between asthma physician visits and O₃;
8 however, seasonal analyses were not conducted. It should be noted that in this study,
9 most of the relative risks for O₃ were less than one and statistically significant, perhaps
10 indicating an inverse correlation with another pollutant or an artifact of the strong
11 seasonality of asthma visits. [Villeneuve et al. \(2006b\)](#) also focused on physician visits to
12 examine the effect of short-term O₃ exposure on allergic rhinitis among individuals aged
13 65 or older in Toronto from 1995 to 2000. The authors did not observe any evidence of
14 an association between allergic rhinitis physician visits and ambient O₃ concentrations in
15 single-day lag models in an all-year analysis (results not presented quantitatively).

16 In a study conducted in Atlanta, [Sinclair et al. \(2010\)](#) examined the association of acute
17 asthma and respiratory infection (e.g., upper respiratory infections and lower respiratory
18 infections) outpatient visits from a managed care organization with ambient O₃
19 concentrations as well as multiple PM size fractions and species from August 1998
20 through December 2002. The authors separated the analysis into two time periods (the
21 first 25 months of the study period and the second 28 months of the study period), in
22 order to compare the air pollutant concentrations and relationships between air pollutants
23 and acute respiratory visits for the 25-month time-period examined in [Sinclair and](#)
24 [Tolsma \(2004\)](#) to an additional 28-month time-period of available data from the Atlanta
25 Aerosol Research Inhalation Epidemiology Study (ARIES). The authors found little
26 evidence of an association between O₃ and asthma visits, for either children or adults, or
27 respiratory infection visits in all-year analyses and seasonal analyses. For example, a
28 slightly elevated relative risk (RR) for childhood asthma visits was observed during the
29 25-month period in the cold season (RR: 1.12 [95% CI: 0.86, 1.41]; lag 0-2 for a 30 ppb
30 increase in 8-h max O₃), but not in the warm season (RR: 0.97 [95% CI: 0.86, 1.10]; lag
31 0-2). During the 28-month period at lag 0-2, a slightly larger positive effect was observed
32 during the warm season (RR: 1.06 [95% CI: 0.97, 1.17]), compared to the cold season
33 (RR: 1.03 [95% CI: 0.87, 1.21]). Overall, these results contradict those from [Strickland et](#)
34 [al. \(2010\)](#) discussed above. Although the mean number of asthma visits and O₃
35 concentrations in [Sinclair et al. \(2010\)](#) and [Strickland et al. \(2010\)](#) are similar the

1 difference in results between the two studies could potentially be attributed to the severity
2 of O₃-induced asthma exacerbations (i.e., more severe symptoms requiring a visit to a
3 hospital) and behavior, such as delaying a visit to the doctor for less severe symptoms.

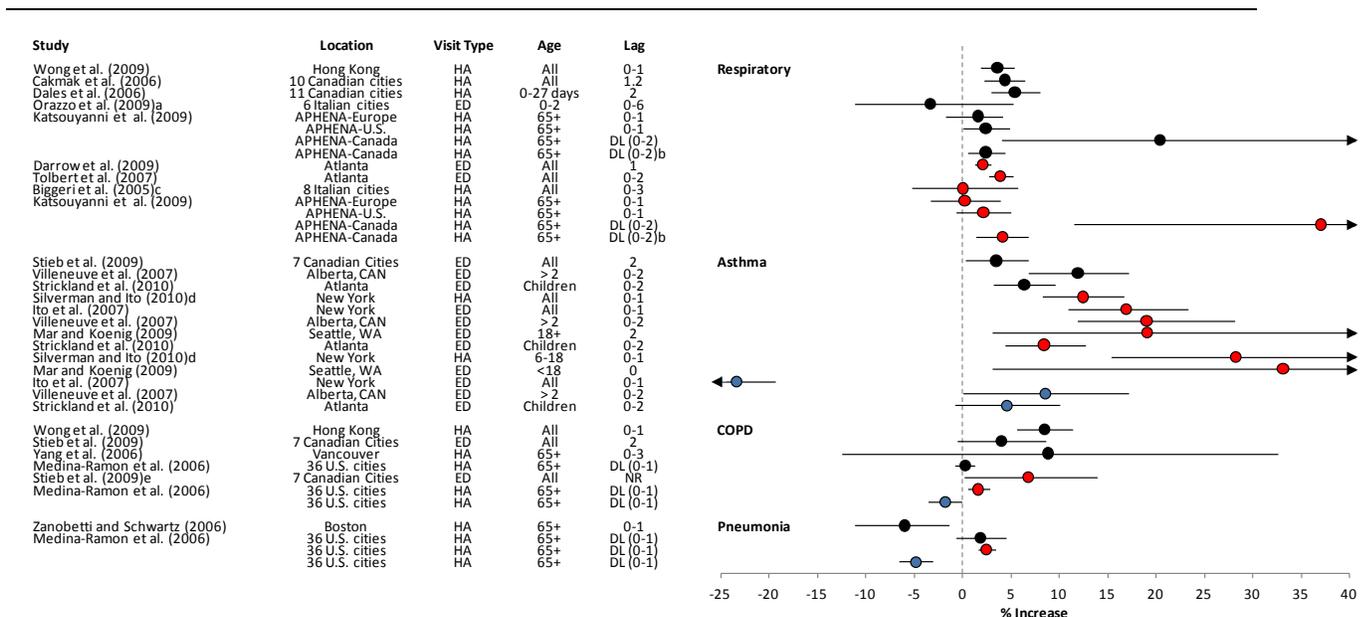
6.2.7.5 Summary

4 The results of the recent studies evaluated largely support the conclusion of the 2006 O₃
5 AQCD. While fewer studies were published overall since the previous review, several
6 multicity studies (e.g., [Cakmak et al., 2006b](#); [Dales et al., 2006](#)) and a multi-continent
7 study ([Katsouyanni et al., 2009](#)) provide supporting evidence for an association between
8 short-term O₃ exposure and an increase in respiratory-related hospital admissions and ED
9 visits. Across studies, different ICD-9 codes were used to define total respiratory causes,
10 which may contribute to some heterogeneity in the magnitude of association. These
11 findings are supported by single-city studies that used different exposure assignment
12 approaches (i.e., average of multiple monitors, single monitor, population-weighted
13 average) and averaging times (i.e., 1-h max and 8-h max).

14 Collectively, in both single-city and multicity studies there is continued evidence for
15 increases in both hospital admissions and ED visits when examining all respiratory
16 outcomes combined. Additionally, recent studies published since the 2006 O₃ AQCD
17 support an association between short-term O₃ exposure and asthma ([Strickland et al.,
18 2010](#); [Stieb et al., 2009](#)) and COPD ([Stieb et al., 2009](#); [Medina-Ramon et al., 2006](#))
19 hospital admissions and ED visits, with more limited evidence for pneumonia-hospital
20 admissions and ED visits ([Medina-Ramon et al., 2006](#); [Zanobetti and Schwartz, 2006](#)).
21 As with total respiratory causes, studies used slightly different ICD-9 codes to define
22 specific conditions. In seasonal analyses, stronger associations were observed in the
23 warm season or summer months compared to the cold season, particularly for asthma
24 ([Strickland et al., 2010](#); [Ito et al., 2007b](#)) and COPD ([Medina-Ramon et al., 2006](#))
25 ([Figure 6-18](#); [Table 6-28](#)), which is consistent with the conclusions of the 2006 O₃
26 AQCD. There is also continued evidence that children are particularly at greatest risk to
27 O₃-induced respiratory effects ([Silverman and Ito, 2010](#); [Strickland et al., 2010](#); [Mar and
28 Koenig, 2009](#); [Villeneuve et al., 2007](#); [Dales et al., 2006](#)). Of note, the consistent
29 associations observed across studies for short-term O₃ exposure and respiratory-related
30 hospital admissions and ED visits was not supported by studies that focused on
31 respiratory-related outpatient or physician visits. These differences could potentially be
32 attributed to the severity of O₃-induced respiratory effects requiring more immediate
33 treatment or behavioral factors that result in delayed visits to a physician. Although the
34 collective evidence across studies indicates a consistent positive association between O₃
35 exposure and respiratory-related hospital admissions and ED visits, the magnitude of

1 these associations may be underestimated due to behavioral modification in response to
 2 forecasted air quality (Neidell and Kinney, 2010; Neidell, 2009) (Section 4.6.5).

3 The studies that examined the potential confounding effects of copollutants found that O₃
 4 effect estimates remained relatively robust upon the inclusion of PM (measured using
 5 different sampling strategies ranging from every-day to every-6th day) and gaseous
 6 pollutants in two-pollutant models (Figure 6-19; Table 6-29). Additional studies that
 7 conducted copollutant analyses, but did not present quantitative results, also support these
 8 conclusions (Strickland et al., 2010; Tolbert et al., 2007; Medina-Ramon et al., 2006).
 9 Overall, recent studies provide copollutant results that are consistent with the studies
 10 evaluated in the 2006 O₃ AQCD [(U.S. EPA, 2006b), Figure 7-12, page 7-80 of the 2006
 11 O₃ AQCD], which found that O₃ respiratory hospital admissions risk estimates remained
 12 robust to the inclusion of PM in copollutant models.



Note: Effect estimates are for a 20 ppb increase in 24-h; 30 ppb increase in 8-h max; and 40 ppb increase in 1-h max O₃ concentrations. HA=hospital admission; ED=emergency department. Black=All-year analysis; Red=Summer only analysis; Blue=Winter only analysis.

^a Wheeze used as indicator of lower respiratory disease.

^b APHENA-Canada results standardized to approximate IQR of 5.1 ppb for 1-h max O₃ concentrations.

^c Study included 8 cities; but of those 8, only 4 had O₃ data.

^d non-ICU effect estimates.

^e The study did not specify the lag day of the summer season estimate.

Figure 6-18 Percent increase in respiratory-related hospital admission and ED visits in studies that presented all-year and/or seasonal results.

Table 6-28 Corresponding Effect Estimates for Figure 6-18.

| Study* | ED Visit or Hospital Admission | Location | Age | Lag | Avg Time | % Increase (95% CI) |
|--|--------------------------------|--------------------|-----------|----------------------|----------|---------------------|
| Respiratory | | | | | | |
| All-year | | | | | | |
| Wong et al. (2009) | Hospital Admission | Hong Kong | All | 0-1 | 8-h max | 3.58 (1.90, 5.29) |
| Cakmak et al. (2006b) | Hospital Admission | 10 Canadian cities | All | 1.2 | 24-h avg | 4.38 (2.19, 6.46) |
| Dales et al. (2006) | Hospital Admission | 11 Canadian cities | 0-27 days | 2 | 24-h avg | 5.41 (2.88, 7.96) |
| Orazio et al. (2009)^a | ED Visit | 6 Italian cities | 0-2 | 0-6 | 8-h max | -3.34 (-11.2, 5.28) |
| Katsouyanni et al. (2009) | Hospital Admission | APHENA-europe | 65+ | 0-1 | 1-h max | 1.58 (-1.71, 4.15) |
| | | APHENA-U.S. | 65+ | 0-1 | 1-h max | 2.38 (0.00, 4.89) |
| | | APHENA-Canada | 65+ | DL(0-2) | 1-h max | 20.4 (4.07, 40.2) |
| | | APHENA-Canada | 65+ | DL(0-2) ^b | 1-h max | 2.4 (0.51, 4.40) |
| Warm | | | | | | |
| Darrow et al. (2011a) | ED Visit | Atlanta | All | 1 | 8-h max | 2.08 (1.25, 2.91) |
| Tolbert et al. (2007) | ED Visit | Atlanta | All | 0-2 | 8-h max | 3.90 (2.70, 5.20) |
| Biggeri et al. (2005)^c | Hospital Admission | 8 Italian cities | All | 0-3 | 8-h max | 0.06 (-5.24, 5.66) |
| Katsouyanni et al. (2009) | Hospital Admission | APHENA-europe | 65+ | 0-1 | 1-h max | 0.24 (-3.32, 3.91) |
| | | APHENA-U.S. | 65+ | 0-1 | 1-h max | 2.14 (-0.63, 4.97) |
| | | APHENA-Canada | 65+ | DL(0-2) | 1-h max | 37.1 (11.5, 67.5) |
| | | APHENA-Canada | 65+ | DL(0-2) ^b | 1-h max | 4.1 (1.40, 6.80) |
| Asthma | | | | | | |
| All-year | | | | | | |
| Stieb et al. (2009) | ED Visit | 7 Canadian cities | All | 2 | 24-h avg | 3.48 (0.33, 6.76) |
| Villeneuve et al. (2007) | ED Visit | Alberta, CAN | >2 | 0-2 | 8-h max | 11.9 (6.8, 17.2) |
| Strickland et al. (2010) | ED Visit | Atlanta | Children | 0-2 | 8-h max | 6.38 (3.19, 9.57) |
| Warm | | | | | | |
| Silverman and Ito (2010)^d | Hospital Admission | New York | All | 0-1 | 8-h max | 12.5 (8.27, 16.7) |
| Ito et al. (2007b) | ED Visit | New York | All | 0-1 | 8-h max | 16.9 (10.9, 23.4) |
| Villeneuve et al. (2007) | ED Visit | Alberta, CAN | >2 | 0-2 | 8-h max | 19.0 (11.9, 28.1) |
| Mar and Koenig (2009) | ED Visit | Seattle, WA | 18+ | 2 | 8-h max | 19.1 (3.00, 40.5) |
| Strickland et al. (2010) | ED Visit | Atlanta | Children | 0-2 | 8-h max | 8.43 (4.42, 12.7) |
| Silverman and Ito (2010)^d | Hospital Admission | New York | 6-18 | 0-1 | 8-h max | 28.2 (15.3, 41.5) |
| Mar and Koenig (2009) | ED Visit | Seattle, WA | <18 | 0 | 8-h max | 33.1 (3.00, 68.5) |

| Study* | ED Visit or Hospital Admission | Location | Age | Lag | Avg Time | % Increase (95% CI) |
|---|--------------------------------|-------------------|----------|-----|----------|----------------------|
| Cold | | | | | | |
| Ito et al. (2007b) | ED Visit | New York | All | 0-1 | 8-h max | -23.4 (-27.3, -19.3) |
| Villeneuve et al. (2007) | ED Visit | Alberta, CAN | >2 | 0-2 | 8-h max | 8.50 (0.00, 17.2) |
| Strickland et al. (2010) | ED Visit | Atlanta | Children | 0-2 | 8-h max | 4.52 (-0.82, 10.1) |
| COPD | | | | | | |
| All-year | | | | | | |
| Stieb et al. (2009) | ED Visit | 7 Canadian cities | All | 2 | 24-h avg | 4.03 (-0.54, 8.62) |
| Medina-Ramon et al. (2006) | Hospital Admission | 36 U.S. cities | 65+ | 0-1 | 8-h max | 0.24 (-0.78, 1.21) |
| Yang et al. (2005b) | Hospital Admission | Vancouver | 65+ | 0-3 | 24-h avg | 8.80 (-12.5, 32.6) |
| Warm | | | | | | |
| Stieb et al. (2009)^e | ED Visit | 7 Canadian cities | All | NR | 24-h avg | 6.76 (0.11, 13.9) |
| Medina-Ramon et al. (2006) | Hospital Admission | 36 U.S. cities | 65+ | 0-1 | 8-h max | 1.63 (0.48, 2.85) |
| Cold | | | | | | |
| Medina-Ramon et al. (2006) | Hospital Admission | 36 U.S. cities | 65+ | 0-1 | 8-h max | -1.85 (-3.60, -0.06) |
| Pneumonia | | | | | | |
| All-year | | | | | | |
| Zanobetti and Schwartz (2006) | Hospital Admission | Boston | 65+ | 0-1 | 24-h avg | -5.96 (-11.1, -1.36) |
| Medina-Ramon et al. (2006) | Hospital Admission | 36 U.S. cities | 65+ | 0-1 | 8-h max | 1.81 (-0.72, 4.52) |
| Warm | | | | | | |
| Medina-Ramon et al. (2006) | Hospital Admission | 36 U.S. cities | 65+ | 0-1 | 8-h max | 2.49 (1.57, 3.47) |
| Cold | | | | | | |
| Medina-Ramon et al. (2006) | Hospital Admission | 36 U.S. cities | 65+ | 0-1 | 8-h max | -4.88 (-6.59, -3.14) |

*Includes studies in [Figure 6-18](#).

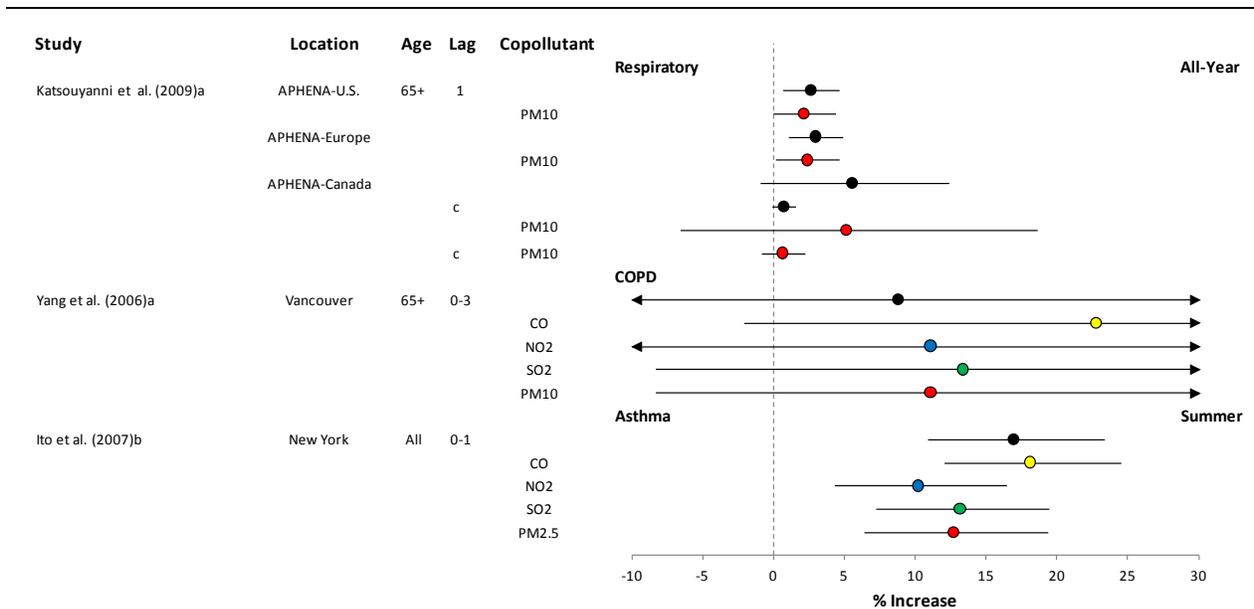
^aWheeze used as indicator of lower respiratory disease.

^bAPHENA-Canada results standardized to approximate IQR of 5.1 ppb for 1-h max O₃ concentrations.

^cStudy included 8 cities, but of those 8 only 4 had O₃ data.

^dNon-ICU effect estimates.

^eThe study did not specify the lag day of the summer season estimate.



Notes: Effect estimates are for a 20 ppb increase in 24 hours; 30 ppb increase in 8-h max; and 40 ppb increase in 1-h max O₃ concentrations.

^aStudies that examined hospital admissions,

^bA study that examined ED visits,

^cRisk estimates from APHENA -Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations. Black = results from single-pollutant models; Red = results from copollutant models with PM₁₀ or PM_{2.5}; Yellow = results from copollutant models with CO; Blue = results from copollutant models with NO₂; Green = results from copollutant models with SO₂.

Figure 6-19 Percent increase in respiratory-related hospital admissions and ED visits for studies that presented single and copollutant model results.

Table 6-29 Corresponding effect estimates for Figure 6-19.

| Study* ^a | Location | Visit Type | Age | Lag | Copollutant | % Increase (95% CI) |
|---|---------------|--------------------|-------------------|------------------|---------------------------------|---------------------------------|
| All-year: Respiratory | | | | | | |
| Katsouyanni et al. (2009) | APHENA-U.S. | Hospital Admission | 65+ | 1 | | 2.62 (0.63, 4.64) |
| | | | | | PM ₁₀ | 2.14 (-0.08, 4.40) |
| | APHENA-europe | | | | | 2.94 (1.02, 4.89) |
| | | PM ₁₀ | 2.38 (0.08, 4.64) | | | |
| | APHENA-Canada | | | | | 5.54 (-0.94, 12.4) |
| | | | | | | 0.69 (-0.12, 1.50) ^b |
| PM ₁₀ | | 5.13 (-6.62, 18.6) | | | | |
| | | | | PM ₁₀ | 0.64 (-0.87, 2.20) ^b | |
| | COPD | | | | | |
| Yang et al. (2005b) | Vancouver | Hospital Admission | 65+ | 0-3 | | 8.80 (-12.5, 32.6) |
| | | | | | CO | 22.8 (-2.14, 50.7) |
| | | | | | NO ₂ | 11.1 (-10.4, 37.6) |
| | | | | | SO ₂ | 13.4 (-8.40, 40.2) |
| | | | | | PM ₁₀ | 11.1 (-8.40, 37.6) |
| Summer: Asthma | | | | | | |
| Ito et al. (2007b) | New York | ED | All | 0-1 | | 16.9 (10.9, 23.4) |
| | | | | | CO | 18.1 (12.1, 24.5) |
| | | | | | NO ₂ | 10.2 (4.29, 16.4) |
| | | | | | SO ₂ | 13.1 (7.16, 19.5) |
| | | | | | PM _{2.5} | 12.7 (6.37, 19.3) |

*Studies include in [Figure 6-19](#).

^aAveraging times: [Katsouyanni et al. \(2009\)](#) = 1-h max; [Yang et al. \(2005b\)](#) = 24-h avg; and [Ito et al. \(2007b\)](#) = 8-h max.

^bRisk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations.

1 To date only a few studies have examined the C-R relationship between short-term O₃
2 exposure and respiratory-related hospital admissions and ED visits. A preliminary
3 examination of the C-R relationship found no evidence of a deviation from linearity when
4 examining the association between short-term O₃ exposure and asthma hospital
5 admissions ([Silverman and Ito, 2010](#)). Additionally, an examination of the C-R
6 relationship for O₃ exposure and pediatric asthma ED visits found no evidence of a
7 threshold with elevated associations with O₃ at concentrations as low as 30 ppb
8 ([Silverman and Ito, 2010](#); [Strickland et al., 2010](#)). However, in both studies there is
9 uncertainty in the shape of the C-R curve at the lower end of the distribution of O₃
10 concentrations due to the low density of data in this range.

1 In totality, building upon the conclusions of the 2006 AQCD, the evidence from recent
2 studies continues to support an association between short-term O₃ exposure and
3 respiratory-related hospital admissions and ED visits. Additional evidence also supports
4 stronger associations during the warm season for specific respiratory outcomes such as
5 asthma and COPD.

6.2.8 Respiratory Mortality

6 The epidemiologic, controlled human exposure, and toxicological studies discussed
7 within this section (Section [6.2](#)) provides evidence for multiple respiratory effects in
8 response to short-term O₃ exposure. Additionally, the evidence from experimental studies
9 indicates multiple potential pathways of O₃-induced respiratory effects, which support the
10 continuum of respiratory effects that could potentially result in respiratory-related
11 mortality. The 2006 O₃ AQCD found inconsistent evidence for an association between
12 short-term O₃ exposure and respiratory mortality ([U.S. EPA, 2006b](#)). Although some
13 studies reported a strong positive association between O₃ exposure and respiratory
14 mortality, additional studies reported a small association or no association. The majority
15 of recent multicity studies found consistent positive associations between short-term O₃
16 exposure and respiratory mortality, specifically during the summer months.

17 The APHENA study, described earlier in Section [6.2.7.2](#), ([Katsouyanni et al., 2009](#)) also
18 examined associations between short-term O₃ exposure and mortality and found
19 consistent positive associations for respiratory mortality in all-year analyses, except in the
20 Canadian data set for ages ≥ 75 , with an increase in the magnitude of associations in
21 analyses restricted to the summer season across data sets and age ranges. Additional
22 multicity studies from the U.S. ([Zanobetti and Schwartz, 2008b](#)), Europe ([Samoli et al.,
23 2009](#)), Italy ([Stafoggia et al., 2010](#)), and Asia ([Wong et al., 2010](#)) that conducted summer
24 season and/or all-year analyses provide additional support for an association between
25 short-term O₃ exposure and respiratory mortality ([Figure 6-36](#)).

26 Of the studies evaluated, only the APHENA study ([Katsouyanni et al., 2009](#)) and the
27 Italian multicity study ([Stafoggia et al., 2010](#)) conducted an analysis of the potential for
28 copollutant confounding of the O₃-respiratory mortality relationship. In the APHENA
29 study, specifically the European dataset, focused on the natural spline model with
30 8 df/year (as discussed in Section [6.2.7.2](#)) and lag 1 results (as discussed in
31 Section [6.6.2.1](#)), respiratory mortality risk estimates were robust to the inclusion of PM₁₀
32 in copollutant models in all-year analyses with O₃ respiratory mortality risk estimates
33 increasing in the Canadian and U.S. datasets compared to single-pollutant model results.
34 In summer season analyses, respiratory O₃ mortality risk estimates were robust in the

1 U.S. dataset and attenuated in the European dataset. Similarly, in the Italian multicity
2 study ([Stafoggia et al., 2010](#)), which was limited to the summer season, respiratory
3 mortality risk estimates were attenuated in copollutant models with PM₁₀. Based on the
4 APHENA and Italian multicity results, O₃ respiratory mortality risk estimates appear to
5 be moderately to substantially sensitive (e.g., increased or attenuated) to inclusion of
6 PM₁₀. However, in the APHENA study, the mostly every-6th-day sampling schedule for
7 PM₁₀ in the Canadian and U.S. datasets greatly reduced their sample size and limits the
8 interpretation of these results.

6.2.9 Summary and Causal Determination

9 The 2006 O₃ AQCD concluded that there was clear, consistent evidence of a causal
10 relationship between short-term O₃ exposure and respiratory effects ([U.S. EPA, 2006b](#)).
11 This conclusion was substantiated by evidence from controlled human exposure and
12 toxicological studies indicating a range of respiratory effects in response to short-term O₃
13 exposure, including pulmonary function decrements and increases in respiratory
14 symptoms, lung inflammation, lung permeability, and airway hyperresponsiveness.
15 Toxicological studies provided additional evidence for O₃-induced impairment of host
16 defenses. Combined, these findings from experimental studies provided support for
17 epidemiologic evidence, in which short-term increases in O₃ concentration were
18 consistently associated with decreases in lung function in populations with increased
19 outdoor exposures, children with asthma, and healthy children; increases in respiratory
20 symptoms and asthma medication use in children with asthma; and increases in
21 respiratory-related hospital admissions and asthma-related ED visits. Short-term
22 increases in ambient O₃ concentration also were consistently associated with increases in
23 all-cause and cardiopulmonary mortality; however, the contribution of respiratory causes
24 to these findings was uncertain.

25 Building on the large body of evidence presented in the 2006 O₃ AQCD, recent studies
26 support associations between short-term O₃ exposure and respiratory effects. Controlled
27 human exposure studies continue to provide the strongest evidence for lung function
28 decrements in young healthy adults over a range of O₃ concentrations. Studies previously
29 reported mean O₃-induced FEV₁ decrements of 6-8% at 80 ppb O₃ ([Adams, 2006a](#),
30 [2003a](#); [McDonnell et al., 1991](#); [Horstman et al., 1990](#)), and recent evidence additionally
31 indicates mean FEV₁ decrements of 6% at 70 ppb O₃ ([Schelegle et al., 2009](#)) and 2-3% at
32 60 ppb O₃ ([Kim et al., 2011](#); [Brown et al., 2008](#); [Adams, 2006a](#)) (Section 6.2.1.1). In
33 healthy young adults, O₃-induced decrements in FEV₁ do not appear to depend on sex
34 ([Hazucha et al., 2003](#)), body surface area or height ([McDonnell et al., 1997](#)), lung size or
35 baseline FVC ([Messineo and Adams, 1990](#)). There is limited evidence that blacks may

1 experience greater O₃-induced decrements in FEV₁ than do age-matched whites ([Que et](#)
2 [al., 2011](#); [Seal et al., 1993](#)). Healthy children experience similar spirometric responses
3 but lesser symptoms from O₃ exposure relative to young adults ([McDonnell et al.,](#)
4 [1985a](#)). On average, spirometric and symptom responses to O₃ exposure appear to decline
5 with increasing age beyond about 18 years of age ([McDonnell et al., 1999b](#); [Seal et al.,](#)
6 [1996](#)). There is also a tendency for slightly increased spirometric responses in mild
7 asthmatics and allergic rhinitics relative to healthy young adults ([Jorres et al., 1996](#)).
8 Spirometric responses in asthmatics appear to be affected by baseline lung function,
9 i.e., responses increase with disease severity ([Horstman et al., 1995](#)).

10 Available information from controlled human exposure studies on recovery from O₃
11 exposure indicates that an initial phase of recovery in healthy individuals proceeds
12 relatively rapidly, with acute spirometric and symptom responses resolving within about
13 2 to 4 hours ([Folinsbee and Hazucha, 1989](#)). Small residual lung function effects are
14 almost completely resolved within 24 h. Effects of O₃ on the small airways persisting
15 a day following exposure, assessed by persistent decrement in FEF_{25-75%} and altered
16 ventilation distribution, may be due in part to inflammation ([Frank et al., 2001](#); [Foster et](#)
17 [al., 1997](#)). In more responsive individuals, this recovery in lung function takes longer (as
18 much as 48 hours) to return to baseline. Some cellular responses may not return to
19 baseline levels in humans for more than 10-20 days following O₃ exposure ([Devlin et al.,](#)
20 [1997](#)). Airway hyperresponsiveness and increased epithelial permeability are also
21 observed as late as 24 hours postexposure ([Que et al., 2011](#)).

22 With repeated O₃ exposures over several days, spirometric and symptom responses
23 become attenuated in both healthy individuals and asthmatics, but this attenuation is lost
24 after about a week without exposure ([Gong et al., 1997a](#); [Folinsbee et al., 1994](#); [Kulle et](#)
25 [al., 1982](#)). Airway responsiveness also appears to be somewhat attenuated with repeated
26 O₃ exposures in healthy individuals, but becomes increased in individuals with
27 preexisting allergic airway disease ([Gong et al., 1997a](#); [Folinsbee et al., 1994](#)). Some
28 indicators of pulmonary inflammation are attenuated with repeated O₃ exposures.
29 However, other markers such as epithelial integrity and damage do not show attenuation,
30 suggesting continued tissue damage during repeated O₃ exposure ([Devlin et al., 1997](#)).

31 Consistent with controlled human exposure study findings, epidemiologic evidence
32 indicates that lung function decrements are related to short-term increases in ambient O₃
33 concentration (Section [6.2.1.2](#)). As described in the 1996 and 2006 O₃ AQCDs, the most
34 consistent observations were those in populations engaged in outdoor recreation,
35 exercise, or work. Epidemiologic evidence also demonstrates that increases in ambient O₃
36 concentration are associated with decreases in lung function in children with asthma
37 ([Figure 6-6](#) and [Figure 6-7](#) and [Table 6-8](#) and [Table 6-9](#)) and children without asthma

1 ([Figure 6-8](#) and [Table 6-12](#)). Evidence in adults with respiratory disease and healthy
2 adults is inconsistent. In children with asthma, lung function mostly was found to
3 decrease by <1-2% per unit increase in O₃ concentration¹. However, in children with
4 asthma, O₃-associated lung function decrements were found in conjunction with O₃-
5 associated increases in respiratory symptoms ([Just et al., 2002](#); [Mortimer et al., 2002](#);
6 [Ross et al., 2002](#); [Gielen et al., 1997](#); [Romieu et al., 1997](#); [Thurston et al., 1997](#); [Romieu](#)
7 [et al., 1996](#)). Biological plausibility for O₃-associated decrements in lung function in
8 controlled human exposure, epidemiologic, and animal studies is provided by the well-
9 documented effects of O₃ on activation of bronchial C-fibers (Section [5.3.2](#)).

10 Across disciplines, studies have examined factors that may potentially increase the risk of
11 O₃-induced decrements in lung function. In the controlled human exposure studies, there
12 is a large degree of intersubject variability in lung function decrements, symptomatic
13 responses, pulmonary inflammation, airway hyperresponsiveness, and altered epithelial
14 permeability in healthy adults exposed to O₃ ([Que et al., 2011](#); [Holz et al., 2005](#);
15 [McDonnell, 1996](#)). The magnitude of pulmonary inflammation, airway
16 hyperresponsiveness, and increases in epithelial permeability do not appear to be
17 correlated, nor are these responses to O₃ correlated with changes in lung function,
18 suggesting that different mechanisms may be responsible for these processes ([Que et al.,](#)
19 [2011](#); [Balmes et al., 1997](#); [Balmes et al., 1996](#); [Aris et al., 1995](#)). However, these
20 responses tend to be reproducible within a given individual over a period of several
21 months indicating differences in the intrinsic responsiveness of individuals ([Holz et al.,](#)
22 [2005](#); [Hazucha et al., 2003](#); [Holz et al., 1999](#); [McDonnell et al., 1985b](#)). Numerous
23 reasons for differences in the risk of individuals to O₃ exposure have been reported in the
24 literature. These include dosimetric and mechanistic differences (Section [5.4](#)). Further,
25 evidence in all three disciplines suggests a role for antioxidant defenses (i.e., vitamin
26 supplementation, genetic variants in oxidative metabolizing enzymes) in modulating
27 respiratory responses to O₃. The biological plausibility of these findings is provided by
28 the well-characterized evidence for O₃ exposure leading to the formation of secondary
29 oxidation products that subsequently activate neural reflexes that mediate lung function
30 decrements (Section [5.3.2](#)) and that initiate pulmonary inflammation (Section [5.3.3](#)).

31 Recent controlled human exposure studies (Section [6.2.3.1](#)) and toxicological studies
32 (Section [6.2.3.3](#)) also continue to demonstrate lung injury and inflammatory responses
33 upon O₃ exposure. Evidence from more than a hundred toxicological studies clearly
34 indicates that O₃ induces damage and inflammation in the lung, and studies continue to
35 elucidate the mechanistic pathways involved (Section [5.3](#)). Though inflammation may
36 resolve, continued cellular damage may alter the structure and function of pulmonary

¹ Effect estimates were standardized to a 40-ppb increase for 1-h max O₃, a 30-ppb increase for 8-h max O₃, and a 20-ppb increase for 24-h avg O₃.

1 tissues. Recent controlled human studies support previous findings for pulmonary
2 inflammation but demonstrate effects at 60 ppb O₃, the lowest concentration evaluated.
3 Building on the extensive experimental evidence, recent epidemiologic studies, most of
4 which were conducted in Mexico City, indicate ambient O₃-associated increases in
5 pulmonary inflammation in children with asthma. Multiple studies examined and found
6 increases in eNO ([Berhane et al., 2011](#); [Khatri et al., 2009](#); [Barraza-Villarreal et al.,
7 2008](#)). In subjects with asthma, these O₃-associated increases in pulmonary inflammation
8 were found concomitantly with O₃-associated increases in respiratory symptoms ([Khatri
9 et al., 2009](#); [Barraza-Villarreal et al., 2008](#)). Although more limited in number,
10 epidemiologic studies also found associations with cytokines such as IL-6 or IL-8
11 ([Barraza-Villarreal et al., 2008](#); [Sienra-Monge et al., 2004](#)), eosinophils ([Khatri et al.,
12 2009](#)), antioxidants ([Sienra-Monge et al., 2004](#)), and indicators of oxidative stress
13 ([Romieu et al., 2008](#)) (Section [6.2.3.2](#)). This epidemiologic evidence is coherent with
14 results from controlled human exposure and toxicological studies that demonstrated an
15 induction or reduction of these same endpoints after O₃ exposure.

16 The evidence for O₃-induced pulmonary inflammation and airway hyperresponsiveness,
17 largely demonstrated in controlled human exposure and toxicological studies, provides
18 mechanistic support for O₃-associated increases in respiratory symptoms observed in both
19 controlled human exposure and epidemiologic studies. Controlled human exposure
20 studies of healthy, young adults demonstrate increases in respiratory symptoms induced
21 by O₃ exposures <80 ppb ([Schelegle et al., 2009](#); [Adams, 2006a](#)) (Section [6.2.1.1](#)).
22 Adding to this evidence, epidemiologic studies find effects in children with asthma.
23 Although the epidemiologic evidence was less consistent in the few available U.S.
24 multicity studies ([O'Connor et al., 2008](#); [Schildcrout et al., 2006](#); [Mortimer et al., 2002](#)),
25 the weight of evidence, provided by a larger body of single-city and -region studies,
26 indicates that short-term increases in ambient O₃ concentration are associated with
27 increases in respiratory symptoms and asthma medication use in children with asthma
28 (Section [6.2.4.1](#)). Several epidemiologic studies found associations between ambient O₃
29 concentrations and respiratory symptoms in populations with asthma that also had a high
30 prevalence of allergy (52-100%) ([Escamilla-Nuñez et al., 2008](#); [Feo Brito et al., 2007](#);
31 [Romieu et al., 2006](#); [Just et al., 2002](#); [Mortimer et al., 2002](#); [Ross et al., 2002](#); [Gielen et
32 al., 1997](#)). The strong evidence in populations with asthma and allergy is supported by
33 observations of O₃-induced inflammation in animal models of allergy (Section [6.2.3.3](#)),
34 and may be explained mechanistically by the action of O₃ to sensitize bronchial smooth
35 muscle to hyperreactivity and thus, potentially act as a primer for subsequent exposure to
36 antigens such as allergens (Section [5.3.5](#)).

37 Modification of innate and adaptive immunity is emerging as a mechanistic pathway
38 contributing to the effects of O₃ on asthma and allergic airways disease (Section [5.3.6](#)).

1 While the majority of evidence comes from animal studies, controlled human exposure
2 studies have found differences between asthmatics and healthy controls in O₃-mediated
3 innate and adaptive immune responses (Section [5.4.2.2](#)), suggesting that these pathways
4 may be relevant to humans and may lead to the induction and exacerbation of asthma
5 ([Alexis et al., 2010](#); [Hernandez et al., 2010](#); [Alexis et al., 2009](#); [Bosson et al., 2003](#)).

6 The subclinical and overt respiratory effects observed across disciplines, as described
7 above, collectively provide support for epidemiologic studies that demonstrate
8 consistently positive associations between short-term O₃ exposure and respiratory-related
9 hospital admissions and ED visits (Section [6.2.7](#)). Consistent with evidence presented in
10 the 2006 O₃ AQCD, recent multicity studies and a multicontinent study (i.e., APHENA)
11 ([Katsouyanni et al., 2009](#)) found risk estimates ranging from an approximate 1.6 to 5.4%
12 increase in all respiratory-related hospital admissions and ED visits in all-year analyses
13 for a unit increase in ambient O₃ concentration (as described in Section [2.1](#)). Positive
14 associations persisted in analyses restricted to the summer season, but the magnitude
15 varied depending on the study location ([Figure 6-18](#)). Compared with studies reviewed in
16 the 2006 O₃ AQCD, a larger number of recent studies examined hospital admissions and
17 ED visits for specific respiratory outcomes. Although limited in number, both single- and
18 multi-city studies found consistent, positive associations between short-term O₃
19 exposures and asthma and COPD hospital admissions and ED visits, with more limited
20 evidence for pneumonia. Consistent with the conclusions of the 2006 O₃ AQCD, in
21 studies that conducted seasonal analyses, risk estimates were elevated in the warm season
22 compared to cold season or all-season analyses, specifically for asthma and COPD.
23 Although recent studies did not include detailed age-stratified results, the increased risk
24 of asthma hospital admissions ([Silverman and Ito, 2010](#); [Strickland et al., 2010](#); [Dales et
25 al., 2006](#)) observed for children strengthens the conclusion from the 2006 O₃ AQCD that
26 children are potentially at increased risk of O₃-induced respiratory effects ([U.S. EPA,
27 2006b](#)). Although the C-R relationship has not been extensively examined, preliminary
28 examinations found no evidence of a threshold between short-term O₃ exposure and
29 asthma hospital admissions and pediatric asthma ED visits, with uncertainty in the shape
30 of the C-R curve at the lower limit of ambient concentrations in the U.S. ([Silverman and
31 Ito, 2010](#); [Strickland et al., 2010](#)).

32 Recent evidence extends the potential range of well-established O₃-associated respiratory
33 effects by demonstrating associations between short-term ambient O₃ exposure and
34 respiratory-related mortality. In all-year analyses, a multicontinent (APHENA) and
35 multicity (PAPA) study found consistent, positive associations with respiratory mortality
36 with evidence of an increase in the magnitude of associations in analyses restricted to the
37 summer months. Further, additional multicity studies conducted in the U.S. and Europe

1 provide evidence supporting stronger O₃-respiratory mortality associations during the
2 summer season (Section [6.2.8](#)).

3 Several studies of respiratory morbidity and mortality evaluated the potential
4 confounding effects of copollutants, in particular, PM₁₀, PM_{2.5}, or NO₂. In most cases,
5 effect estimates remained robust to the inclusion of copollutants. In some studies of lung
6 function and respiratory symptoms, larger effects were estimated for O₃ when
7 copollutants were added to models. Ozone effect estimates for respiratory-related hospital
8 admissions and ED visits remained relatively robust upon the inclusion of PM and
9 gaseous pollutants in two-pollutant models ([Strickland et al., 2010](#); [Tolbert et al., 2007](#);
10 [Medina-Ramon et al., 2006](#)). Although copollutant confounding was not extensively
11 examined in studies of cause-specific mortality, O₃-respiratory mortality risk estimates
12 remained positive but were moderately to substantially sensitive (e.g., increased or
13 attenuated) to the inclusion of PM₁₀ in copollutant models ([Stafoggia et al., 2010](#);
14 [Katsouyanni et al., 2009](#)). However, interpretation of these results requires caution due to
15 the limited PM datasets used in these studies as a result of the every 3rd- or 6th-day PM
16 sampling schedule employed in most cities. Together, these copollutant-adjusted findings
17 across respiratory endpoints provide support for the independent effects of short-term
18 exposures to ambient O₃.

19 Across the respiratory endpoints examined in epidemiologic studies, associations were
20 found using several different exposure assessment methods that likely vary in how well
21 ambient O₃ concentrations represent ambient exposures and between-subject variability
22 in exposures. Evidence clearly demonstrated O₃-associated lung function decrements in
23 populations with increased outdoor exposures for whom ambient O₃ concentrations
24 measured on site of outdoor activity and/or at the time of outdoor activity have been more
25 highly correlated and similar in magnitude to personal O₃ exposures (Section [4.3.3](#)).
26 However, associations with respiratory effects also were found with ambient O₃
27 concentrations expected to have weaker personal-ambient relationships, including those
28 measured at home or school, measured at the closest site, averaged from multiple
29 community sites, and measured at a single site. Overall, there was no clear indication that
30 a particular method of exposure assessment produced stronger findings.

31 An additional consideration in the evaluation of the epidemiologic evidence is the impact
32 of behavioral modifications on observed associations. A study demonstrated that the
33 magnitude of O₃-associated asthma hospitalizations in Los Angeles, CA was
34 underestimated due to behavioral modification in response to forecasted air quality
35 (Section [4.6.5](#)). It is important to note that the study was limited to one metropolitan area
36 and used air quality data for the years 1989-1997, when the O₃ concentration that
37 determines the designation of an O₃ action day, was much higher than it is currently.

1 Both panel and time-series epidemiologic studies found increases in respiratory effects in
2 association with increases in O₃ concentrations using various exposure metrics
3 (i.e., 24-h avg, 1-h max, and 8-h max O₃ concentrations). However, for respiratory
4 symptoms and pulmonary inflammation, a majority of studies examined and found
5 associations with 1-h max or 8-h max and 8-h max or daytime avg O₃, respectively.
6 Within study comparisons of associations among various exposure metrics with lung
7 function and respiratory symptoms yielded mixed evidence. Within some studies, larger
8 effects were estimated for shorter O₃ averaging times whereas in other studies, larger
9 effects were estimated for longer averaging times or no difference was found among
10 averaging times. Comparisons in a limited number of time-series studies indicate rather
11 comparable risk estimates across exposure metrics with some evidence indicating that
12 24-h avg O₃ was associated with a smaller increase in risk of respiratory ED visits
13 (Section [6.2.7.3](#)). Overall, there was no indication that the consistency or magnitude of
14 the observed association was stronger for a particular O₃ exposure metric. In examination
15 of the lag structure of associations, the weight of epidemiologic evidence for the range of
16 respiratory endpoints supports associations with ambient O₃ concentrations lagged 0 to
17 1 day, which is consistent with the O₃-induced respiratory effects observed in controlled
18 human exposure studies. Several studies also found increased respiratory morbidity in
19 association with O₃ concentrations averaged over multiple days (2 to 5 days). Across
20 respiratory endpoints examined in epidemiologic studies, there was not strong evidence
21 that the magnitude of association was larger for any particular lag.

22 In summary, recent studies evaluated since the completion of the 2006 O₃ AQCD support
23 and expand upon the strong body of evidence that indicated a causal relationship between
24 short-term O₃ exposure and respiratory health effects. Controlled human exposure studies
25 continue to demonstrate O₃-induced decreases in FEV₁ and pulmonary inflammation at
26 concentrations as low as 60 ppb. Epidemiologic studies provide evidence that increases in
27 ambient O₃ exposure can result in lung function decrements, increases in respiratory
28 symptoms, and pulmonary inflammation in children with asthma; increases in
29 respiratory-related hospital admissions and ED visits; and increases in respiratory
30 mortality. Recent toxicological studies demonstrating O₃-induced inflammation, airway
31 hyperresponsiveness, and impaired lung host defense have continued to support the
32 biological plausibility for the O₃-induced respiratory effects observed in the controlled
33 human exposure and epidemiologic studies. Additionally, recent epidemiologic studies
34 further confirm that respiratory morbidity and mortality associations are stronger during
35 the warm/summer months and remain relatively robust after adjustment for copollutants.
36 The recent evidence integrated across toxicological, controlled human exposure, and
37 epidemiologic studies, along with the total body of evidence evaluated in previous
38 AQCDs, is sufficient to conclude that there **is a causal relationship between short-**
39 **term O₃ exposure and respiratory health effects.**

6.3 Cardiovascular Effects

1 Overall, there have been a relatively small number of studies that have examined the
2 potential effect of short-term O₃ exposure on the cardiovascular system. This was
3 reflected in the 1996 O₃ AQCD by the limited discussion on possible O₃-related
4 cardiovascular effects. The 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) built upon the limited
5 evidence described in the 1996 O₃ AQCD and further explored the potential relationship
6 between short-term O₃ exposure and cardiovascular outcomes. The 2006 O₃ AQCD
7 concluded that “O₃ directly and/or indirectly contributes to cardiovascular-related
8 morbidity” but added that the body of evidence was limited. This conclusion was based
9 on a controlled human exposure study that included hypertensive adult males, a few
10 epidemiologic studies of physiologic effects, heart rate variability, arrhythmias,
11 myocardial infarctions, and hospital admissions, and toxicological studies of heart rate,
12 heart rhythm, and blood pressure.

6.3.1 Controlled Human Exposure

13 O₃ reacts rapidly on contact with respiratory system tissue and is not absorbed or
14 transported to extrapulmonary sites to any significant degree as such. Controlled human
15 exposure studies discussed in the previous AQCDs failed to demonstrate any consistent
16 extrapulmonary effects. Some controlled human exposure studies have attempted to
17 identify specific markers of exposure to O₃ in blood. [Buckley et al. \(1975\)](#) reported a
18 28% increase in serum α -tocopherol and a 26% increase in erythrocyte fragility in healthy
19 males immediately following exposure to 500 ppb O₃ for 2.75 hours with exercise
20 (unspecified activity level). However, in healthy adult males exposed during exercise
21 ($\dot{V}_E=44$ L/min) to 323 ppb O₃ (on average) for 130 min on 3 consecutive days, [Foster et](#)
22 [al. \(1996\)](#) found a 12% reduction in serum α -tocopherol 20 hours after the third day of O₃
23 exposure. [Liu et al. \(1999\)](#); [\(1997\)](#) used a salicylate metabolite, 2,3, dehydroxybenzoic
24 acid (DHBA), to indicate increased levels of hydroxyl radical which hydroxylates
25 salicylate to DHBA. Increased DHBA levels after exposure to 120 and 400 ppb suggest
26 that O₃ increases production of hydroxyl radical. The levels of DHBA were correlated
27 with changes in spirometry. Interestingly, simultaneous exposure of healthy adults to O₃
28 (120 ppb for 2 hours at rest) and concentrated ambient particles (CAPs) resulted in a
29 diminished systemic IL-6 response compared with exposure to CAPs alone ([Urch et al.,](#)
30 [2010](#)).

31 [Gong et al. \(1998\)](#) exposed hypertensive (n = 10) and healthy (n = 6) adult males, 41 to
32 78 years of age, to FA and on the subsequent day to 300 ppb O₃ for 3 hours with
33 intermittent exercise ($\dot{V}_E = 30$ L/min). The overall results did not indicate any major acute

1 cardiovascular effects of O₃ in either the hypertensive individuals or healthy controls.
2 Statistically significant O₃ effects for both groups combined were increases in heart rate,
3 rate-pressure product, and the alveolar-to-arterial PO₂ gradient, suggesting that impaired
4 gas exchange was being compensated for by increased myocardial work. The mechanism
5 for the decrease in arterial oxygen tension in the [Gong et al. \(1998\)](#) study could be due to
6 an O₃-induced ventilation-perfusion mismatch. [Gong et al. \(1998\)](#) suggested that by
7 impairing alveolar-arterial oxygen transfer, the O₃ exposure could potentially lead to
8 adverse cardiac events by decreasing oxygen supply to the myocardium. The subjects in
9 the [Gong et al. \(1998\)](#) study had sufficient functional reserve so as to not experience
10 significant ECG changes or myocardial ischemia and/or injury. In studies evaluating the
11 exercise performance of healthy adults, no significant effect of O₃ on arterial O₂
12 saturation has been observed ([Schelegle and Adams, 1986](#)).

13 [Fakhri et al. \(2009\)](#) evaluated changes in HRV among adult volunteers (n = 50;
14 27 ± 7 years) during 2-hour exposures to PM_{2.5} CAPs (127 ± 62 µg/m³) and O₃
15 (114 ± 7 ppb), alone and in combination. High frequency HRV was increased following
16 CAPs-only (p = 0.046) and O₃-only (p = 0.051) exposures, but not in combination. The
17 standard deviation of NN intervals and the square root of the mean squared differences of
18 successive NN intervals also showed marginally significant (0.05 < p < 0.10) increase due
19 to O₃ but not CAPS. Ten of the subjects in this study were characterized as “mildly”
20 asthmatic, however, asthmatic status was not found to modify these effects. [Power et al.](#)
21 [\(2008\)](#) also investigated HRV in a small group of mild-to-moderate allergic asthmatics
22 (n = 5; mean age = 37 years) exposed for 4 hours during moderate intermittent exercise to
23 FA, carbon and ammonium nitrate particles (313 ± 20 µg/m³), and carbon and ammonium
24 nitrate particles (255 ± 37 µg/m³) + O₃ (200 ppb). Changes in frequency-domain variables
25 for the particle and particle + O₃ exposures were not statistically significant compared
26 with FA. Seemingly in contrast to [Fakhri et al. \(2009\)](#), the standard deviation of NN
27 intervals and the square root of the mean squared differences of successive NN intervals
28 also showed a significant (p = 0.01) decrease for both the particle and particle + O₃
29 exposures relative to FA responses. Using a similar protocol, [Sivagangabalan et al.](#)
30 [\(2011\)](#) concluded that spatial dispersion of cardiac repolarization was most affected by
31 the combined pollutant exposure of CAP + O₃ compared to FA in healthy adults.

32 Diastolic blood pressure increased by 2 mmHg following the combined O₃ + CAPs
33 exposure, but was not altered by either O₃ or CAPs alone in the [Fakhri et al. \(2009\)](#) study.
34 For a subset of the subjects without asthma in the [Fakhri et al. \(2009\)](#) study, [Urch et al.](#)
35 [\(2005\)](#) previously reported a 6 mmHg increase in diastolic blood pressure following a
36 2-hour resting exposure to O₃ (120 ppb) + PM_{2.5} CAPs (150 µg/m³) in healthy adults
37 (n = 23; 32 ± 10 years), which was statistically different from the 1 mmHg increase seen
38 following FA exposure. [Brook et al. \(2002\)](#) found O₃ (120 ppb) + PM_{2.5} CAPs (150

1 $\mu\text{g}/\text{m}^3$) in healthy adults ($n = 25$; 35 ± 10 years) caused brachial artery vasoconstriction.
2 However, minimal change in diastolic blood pressure (0.9 mmHg increase) relative to FA
3 (0.4 mmHg decrease) was observed. More recently, [Sivagangabalan et al. \(2011\)](#)
4 observed reported a 4.2 mmHg increase in diastolic blood pressure following a 2-hour
5 resting exposure to O_3 (110 ppb) + $\text{PM}_{2.5}$ CAPs ($150 \mu\text{g}/\text{m}^3$) in healthy adults ($n = 25$;
6 27 ± 8 years), which was statistically different from the 1.7 mmHg increase seen
7 following the FA exposure. The CAP exposure alone also caused a 3 mmHg increase in
8 diastolic blood pressure which was significantly more than following FA. However,
9 similar to FA, the O_3 exposure alone caused a 1.8 mmHg increase in diastolic blood
10 pressure. Overall, these studies indicate an effect of CAPs and CAP + O_3 , but not O_3
11 alone, on diastolic blood pressure.

6.3.2 Epidemiology

12 The 2006 O_3 AQCD concluded that the “generally limited body of evidence is highly
13 suggestive that O_3 directly and/or indirectly contributes to cardiovascular-related
14 morbidity,” including physiologic effects (e.g., release of platelet activating factor
15 [PAF]), HRV, arrhythmias, and myocardial infarctions, although the available body of
16 evidence reviewed during the 2006 O_3 AQCD does not “fully substantiate links between
17 ambient O_3 exposure and adverse cardiovascular outcomes” ([U.S. EPA, 2006b](#)). Since
18 the completion of the 2006 O_3 AQCD an increasing number of studies have examined the
19 relationship between short-term O_3 exposure and cardiovascular morbidity and mortality.
20 These recent studies, as well as evidence from the previous AQCDs, are presented within
21 this section.

6.3.2.1 Arrhythmia

22 In the 2006 O_3 AQCD, conflicting results were observed when examining the effect of O_3
23 on arrhythmias ([Dockery et al., 2005](#); [Rich et al., 2005](#)). A study by [Dockery et al. \(2005\)](#)
24 reported no association between O_3 concentration and ventricular arrhythmias among
25 patients with implantable cardioverter defibrillators (ICD) living in Boston, MA,
26 although when O_3 concentration was categorized into quintiles, there was weak evidence
27 of an association with increasing O_3 concentration (median O_3 concentration: 22.9 ppb).
28 [Rich et al. \(2005\)](#) performed a re-analysis of this cohort using a case-crossover design
29 and detected a positive association between O_3 concentration and ventricular arrhythmias.
30 Recent studies were conducted in various locations and each used a different cardiac
31 episode to define an arrhythmic event and a different time period of exposure, which may

1 help explain observed differences across studies. Study-specific characteristics and air
 2 quality data for recent studies are reported in [Table 6-30](#).

Table 6-30 Characterization of ozone concentrations (in ppb) from studies of arrhythmias.

| Study* | Location | Averaging Time | Mean Concentration (Standard Deviation) | Upper Range of Concentration |
|--|------------------|------------------------------|---|------------------------------|
| Metzger et al. (2007) | Atlanta, GA | 8-h max Summer only | 53.9 (23) | Max: 148 |
| Rich et al. (2006b) | Boston, MA | 1-h | 22.2* | 75th: 33 Max: 119.5 |
| | | 24-h | 22.6* | 75th: 30.9 Max: 77.5 |
| Rich et al. (2006a) | St. Louis, MO | 24-h | 21* | 75th: 31 |
| Anderson et al. (2010) | London, England | 8-h max | 8.08 | 75th: 11.5 |
| Sarnat et al., 2006b) | Steubenville, OH | 24-h Summer and Fall only | 21.8 (12.6) | 75th: 28.5 Max: 74.8 |
| | | 5 days | 22.2 (9.1) | 75th: 29.1 Max: 44 |

Note: Median presented (information on mean not given); studies presented in order of first appearance in the text of this section.

3 Multiple studies examined O₃-related effects on individuals with ICDs. A study of 518
 4 ICD patients who had at least 1 tachyarrhythmia within a 10-year period (totaling 6,287
 5 tachyarrhythmic event-days; 1993-2002) was conducted in Atlanta, Georgia ([Metzger et
 6 al., 2007](#)). Tachyarrhythmic events were defined as any ventricular tachyarrhythmic
 7 event, any ventricular tachyarrhythmic event that resulted in electrical therapy, and any
 8 ventricular tachyarrhythmic event that resulted in defibrillation. In the primary analysis,
 9 no evidence of an association was observed for a 30 ppb increase in 8-h max O₃
 10 concentrations and tachyarrhythmic events (OR: 1.00 [95% CI: 0.92, 1.08]; lag 0).
 11 Season-specific as well as several sensitivity analyses (including the use of an
 12 unconstrained distributed lag model [lags 0-6]) were conducted resulting in similar null
 13 associations.

14 In a case-crossover analysis, a population of ICD patients in Boston, previously examined
 15 by ([Rich et al., 2005](#)) was used to assess the association between air pollution and
 16 paroxysmal atrial fibrillation (PAF) episodes ([Rich et al., 2006b](#)). In addition to
 17 ventricular arrhythmias, ICD devices may also detect supraventricular arrhythmias, of
 18 which atrial fibrillation is the most common. Although atrial fibrillation is generally not
 19 considered lethal, it has been associated with increased premature mortality as well as
 20 hospitalization and stroke. Ninety-one electrophysiologist-confirmed episodes of PAF

1 were ascertained among 29 patients. An association (OR: 3.86 [95% CI: 1.44, 10.28] per
2 40 ppb increase in 1-h max O₃ concentrations) was observed between increases in O₃
3 concentration during the concurrent hour (lag 0-h) and PAF episodes. The estimated OR
4 for the 24-hour moving average concentration was elevated (OR: 1.81 [95% CI: 0.86,
5 3.83] per 20 ppb), but weaker than the estimate for the shorter exposure window. The
6 association between PAF and O₃ concentration in the concurrent hour during the cold
7 months was comparable to that during the warm months. In addition, no evidence of a
8 deviation from linearity between O₃ concentration and the log odds of PAF was observed.
9 Authors report that the difference between O₃ concentration and observed effect between
10 this study (PAF and 1-hour O₃) and their previous study (ventricular arrhythmias and
11 24-hour moving average O₃) ([Rich et al., 2005](#)) suggest a more rapid response to air
12 pollution for PAF ([Rich et al., 2006b](#)).

13 In an additional study, [Rich et al. \(2006a\)](#) employed a case-crossover design to examine
14 the association between air pollution and 139 confirmed ventricular arrhythmias among
15 56 ICD patients in St Louis, Missouri. The authors observed a positive association with
16 O₃ concentration (OR: 1.17 [95% CI: 0.58, 2.38] per 20 ppb increase in 24-hour moving
17 avg O₃ concentrations [lags 0-23 hours]). Although the authors concluded these results
18 were similar to their results from Boston ([Rich et al., 2005](#)), they postulated that the
19 pollutants responsible for the increased risk in ventricular arrhythmias are different (O₃
20 and PM_{2.5} in Boston and sulfur dioxide in St Louis).

21 [Anderson et al. \(2010\)](#) used a case-crossover framework to assess air pollution and
22 activation of ICDs among patients from all 9 ICD clinics in the London National Health
23 Service hospitals. “Activation” was defined as tachycardias for which the defibrillator
24 delivered treatment. Investigators modeled associations using unconstrained distributed
25 lags from 0 to 5 days. The sample consisted of 705 patients with 5,462 activation days
26 (O₃ concentration information was for 543 patients and 4,092 activation days). Estimates
27 for the association with O₃ concentration were consistently positive, although weak (OR:
28 1.09 [95% CI: 0.76, 1.55] per 30 ppb increase in 8-h max O₃ concentrations at 0-1 day
29 lag; OR: 1.04 [95% CI: 0.60, 1.81] per 30 ppb increase in 8-h max O₃ concentrations at
30 0-5 day lag) ([Anderson et al., 2010](#)).

31 In contrast to arrhythmia studies conducted among ICD patients, [Sarnat et al. \(2006b\)](#)
32 recruited non-smoking adults (age range: 54-90 years) to participate in a study of air
33 pollution and arrhythmias conducted over two 12-week periods during summer and fall
34 of 2000 in a region characterized by industrial pollution (Steubenville, Ohio). Continuous
35 ECG data acquired on a weekly basis over a 30-minute sampling period were used to
36 assess ectopy, defined as extra cardiac depolarizations within the atria (supraventricular
37 ectopy, SVE) or the ventricles (ventricular ectopy, VE). Increases in the 5-day moving

1 average (days 1-5) of O₃ concentration were associated with an increased odds of SVE
2 (OR: 2.17 [95% CI: 0.93, 5.07] per 20 ppb increase in 24-h avg O₃ concentrations). A
3 weaker association was observed for VE (OR: 1.62 [95% CI: 0.54, 4.90] per 20 ppb
4 increase in 24-h avg O₃ concentrations). The results of the effect of 5-day O₃
5 concentration on SVE were robust to the inclusion of SO₄²⁻ in the model [OR: 1.62
6 (95% CI: 0.54, 4.90)]. The authors indicate that the strong associations observed at the
7 5-day moving averages, as compared to shorter time periods, suggests a relatively long-
8 acting mechanistic pathways, such as inflammation, may have promoted the ectopic beats
9 in this population ([Sarnat et al., 2006b](#)).

10 Although many studies report positive associations, collectively, studies of arrhythmias
11 report inconsistent results. This may be due to variation in study populations, length and
12 season of averaging time, and outcome under study.

6.3.2.2 Heart Rate/Heart Rate Variability

13 In the 2006 O₃ AQCD, two large population-based studies of air pollution and HRV were
14 summarized ([Park et al., 2005b](#); [Liao et al., 2004a](#)). In addition, the biological
15 mechanisms and potential importance of HRV were discussed. Briefly, the study of acute
16 effects of air pollution on cardiac autonomic control is based on the hypothesis that
17 increased air pollution levels may stimulate the autonomic nervous system and lead to an
18 imbalance of cardiac autonomic control characterized by sympathetic activation
19 unopposed by parasympathetic control ([U.S. EPA, 2006b](#)). Examples of HRV indices
20 include the standard deviation of normal-to-normal intervals (SDNN), the square root of
21 the mean of the sum of the squares of differences between adjacent NN intervals (r-
22 MSSD), high-frequency power (HF), low-frequency power (LF), and the LF/HF ratio.
23 [Liao et al. \(2004a\)](#) examined the association between air pollution and cardiac autonomic
24 control in the fourth cohort examination (1996-1998) of the U.S.-based Atherosclerosis
25 Risk in Communities Study. A decrease in log-transformed HF was associated with an
26 increase in O₃ concentration among white study participants. [Park et al. \(2005b\)](#)
27 examined the effects of air pollution on indices of HRV in a population-based study
28 among men from the Normative Aging Study in Boston, Massachusetts. Several
29 associations were observed with O₃ concentration and HRV outcomes. A reduction in LF
30 was associated with increased O₃ concentration, which was robust to inclusion of PM_{2.5}.
31 The associations with all HRV indices and O₃ concentration were stronger among those
32 with ischemic heart disease and hypertension. In addition to the population-based studies
33 included in the 2006 O₃ AQCD was a study by [Schwartz et al. \(2005\)](#), who conducted a
34 panel study to assess the relationship between exposure to summertime air pollution and
35 HRV. A weak association of O₃ concentration during the hour immediately preceding the

health measures was observed with r-MSSD among a study population that consisted of mostly older female participants. In summary, these studies suggest that short-term exposures to ambient O₃ concentrations are predictors of decreased HRV and that the relationship may be stronger among certain subgroups. More recent studies that examined the association between O₃ concentration and HRV are described below. Study-specific characteristics and O₃ concentrations for these studies are presented in [Table 6-31](#).

Table 6-31 Characterization of ozone concentrations (in ppb) from studies of heart rate variability.

| Study* | Location | Averaging Time | Mean Concentration (Standard Deviation) | Upper Range of Concentration |
|--|------------------|----------------|---|------------------------------|
| Park et al. (2007) | Boston, MA | 24-h | Range of 17.0-29.1 | |
| Park et al. (2008) | Boston, MA | 24-h | 23.4 (13) | |
| Baja et al. (2010) | Boston, MA | 0 lag | 23 (16) | |
| | | 10-h lag | 21 (15) | |
| Wheeler et al. (2006) | Atlanta, GA | 4-h | 18.5 | 75th: 22.5 |
| | | 24-h | 29.4 | |
| Zanobetti et al. (2010) | Boston, MA | 0.5-h | 20.7* | 75th: 30.33 |
| | | 2-h | 20.5* | 75th: 30.08 |
| | | 3-D | 21.9* | 75th: 28.33 |
| | | 5-D | 22.8* | 75th: 29.28 |
| Chan et al. (2005a) | Taipei, Taiwan | 1-h | 21.9 (15.4) | Max: 114.9 |
| Wu et al. (2010) | Taipei, Taiwan | Working period | 24.9 (14.0) | Max: 59.2 |
| Ruidavets et al. (2005a) | Toulouse, France | 8-h max | 38.3 (14.8) | 75th: 46.9 Max: 80.3 |
| Chuang et al. (2007a) | Taipei, Taiwan | 24-h | 28.4 (12.1) | Max: 49.3 |
| | | 48-h | 33.3 (8.9) | Max: 47.8 |
| | | 72-h | 33.8 (7.1) | Max: 48.3 |
| Chuang et al. (2007b) | Taipei, Taiwan | 1-h | 35.1 | Max: 192.0 |

*Note: Median presented (information on mean not given); studies presented in order of first appearance in the text of this section.

Several follow-up examinations of HRV were conducted among the participants of the Normative Aging Study in Boston. A trajectory cluster analysis was used to assess whether pollution originating from different locations had varying relationships with HRV ([Park et al., 2007](#)). Subjects who were examined on days when air parcels originated in the west had the strongest associations with O₃; however, the O₃ concentration in this cluster was low (24-h avg, 17.0 ppb) compared to the other clusters (24-h avg of 21.3-29.1 ppb). LF and SDNN decreased with increases in the 4-hour moving average of O₃ concentration from the west (LF decreased by 51.2% [95% CI: 1.6, 75.9%] and SDNN decreased by 28.2% [95% CI: -0.5, 48.7%] per 30 ppb increase in 4-h avg O₃ concentrations) ([Park et al., 2007](#)). The Boston air mass originating in the

1 west traveled over Illinois, Indiana, and Ohio; states typically characterized by coal-
2 burning power plants. Due to the low O₃ concentrations observed in the west cluster, the
3 authors hypothesize that O₃ concentration on those days could be capturing the effects of
4 other, secondary and/or transported pollutants from the coal belt or that the relationship
5 between ambient O₃ concentration and personal exposure to O₃ is stronger during that
6 period (supported by a comparatively low apparent temperature which could indicate a
7 likelihood to keep windows open and reduced air conditioning use) ([Park et al., 2007](#)).
8 An additional follow-up evaluation using the Normative Aging Study examined the
9 potential for effect modification by chronic lead (Pb) exposure on the relationship
10 between air pollution and HRV ([Park et al., 2008](#)). Authors observed graded reductions in
11 HF and LF of HRV in relation to O₃ (and sulfate) concentrations across increasing
12 quartiles of tibia and patella lead (HF: percent change 32.3% [95% CI: -32.5, 159.3] for
13 the first quartile of tibia Pb and -59.1 [95% CI: -77.3, -26.1] for the fourth quartile of
14 tibia Pb per 30 ppb increase in 4-h avg O₃ concentrations; LF: percent change 8.0%
15 [95% CI: -36.9, 84.9] for the first quartile of tibia Pb and -59.3 [95% CI: -74.6, -34.8] for
16 the fourth quartile of tibia Pb per 30 ppb increase in 4-h avg O₃ concentrations). In
17 addition, associations were similar when education and cumulative traffic-adjusted bone
18 Pb levels were used in analyses. Authors indicate the possibility that O₃ (which has low
19 indoor concentrations) was acting as a proxy for sulfate (correlation coefficient for O₃
20 and sulfate = 0.57). Investigators of a more recent follow-up to the Normative Aging
21 Study hypothesized that the relationships between short-term air pollution exposures and
22 ventricular repolarization, as measured by changes in the heart-rate corrected QT interval
23 (QTc), would be modified by participant characteristics (e.g., obesity, diabetes, smoking
24 history) and genetic susceptibility to oxidative stress ([Baja et al., 2010](#)). No evidence of
25 an association between O₃ concentration (using a quadratic constrained distributed lag
26 model and hourly exposure lag models over a 10-hour time window preceding the visit)
27 and QTc was reported (change in mean QTc -0.74 [95% CI: -3.73, 2.25]); therefore,
28 potential effect modification of personal and genetic characteristics with O₃ concentration
29 was not assessed ([Baja et al., 2010](#)). Collectively, the results from studies that examined
30 the Normative Aging Study cohort found an association between increases in short-term
31 O₃ concentration and decreases in HRV ([Park et al., 2008](#); [Park et al., 2007](#); [Park et al.,](#)
32 [2005b](#)) although not consistently in all of the studies ([Baja et al., 2010](#)). Further, observed
33 relationships appear to be stronger among those with ischemic heart disease,
34 hypertension, and elevated bone lead levels, as well as when air masses arrive from the
35 west (the coal belt). However, it is not clear if O₃ concentration is acting as a proxy for
36 other, secondary particle pollutants (such as sulfate) ([Park et al., 2008](#)). In addition, since
37 the Normative Aging Study participants were older, predominately white men, results
38 may not be generalizable to the a large proportion of the U.S. population.

1 Additional studies of populations not limited to the Normative Aging Study have also
2 examined associations between O₃ exposure and HRV. A panel study among 18
3 individuals with COPD and 12 individuals with recent myocardial infarction (MI) was
4 conducted in Atlanta, Georgia ([Wheeler et al., 2006](#)). HRV was assessed for each
5 participant on 7 days in fall 1999 and/or spring 2000. Ozone concentrations were not
6 associated with HRV (SDNN) among all subjects (percent change of 2.36% [95% CI:
7 -10.8%, 17.5%] per 30 ppb 4-hour O₃ increase) or when stratified by disease type
8 (COPD, recent MI, and baseline FEV₁) ([Wheeler et al., 2006](#)).

9 HRV and air pollution was assessed in a panel study among 46 predominately white male
10 patients (study population: 80.4% male, 93.5% white) aged 43-75 years in Boston,
11 Massachusetts, with coronary artery disease ([Zanobetti et al., 2010](#)). Up to four home
12 visits were made to assess HRV over the year following the index event. Pollution lags
13 used in analyses ranged between 30 minutes to a few hours and up to 5 days prior to the
14 HRV assessments, calculated from hourly O₃ measurements averaged over three
15 monitoring sites in Boston. Decreases in r-MSSD were reported for all averaging times of
16 O₃ concentration (percent change of -5.18% [95% CI: -7.89, -2.30] per 20 ppb of 5-day
17 moving average of O₃ concentration), but no evidence of an association between O₃
18 concentration and HF was observed (quantitative results not provided). In two-pollutant
19 models with O₃ and either PM_{2.5} or BC, O₃ associations remained robust.

20 A few recent studies were conducted outside of the U.S. that examined the relationship
21 between air pollution concentrations and heart rate and HRV ([Wu et al., 2010](#); [Chuang et](#)
22 [al., 2007b](#); [Chuang et al., 2007a](#); [Chan et al., 2005a](#); [Ruidavets et al., 2005a](#)). No
23 associations were reported between O₃ concentration and HRV among CHD patients and
24 patients with one or more major CHD risk factors residing in Taipei, Taiwan ([Chan et al.,](#)
25 [2005a](#)). Another study in Taipei, Taiwan examined mail carriers and reported O₃
26 concentration measured using personal monitors. No association was observed between
27 O₃ concentration and the measures of HRV (percent change for SDNN: 0.57 [95% CI:
28 -21.27, 28.46], r-MSSD: -7.10 [95% CI: -24.24, 13.92], HF: -1.92 [95% CI: -23.68,
29 26.02], LF: -4.82 [95% CI: -25.34, 21.35] per 40 ppb O₃) ([Wu et al., 2010](#)). In addition,
30 no consistent relationships were identified between O₃ concentration and resting heart
31 rate among middle-aged (35-64 years) participants residing in Toulouse, France
32 ([Ruidavets et al., 2005a](#)). A negative trend was reported for the 3-day cumulative
33 (lag days 1-3) concentration of 8-h max O₃ with heart rate (p for trend = 0.02); however,
34 the individual odds ratios comparing quintiles of exposure showed no association (OR for
35 O₃ concentration of 0.93 [95% CI: 0.86, 1.01] for the highest quintile of resting heart rate
36 compared to the lowest). When stratified by current smoking status, non-smokers had a
37 decreased trend with increased 3-day cumulative O₃ concentrations but none of the
38 quintiles for heart rate were statistically significant. A panel study was conducted in

1 Taiwan to assess the relationship between air pollutants and inflammation, oxidative
2 stress, blood coagulation, and autonomic dysfunction ([Chuang et al., 2007b](#); [Chuang et](#)
3 [al., 2007a](#)). Participants were apparently healthy college students (aged 18-25 year) who
4 were living in a university dormitory in metropolitan Taipei. Health endpoints were
5 measured three times from April to June in 2004 or 2005. Ozone concentration was
6 assessed in statistical models using the average of the 24, 48, and 72 hours before the
7 hour of each blood sampling. Decreases in HRV (measured as SDNN, r-MSSD, LF, and
8 HF) were associated with increases in O₃ concentrations in single-pollutant models
9 (percent change for SDNN: -13.45 [95% CI: -16.26, -10.60], r-MSSD -13.76 [95% CI:
10 -21.62, -5.44], LF -9.16 [95% CI: -13.29, -4.95], HF -10.76 [95% CI: -18.88, -2.32] per
11 20 ppb cumulative 3-day avg O₃ concentrations) and remained associated with 3-day O₃
12 concentrations in two-pollutant models with sulfate. Another study in Taiwan recruited
13 individuals with CHD or at risk for cardiovascular disease from outpatient clinics during
14 the study period (two weeks in February) ([Chuang et al., 2007b](#)). No association was
15 observed between O₃ concentration and HRV measures (SDNN, r-MSSD, LF, HF)
16 (numerical results not provided in publication).

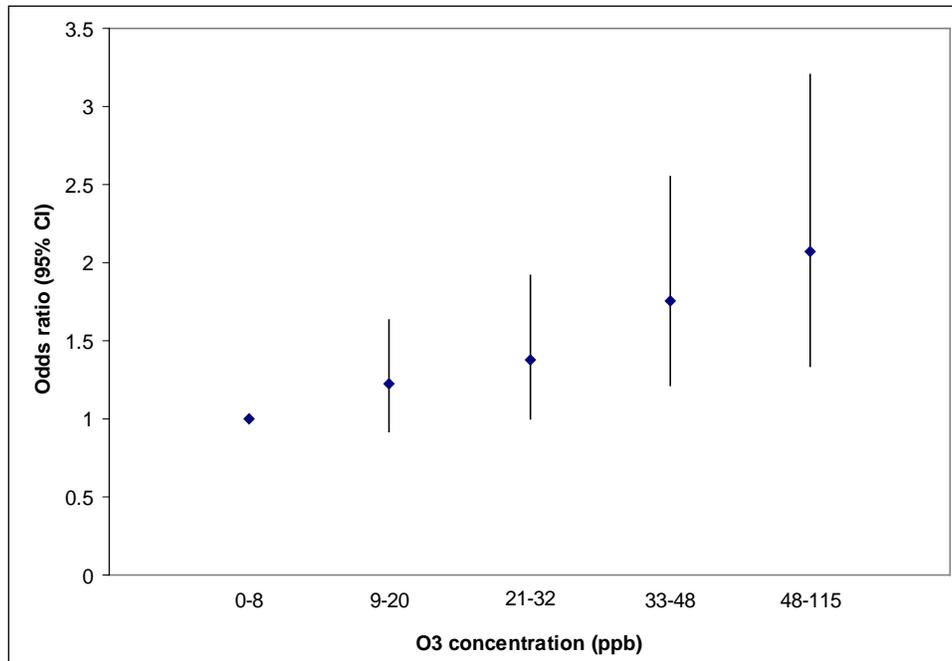
17 Overall, studies of O₃ concentration and HRV report inconsistent results. Multiple studies
18 conducted in Boston observed positive associations but the authors of many of these
19 studies postulated that O₃ concentration was possibly acting as a proxy for other
20 pollutants. The majority of other studies, both in the U.S. and internationally, report null
21 findings. The inconsistencies observed are further complicated by the different HRV
22 measures and averaging times used by the studies.

6.3.2.3 Stroke

23 The 2006 O₃ AQCD did not identify any studies that examined the association between
24 short-term O₃ exposure and stroke. However, recent studies have attempted to examine
25 this relationship. [Lisabeth et al. \(2008\)](#) used a time-series approach to assess the
26 relationship between daily counts of ischemic stroke and transient ischemic attack (TIA)
27 with O₃ concentrations in a southeast Texas community among residents 45 years and
28 older (2001-2005; median age of cases, 72 years). The median O₃ concentration (hourly
29 average per 24-hour time-period) was 25.6 ppb (IQR 18.1-33.8). The associations
30 between same-day O₃ concentrations and stroke/TIA risk were positive (RR: 1.03
31 [95% CI: 0.96, 1.10] per 20 ppb increase in 24-h avg O₃ concentrations) and previous-day
32 (RR: 1.05 [95% CI: 0.99, 1.12] per 20 ppb increase in 24-h avg O₃ concentrations).
33 Associations were robust to adjustment for PM_{2.5}.

1 A case-crossover design was used in a study conducted in Dijon, France between March
2 1994 and December 2004, among those 40 years of age and older who presented with
3 first-ever stroke ([Henrotin et al., 2007](#)). The mean O₃ concentration, calculated over
4 8-hour daytime periods, was 14.95 ppb (IQR: 6-22 ppb). No association was observed
5 between O₃ concentration at any of the single-day lags examined (i.e., 0-3 days) and
6 hemorrhagic stroke. However, an association between ischemic stroke occurrence and O₃
7 concentrations with a 1-day lag was observed (OR: 1.54 [95% CI: 1.14, 2.09] per 30 ppb
8 increase in 8-h max O₃ concentrations). The observed association between short-term O₃
9 exposure and ischemic stroke persisted in two-pollutant models with PM₁₀, SO₂, NO₂, or
10 CO. This association was stronger among men (OR: 2.12 [95% CI: 1.36, 3.30] per 30 ppb
11 increase in 8-h max O₃ concentrations) than among women (OR: 1.17 [95% CI: 0.77,
12 1.78] per 30 ppb increase in 8-h max O₃ concentrations) in single pollutant models. When
13 stroke was examined by subtype among men, an association was observed for ischemic
14 strokes of large arteries and for transient ischemic attacks, but not for cardioembolic or
15 lacunar ischemic strokes. The subtype analysis was not performed for women.
16 Additionally, for men a linear exposure-response was observed when O₃ concentration
17 was assessed based on quintiles (p for trend = 0.01) ([Figure 6-20](#)). A potential limitation
18 of this study is that 67.4% of the participating men were smokers compared to 9.3% of
19 the women.

20 Another case-crossover study performed in Dijon, France examined the association
21 between O₃ concentration and incidence of fatal and non-fatal ischemic cerebrovascular
22 events (ICVE) ([Henrotin et al., 2010](#)). Mean 8-hour O₃ concentration was 19.1 ppb (SD
23 12.2 ppb). A positive association was observed between recurrent ICVE and 8-h O₃
24 concentration with a 3-day lag (OR: 1.92 [95% CI 1.17, 3.12]), but not for other lags (0,
25 1, 2, 4) or cumulative days (0-1, 0-2, 1-2, 1-3). Although some ORs for incident ICVEs
26 were elevated, none were statistically significant. Results for associations using the
27 maximum daily 1-hour O₃ concentrations were similar to the 8-hour results but slightly
28 attenuated. ORs were similar in two pollutant models with SO₂, NO₂, CO, and PM₁₀ (data
29 not given). In stratified analyses, the association between 1-day lagged O₃ concentration
30 and incident and recurrent ICVE was greater among individuals with diabetes or
31 individuals with multiple preexisting vascular conditions.



Source: [Henrotin et al. \(2007\)](#).

Figure 6-20 Odds ratio (95% confidence interval) for ischemic stroke by quintiles of ozone exposure.

6.3.2.4 Biomarkers

1 An increasing number of studies have examined the relationship between air pollution
2 and biomarkers in an attempt to elucidate the biological mechanisms linking air pollution
3 and cardiovascular disease. A wide range of markers assessed as well as different types
4 of study designs and locations chosen make comparisons across studies difficult.
5 [Table 6-32](#) provides an overview of the O₃ concentrations reported in each of the studies
6 evaluated.

Table 6-32 Characterization of ozone concentrations (in ppb) from studies of biomarkers.

| Study* | Location | Averaging Time | Mean Concentration (Standard Deviation) | Upper Range of Concentration |
|--|-----------------------------------|----------------|---|------------------------------|
| Liao et al. (2005) | 3 U.S. counties | 8-h | 40 (20) | |
| Thompson et al. (2010) | Toronto, Ontario | 1-h / 1 yr | 21.94 (15.78) | |
| Rudez et al. (2009) | Rotterdam, the Netherlands | 24-h | 22* | 75th: 31.5 Max: 90 |
| Chuang et al. (2007a) | Taipei, Taiwan | 24-h | 28.4 (12.1) | Max: 49.3 |
| | | 48-h | 33.3 (8.9) | Max: 47.8 |
| | | 72-h | 33.8 (7.1) | Max: 48.3 |
| Steinvil et al. (2008) | Tel-Aviv, Israel | 0.5-h | 29.2 (9.7) | 75th: 36 |
| Chen et al. (2007a) | Los Angeles and San Francisco, CA | 8-h / 2 weeks | 30.8* | Max: 47.9 |
| | | 8-h / 1 mo | 28.3* | Max: 43.1 |
| Wellenius et al. (2007) | Boston, MA | 1-h / 24-h | 25.1 (12.9) | |
| Goldberg et al. (2008) | Montreal, Quebec | 24-h | NS | |
| Baccarelli et al. (2007) | Lombardia, Italy | 1-h | 18.3* | 75th: 35.1 Max: 202.3 |
| Chuang et al. (2010) | Taiwan | | 26.83 (9.7) | Max: 62.1 |

*Note: Median presented (information on mean not given); studies presented in order of first appearance in the text of this section.

Hemostasis and coagulation markers

1 Multiple studies used various markers to examine if associations were present between
 2 short-term O₃ exposure and hemostasis and coagulation. Some of the markers included in
 3 these studies were as follows: fibrinogen, von Willebrand factor (vWF), plasminogen
 4 activator fibrinogen inhibitor-1 (PAI-1), tissue-type plasminogen activator (tPA), platelet
 5 aggregation, and thrombin generation.

6 A population-based study in the United States was conducted to assess the relationship
 7 between short-term exposure to air pollution and markers of blood coagulation using the
 8 Atherosclerosis Risk in Communities (ARIC) study cohort ([Liao et al., 2005](#)). Significant
 9 curvilinear associations were observed for O₃ (1 day prior to blood draw) and fibrinogen
 10 and vWF (quantitative results not provided for regression models although adjusted
 11 means [SE] of vWF were given as 118% [0.79%] for O₃ concentrations <40 ppb, 117%
 12 [0.86%] for O₃ concentrations 40-70 ppb, and 124% [1.97%] for O₃ concentrations of
 13 70 ppb). The association between short-term O₃ exposure and fibrinogen was more

1 pronounced among those with a history of cardiovascular disease (CVD) and was
2 statistically significant among only this subgroup of the population. The curvilinear
3 relationship between concentration and outcome suggested stronger relationships at
4 higher concentrations of O₃. The authors note that the most pronounced associations
5 occurred when the pollutant concentrations were 2-3 standard deviations above the mean.
6 The results from this relatively large-scale cross-sectional study suggest weak
7 associations with between short-term O₃ exposure and increases in fibrinogen (among
8 those with a history of CVD) and vWF. A retrospective repeated measures analysis was
9 performed in Toronto, Canada among adults aged 18-40 years (n = 45) between the years
10 of 1999 and 2006 ([Thompson et al., 2010](#)). Single pollutant models were used with
11 moving averages up to 7 days. No evidence of an association was observed between
12 short-term O₃ exposure and increases in fibrinogen.

13 A repeated measures study was conducted among 40 healthy individuals living or
14 working in the city center of Rotterdam, the Netherlands to assess the relationship
15 between air pollution and markers of hemostasis and coagulation (platelet aggregation,
16 thrombin generation, and fibrinogen) ([Rudez et al., 2009](#)). Each participant provided
17 between 11 and 13 blood samples throughout a 1-year period (498 samples on 197 days).
18 Examined lags ranged from 6 hours to 3 days prior to blood sampling. No consistent
19 evidence of an association was observed between O₃ concentration and any of the
20 biomarkers (percent change of max platelet aggregation: -6.87 [95% CI: -21.46, 7.70] per
21 20 ppb increase in 24-h avg O₃ concentration at 4-day average; percent change of
22 endogenous thrombin potential: 0.95 [95% CI: -3.05, 4.95] per 20 ppb increase in
23 24-h avg O₃ concentration at 4-day avg; percent change of fibrinogen: -0.57 [95% CI:
24 -3.05, 2.00] per 20 ppb increase in 24-h avg O₃ concentration at lag 1-day). Some
25 associations with O₃ were in the opposite direction to that hypothesized which may be
26 explained by the negative correlation between O₃ and other pollutants (correlation
27 coefficients ranged from -0.4 to -0.6). The statistically significant inverse effects
28 observed in single-pollutant models with O₃ were no longer apparent when PM₁₀ was
29 included in the model ([Rudez et al., 2009](#)).

30 A panel study in Taiwan measured health endpoints using blood samples from healthy
31 individuals (n = 76) at three times from April to June in 2004 or 2005 ([Chuang et al.,
32 2007a](#)). Increases in fibrinogen and PAI-1 were associated with increases in O₃
33 concentrations in single-pollutant models (percent change in fibrinogen: 11.76 [95% CI:
34 4.03, 19.71] per 20 ppb 3-day cumulative avg O₃ concentration; percent change in PAI-1:
35 6.08 [95% CI: 38.91, 84.27] per 20 ppb 3-day cumulative avg O₃ concentration). These
36 associations were also observed at 1 and 2 day averaging times. Associations between
37 PAI-1 and 3-day O₃ concentrations remained robust in two-pollutant models with sulfate.

1 No association was observed between O₃ concentration and tPA, a fibrinolytic factor
2 (percent change 16.15 [95% CI: -4.62, 38.34] per 20 ppb 3-day avg O₃ concentration).

3 A study in Israel examined the association between pollutant concentrations and
4 fibrinogen among 3659 apparently healthy individuals ([Steinvil et al., 2008](#)). In single
5 pollutant models, O₃ was associated with an increase in fibrinogen at a 4-day lag among
6 men and a same-day O₃ concentration among women but results for other lags (0 through
7 7 days) were mixed (i.e., some positive and some negative; none statistically significant).

Inflammatory markers

8 Potential associations between short-term exposures to air pollution and inflammatory
9 markers (C-reactive protein [CRP], white blood cell [WBC] count, albumin, and
10 Interleukin-6 [IL-6]) were also examined in several studies.

11 The ARIC study cohort, which included men and women aged 45-64 years old at the start
12 of the study, was utilized to assess the association between O₃ concentrations and
13 markers of inflammation, albumin and WBC count ([Liao et al., 2005](#)). No association
14 was observed between O₃ concentrations and albumin or WBC count.

15 [Thompson et al. \(2010\)](#) assessed ambient air pollution exposures and IL-6. This
16 retrospective repeated measures analysis was conducted among 45 adults (18-40 years of
17 age) in Toronto, Canada between the years of 1999 and 2006. Single pollutant models
18 were used to analyze the repeated-measures data using moving averages up to 7 days. A
19 positive association was observed between IL-6 and short-term 1-h O₃ exposure with the
20 strongest effects observed for the average of lags 0-3 days (quantitative results not
21 provided). No association was observed for shorter averaging times (average lags of
22 <1 day). When examined by season using 2-day moving averages, the association
23 between short-term O₃ exposure and IL-6 was positive during only the spring and
24 summer.

25 In Rotterdam, the Netherlands, a repeated measures study of healthy individuals living or
26 working in the city center reported no association between short-term O₃ exposure and
27 CRP ([Rudez et al., 2009](#)). Each of the 40 participants provided between 11 and 13 blood
28 samples throughout a 1-year period (498 samples on 197 days). No consistent evidence of
29 an association was observed between O₃ concentration and CRP (percent change: -0.48
30 [95% CI: -14.05, 13.10] per 20 ppb increase in 24-h avg O₃ concentration at lag 1-day).
31 Additionally, no association was observed with 2 or 3 day lags.

32 The relationship between pollutant concentrations and one-time measures of
33 inflammatory biomarkers was assessed in sex-stratified analyses among 3,659 apparently

1 healthy individuals in Tel Aviv, Israel ([Steinvil et al., 2008](#)). No evidence of an
2 association was observed between O₃ concentration and CRP or WBC for men and
3 women.

4 A panel study of healthy individuals (n = 76) was conducted in Taiwan to assess the
5 relationship between air pollutants and inflammation ([Chuang et al., 2007a](#)). Health
6 endpoints were measured three times from April to June in 2004 or 2005. Ozone effects
7 were assessed in statistical models using the average of the 24 hours (1 day), 48 hours
8 (2 days), and 72 hours (3 days) before the hour of each blood sampling. Increases in CRP
9 were associated with increases in O₃ concentrations in single-pollutant models (percent
10 change in CRP: 244.38 [95% CI: 4.54, 585.15] per 20 ppb 3-day avg O₃ concentration).
11 The association was also observed using a 2-day cumulative averaging time, but no
12 association was present with a 1-day averaging time.

Oxidative stress markers

13 A few studies have reported on the relationships between short-term O₃ exposure and
14 increases in markers of oxidative stress. The association between O₃ concentration and
15 markers of lipid peroxidation and antioxidant capacity was examined among 120
16 nonsmoking healthy college students, aged 18-22 years, from the University of
17 California, Berkeley (February-June 2002) ([Chen et al., 2007a](#)). By design, students were
18 chosen that had experienced different geographic concentrations of O₃ over their lifetimes
19 and during recent summer vacation in either greater Los Angeles (LA) or the
20 San Francisco Bay Area (SF). Long-term (based on lifetime residential history) and
21 shorter-term (based on the moving averages of 8-h max concentrations 1-30 days prior to
22 the day of blood collection) O₃ concentration were estimated (lifetime exposure results
23 are presented in Chapter 7). A marker of lipid peroxidation, 8-isoprostane (8-iso-PGF),
24 was assessed. This marker is formed continuously under normal physiological conditions
25 but has been found at elevated concentrations in response to environmental exposures. A
26 marker of overall antioxidant capacity, ferric reducing ability of plasma (FRAP), was also
27 measured. Levels of 8-iso-PGF were associated with 2-week ($\beta = 0.035$
28 [pg/mL]/8-hour ppb O₃, p = 0.007) and 1-month ($\beta = 0.031$ [pg/mL]/8-hour ppb O₃,
29 p = 0.006) estimated O₃ concentrations. No evidence of association was observed
30 between short-term O₃ exposure and increases in FRAP. A chamber study performed
31 among a subset of study participants supported the primary study results. The
32 concentrations of 8-iso-PGF increased immediately after the 4-hour controlled O₃
33 exposure ended (p = 0.10). However, levels returned to near baseline by 18 hours without
34 further exposure. The authors note that O₃ was highly correlated with PM_{10-2.5} and NO₂ in
35 this study population; however, O₃ associations remained robust in copollutant models.

1 Using blood samples collected between April and June of 2004 or 2005 in Taiwan, the
2 association between short-term O₃ exposure and a marker of oxidative stress (i.e., 8-
3 hydroxy-2'-deoxyguanosine (8-OHdG)) was studied among healthy individuals (n = 76)
4 ([Chuang et al., 2007a](#)). Increases in 8-OHdG were associated with increases in O₃
5 concentrations in single-pollutant models (percent change in 8-OHdG: 2.46 [95% CI:
6 1.01, 3.92] per 20 ppb increase in 24-h avg O₃). The association did not persist with 2- or
7 3-day cumulative averaging times.

Markers of overall cardiovascular health

8 Multiple studies used markers that assess overall cardiovascular well-being. [Wellenius et](#)
9 [al. \(2007\)](#) examined B-type natriuretic peptide (BNP), a marker of heart failure, in a
10 repeated-measures study conducted in Boston among 28 patients with congestive heart
11 failure and impaired systolic function. The authors found no evidence of an association
12 between BNP and short-term O₃ exposures at lags 0-3 days (quantitative results not
13 provided). BNP was chosen because it is directly associated with cardiac hemodynamics
14 and symptom severity among those with heart failure and is considered a marker of
15 functional status. However, the authors conclude that the use of BNP may not be useful
16 in studies of the health effects of ambient air pollutants due to the large amount of within-
17 person variability in BNP levels observed in this population.

18 The relationship between air pollution and oxygen saturation and pulse rate, markers of
19 physiological well-being, was examined in a 2-month panel study among 31 congestive
20 heart failure patients (aged 50-85 years) in Montreal, Canada from July 2002 to October
21 2003 ([Goldberg et al., 2008](#)). All participants had limited physical functioning
22 (New York Heart Association Classification \geq II) and an ejection fraction (the fraction of
23 blood pumped out of the heart per beat) less than or equal to 35% (normal is above 55%).
24 Daily mean O₃ concentrations were calculated based on hourly measures at 10 monitoring
25 stations. There was an inverse association between O₃ concentration (lag-0) and oxygen
26 saturation when adjustment was made for temporal trends. In the models incorporating
27 personal covariates and weather factors, the association remained but was not statistically
28 significant. The associations of O₃ concentration with a lag of 1 day or a 3-day mean
29 were not statistically significant. No evidence of association was observed between O₃
30 concentration and pulse rate.

31 Total homocysteine (tHcy) is an independent risk factor for vascular disease and
32 measurement of this marker after oral methionine load is used to identify individuals with
33 mild impairment of homocysteine metabolism. The effects of air pollution on fasting and
34 postmethionine-load tHcy levels were assessed among 1,213 apparently healthy
35 individuals from Lombardia, Italy from January 1995 to September 2005 ([Baccarelli et](#)

1 [al., 2007](#)). A 20-ppb increase in the 24-h avg O₃ concentrations was associated with an
2 increase in fasting tHcy (percent change 6.25 [95% CI: 0.84, 11.91]) but no association
3 was observed with postmethionine-load tHcy (percent change 3.36 [95% CI: -1.30,
4 8.39]). In addition, no evidence of an association was observed between 7-day
5 cumulative averaged O₃ concentrations and tHcy (percent change for fasting tHcy 4.16
6 [95% CI: -1.76, 10.42] and percent change for postmethionine-load tHcy -0.65 [95% CI:
7 -5.66, 4.71] per 20 ppb increase in 24-h avg O₃ concentrations). No evidence of effect
8 modification by smoking was observed.

Blood lipids and glucose metabolism markers

9 [Chuang et al. \(2010\)](#) conducted a population-based cross-sectional analysis of data
10 collected on 7,778 participants during the Taiwanese Survey on Prevalence of
11 Hyperglycemia, Hyperlipidemia, and Hypertension in 2001. Apolipoprotein B (ApoB),
12 the primary apolipoprotein among low-density lipoproteins, was associated with 3-day
13 avg O₃ concentration at the p <0.10 level. The 5-day mean O₃ concentration was
14 associated with an increase in triglycerides at p <0.10. In addition, the 1-, 3-, and 5-day
15 mean O₃ concentrations were associated with increased HbA1c levels (a marker used to
16 monitor the degree of control of glucose metabolism) at the p <0.05 level. The 5-day
17 mean O₃ concentration was associated with increased fasting glucose levels (p <0.10). No
18 association was observed between O₃ concentration and ApoA1.

6.3.2.5 Myocardial Infarction (MI)

19 The 2006 O₃ AQCD did not report consistent results indicating an association between
20 short-term O₃ exposure and MI. One study reported a positive association between
21 current day O₃ concentration and acute MI, especially among the oldest age group (55 to
22 64 year-olds) ([Ruidavets et al., 2005b](#)). No association was observed in a case-crossover
23 study of O₃ concentration during the surrounding hours and MI ([Peters et al., 2001](#)). Since
24 the 2006 O₃ AQCD, a few recent epidemiologic studies have examined the association
25 between O₃ concentration and MI ([Henrotin et al., 2010](#); [Rich et al., 2010](#)), arterial
26 stiffness ([Wu et al., 2010](#)) and ST-segment depression ([Delfino et al., 2011](#)).

27 One of the studies conducted in the U.S. examined hospital admissions for first MI and
28 reported no association with O₃ concentration ([Rich et al., 2010](#)). More details on this
29 study are reported in the section on hospital admissions (Section [6.3.2.7](#)). A study
30 performed in Dijon, France examined the association between O₃ concentration and
31 incident and recurrent MI ([Henrotin et al., 2010](#)). The mean 8-hour O₃ concentration was
32 19.1 ppb (SD 12.2 ppb). Odds ratios for the association between cumulative O₃

1 concentrations and recurrent MIs were elevated but none of the results were statistically
2 significant (OR: 1.71 [95% CI: 0.91, 3.20] per 20 ppb increase in 24-h avg O₃
3 concentration for a cumulative lag of 1-3 days). No association was observed for incident
4 MIs. In analyses stratified by vascular risk factors, positive associations were observed
5 between 1-day lagged O₃ concentration and MIs (incident and recurrent combined)
6 among those who reported having hypercholesterolaemia (OR: 1.52 [95% CI: 1.08, 2.15]
7 per 20 ppb increase in 24-h avg O₃ concentration) and a slight inverse association was
8 observed among those who reported not having hypercholesterolaemia (OR: 0.69
9 [95% CI: 0.50, 0.94] per 20 ppb increase in 24-h avg O₃ concentration). In other stratified
10 analyses combining different vascular factors, only those containing individuals with
11 hypercholesterolaemia demonstrated a positive association; none were inverse
12 associations.

13 [Wu et al. \(2010\)](#) examined mail carriers aged 25-46 years and measured exposure to O₃
14 concentrations through personal monitors [mean O₃ 24.9 (SD 14.0) ppb]. Ozone
15 concentration was positively associated with arterial stiffness (percent change 11.24%
16 [95% CI: 3.67, 19.62] per 40 ppb O₃) and was robust to adjustment for ultrafine PM.

17 A study performed in the Los Angeles basin reported on the association between O₃
18 concentration and ST-segment depression, a measure representing cardiac ischemia
19 ([Delfino et al., 2011](#)). Study participants were nonsmokers, at least 65 years old, had a
20 history of coronary artery disease, and were living in a retirement community. Study
21 periods included five consecutive days in both July to mid-October and mid-October to
22 February. Mean 24-hour O₃ concentrations were 27.1 ppb (SD 11.5 ppb). No association
23 was observed between O₃ concentration and ST-segment depression of at least 1.0 mm
24 during any of the exposure periods (i.e., 1-h, 8-h, 1-day, 2-day avg, 3-day avg,
25 4-day avg).

6.3.2.6 Blood Pressure

26 In the 2006 O₃ AQCD, no epidemiologic studies examined O₃-related effects on blood
27 pressure (BP). Recent studies have been conducted to evaluate this relationship and
28 overall the findings are inconsistent. The O₃ concentrations for these studies are listed in
29 [Table 6-33](#).

Table 6-33 Characterization of ozone concentrations (in ppb) from studies of blood pressure.

| Study* | Location | Averaging Time | Mean Concentration (Standard Deviation) | Upper Range of Concentration |
|---|-------------------------|----------------------|---|------------------------------|
| Zanobetti et al. (2004) | Boston, Massachusetts | 1-h | 20 | |
| | | 5-days | 24 | |
| Delfino et al. (2010b) | Los Angeles, California | 24-h | 27.1 (11.5) | Max: 60.7 |
| Choi et al. (2007) | Incheon, South Korea | 8-h (warm season) | 26.6 (11.8) | 75th: 34.8 Max: 62.4 |
| | | 8-h (cold season) | 17.5 (7.3) | 75th: 22.9 Max: 33.9 |
| Chuang et al. (2010) | Taiwan | | 26.83 (9.7) | Max: 62.1 |

*Note: Studies presented in order of first appearance in the text of this section.

1 [Zanobetti et al. \(2004\)](#) examined the relationship between air pollutants and BP from
2 May 1999 to January 2001 for 631 repeat visits among 62 Boston residents with CVD. In
3 single-pollutant models, higher resting diastolic blood pressure (DBP) was associated
4 with the 5-day (0-4 days) averages of O₃ concentration (RR: 1.03 [95% CI: 1.00, 1.05]
5 per 20 ppb increase in 24-hour O₃ concentrations). However, this effect was no longer
6 apparent when PM_{2.5} was included in the model (data were not presented) ([Zanobetti et
7 al., 2004](#)). [Delfino et al. \(2010b\)](#) examined 64 subjects 65 years and older with coronary
8 artery disease, no tobacco smoke exposure, and living in retirement communities in the
9 Los Angeles air basin with hourly (up to 14-h/day) ambulatory BP monitoring for 5 days
10 during a warm period (July-mid-October) and 5 days during a cool period (mid-October-
11 February). Investigators assessed lags of 1, 4, and 8 hours, 1 day, and up to 9 days before
12 each BP measure; no evidence of an association was observed for O₃ (change in BP
13 associated with a 20 ppb increase in 24-h avg O₃ concentration was 0.67 [95% CI: -1.16,
14 2.51 for systolic BP [SBP] and -0.25 [95% CI: -1.25, 0.75] for DBP) ([Delfino et al.,
15 2010b](#)). [Choi et al. \(2007\)](#) conducted a cross-sectional study to investigate the
16 relationship between air pollutants and BP among 10,459 participants of the Inha
17 University Hospital health examination from 2001 to 2003. These individuals had no
18 medical history of cardiovascular disease or hypertension. O₃ concentration was
19 associated with an increase in SBP for 1-day lag in the warm season and similar effect
20 estimates were observed during the cold season but were not statistically significant
21 (quantitative results not provided). Associations between O₃ concentration and DBP were
22 present in the cold season but not the warm season (quantitative results not provided).
23 [Chuang et al. \(2010\)](#) conducted a similar type of study among 7,578 participants of the
24 Taiwanese Survey on Prevalence of Hyperglycemia, Hyperlipidemia, and Hypertension
25 in 2001. Investigators examined 1-, 3-, and 5-day avg O₃ concentrations. An increase in

1 DBP was associated with the 3-day mean O₃ concentration (change in BP for a 20 ppb
2 increase in 24-h avg O₃ concentration was 0.61 [95% CI: 0.07, 1.14]) ([Chuang et al.,](#)
3 [2010](#)). Associations were not observed for other days or with SBP.

6.3.2.7 Hospital Admissions and Emergency Department Visits

4 Upon evaluating the collective evidence for O₃-related cardiovascular hospital admissions
5 and emergency department (ED) visits, the 2006 O₃ AQCD concluded that “a few studies
6 observed positive O₃ associations, largely in the warm season. Overall, however, the
7 currently available evidence is inconclusive regarding any association between ambient
8 O₃ exposure on cardiovascular hospitalizations” ([U.S. EPA, 2006b](#)). [Table 6-34](#) below
9 provides information on the O₃ concentrations reported in each of the recent hospital
10 admission and ED visit studies evaluated.

Table 6-34 Characterization of ozone concentrations (in ppb) from studies of hospital admissions and ED visits.

| Study* | Location | Averaging Time | Mean Concentration (Standard Deviation) | Upper Range of Concentration |
|---|-------------------------|------------------------|---|------------------------------|
| Peel et al. (2007) | Atlanta, GA | 8-h max warm season | 55.6 (23.8) | |
| Tolbert et al. (2007) | Atlanta, GA | 8-h max warm season | 53.0 | 75th: 67.0 Max: 147.5 |
| Katsouyanni et al. (2009) | 12 Canadian cities | 1-h | 6.7-8.3* | 75th: 8.4-12.4 |
| | 8 European cities | 1-h | 11.0-38.1* | 75th: 15.3-49.4 |
| | 14 United States cities | 1-h | 34.9-60.0* | 75th: 46.8-68.8 |
| Rich et al. (2010) | New Jersey | 24-h | NR | |
| Cakmak et al. (2006a) | 10 Canadian cities | 1-h max | 17.4 | |
| Stieb et al. (2009) | 7 Canadian cities | 24-h | 18.4 | |
| Szyszkowicz (2008) | Edmonton, Canada | 24-h | 18.6 (9.3) | |
| Villeneuve et al. (2006a) | Edmonton, Canada | 24-h | 17 (9.1) | 75th: 23.5 |
| | | 24-h warm season | 21.8 (8) | 75th: 27.0 |
| | | 24-h cold season | 12.2 (7.4) | 75th: 17.0 |
| Symons et al. (2006) | Baltimore, MD | 8-h warm season | 31.0 (20.0) | Max: 120.0 |
| Wellenius et al. (2005) | Allegheny County, PA | 24-h | 24.3 (12.2) | 75th: 32.0 |
| Zanobetti and Schwartz (2006) | Boston, MA | 24-h | 22.4* | 75th: 31.0 |
| Yang (2008) | Taipei, Taiwan | 24-h | 21.0 | 75th: 26.3 Max: 62.8 |
| Lee et al. (2007) | Kaohsiung, Taiwan | 24-h | 26.5 | 75th: 35.5 Max: 83.0 |
| Chan et al. (2006) | Taipei, Taiwan | 1-h max | 50.9 (26.4) | Max: 150.3 |
| Chiu and Yang (2009) | Taipei, Taiwan | 24-h | 23.0 | 75th: 28.7 Max: 62.8 |
| Lee et al. (2008a) | Taipei, Taiwan | 24-h | 21.0 | 75th: 26.4 Max: 62.8 |
| Wong et al. (2009) | Hong Kong | 8-h | 18.5 (11.5) | 75th: 25.4 Max: 48.3 |
| Bell et al. (2008) | Taipei, Taiwan | 24-h | 21.4 | Max: 53.4 |
| Buadong et al. (2009) | Bangkok, Thailand | 1-h | 14.4 (3.2) | Max: 41.9 |
| Lee et al. (2003b) | Seoul, Korea | 1-h max | 36.0 (18.6) | 75th: 44.9 |
| Azevedo et al. (2011) | Portugal | 1-h | NR | |
| Linares and Diaz (2010) | Madrid, Spain | 24-h | 17.4 (8.9) | |
| Middleton et al. (2008) | Nicosia, Cyprus | 8-h max | 28.7 - 54.9 | |

| Study* | Location | Averaging Time | Mean Concentration (Standard Deviation) | Upper Range of Concentration |
|---|----------------------|------------------------|---|------------------------------|
| Turner et al. (2007) | Sydney, Australia | 24-h | 28 | 75th: 33 |
| Ballester et al. (2006) | 14 Spanish cities | 8-h warm season | 24.2 - 44.3 | |
| DePablo et al. (2006) | Castilla-Leon, Spain | 24-h | 23.2-33.6 | |
| VonKlot et al. (2005) | 5 European cities | 8 h max warm season | 16.4 - 28.0 | |
| Oudin et al. (2010) | Scania, Sweden | 24-h | 30.5 | |
| Halonen et al. (2009) | Helsinki, Finland | 8-h max warm season | 35.7* | 75th: 42.1 Max: 79.6 |
| Larrieu et al. (2007) | 8 French cities | 8-h max warm season | 34.2 - 53.1 | |
| Barnett et al. (2006) | 4 Australian cities | 8-h | 19.0-28.5 | Max: 58.4-86.8 |
| Hinwood et al. (2006) | Perth, Australia | 8-h max | 25.9 (6.5) | |
| Lanki et al. (2006) | 5 European cities | 8-h max warm season | 31.7 - 57.2* | |
| Hosseinpoor et al. (2005) | Tehran, Iran | 8-h max | 4.9 (4.8) | 75th: 7.2 Max: 99.0 |
| Simpson et al. (2005) | 4 Australian cities | 1-h max | 24.4-33.8 | Max: 96.0-111.5 |
| Dennekamp et al. (2010) | Melbourne, Australia | 24-h | 13.34 | 75th: 16.93 |
| Silverman et al. (2010) | New York City, NY | 8-h max | 28* | 75th: 40 |

*Notes: Median presented (information on mean not given); NR: Not reported; studies presented in order of first appearance in the text of this section.

1 Multiple recent studies of O₃ concentration and cardiovascular hospital admissions and
2 ED visits have been conducted in the U.S. and Canada. [Peel et al. \(2007\)](#) used a case-
3 crossover framework (using a time-stratified approach matching on day of the week in
4 the calendar month of the event) to assess the relationship between air pollutants and
5 cardiovascular disease ED visits among those with and without secondary comorbid
6 conditions (hypertension, diabetes, chronic obstructive pulmonary disease [COPD],
7 congestive heart failure [CHF], and dysrhythmia). Data on over 4 million ED visits from
8 31 hospitals were collected from January 1993 to August 2000. Ozone was monitored
9 from March to October. This study was a re-analysis of a time series study conducted to
10 assess the main effects of air pollutants on cardiovascular ED visits in Atlanta ([Tolbert et](#)
11 [al., 2007](#); [Metzger et al., 2004](#)). In the initial study, no evidence of associations was
12 observed between O₃ concentration and all CVD visits or visits for CVD subgroups, such
13 as dysrhythmia, CHF, ischemic heart disease (IHD), and peripheral vascular and
14 cerebrovascular disease. The relative risk for all CVD visits was 1.01 (95% CI: 0.98,
15 1.04) for a 30 ppb increase in the 3-day moving avg (lags 0-2 days) of 8-hour O₃
16 concentration ([Metzger et al., 2004](#)). Similar to the initial investigation using a time-
17 series analysis, no evidence of an association was observed between short-term O₃

1 exposure and CVD visits at lag 0-2 among the entire population using the case-crossover
2 design ([Peel et al., 2007](#)). However, the relationship between O₃ concentration and
3 peripheral and cerebrovascular disease visits was stronger among patients with comorbid
4 COPD (OR: 1.29 [95% CI: 1.05-1.59] per 30 ppb, lag 0-2 days) as compared to patients
5 without COPD (OR: 1.01 [95% CI: 0.96-1.06] per 30 ppb, lag 0-2 days). The same
6 research group expanded upon the number of Atlanta hospitals providing ED visit data
7 (41 hospitals) as well as the length of the study period (1993-2004) ([Tolbert et al., 2007](#)).
8 Again, models assessing the health effects of O₃ concentration utilized data collected
9 from March through October. Similar to the results presented by [Metzger et al. \(2004\)](#)
10 and [Peel et al. \(2007\)](#) among the entire study population, no evidence of associations was
11 observed for O₃ concentration and CVD visits ([Tolbert et al., 2007](#)).

12 Existing multicity studies in North America and Europe were evaluated under a common
13 framework in the Air Pollution and Health: A European and North American Approach
14 (APHENA) study ([Katsouyanni et al., 2009](#)). One component of the study examined the
15 relationship between short-term O₃ exposure and CVD hospital admissions among
16 individuals 65 years of age and older. The study presented multiple models but this
17 section focuses on the results for the models that used 8 df to account for temporal trends
18 and natural splines (see Section [6.2.7.2](#) for additional explanation). Across the study
19 locations, no associations were observed between O₃ concentration and CVD hospital
20 admissions at lags 0-1, lag 1, or a distributed lag of 0-2. Additionally, there was no
21 evidence of an association when restricting the analysis to the summer months.

22 A study of hospital admissions for MI was performed using a statewide registry from
23 New Jersey between January 2004 and December 2006 ([Rich et al., 2010](#)). Using a case-
24 crossover design, the association between the previous 24-h O₃ concentration and
25 transmural infarction (n = 1,003) was examined. No association was observed (OR: 0.94
26 [95% CI: 0.79, 1.13] per 20 ppb increase in 24-h avg O₃ concentration) and this did not
27 change with the inclusion of PM_{2.5} in the model.

28 [Cakmak et al. \(2006a\)](#) investigated the relationship between gaseous air pollutants and
29 cardiac hospitalizations in 10 large Canadian cities using a time-series approach. A total
30 of 316,234 hospital discharge records for primary diagnosis of congestive heart failure,
31 ischemic heart disease, or dysrhythmia were obtained from April 1993 through March
32 2000. Correlations between pollutants varied substantially across cities, which could
33 partially explain discrepancies in effect estimates observed across the cities. In addition,
34 pollutant lags differed across cities; the average lag for O₃ was 2.9 days. The pooled
35 effect estimate for a 20 ppb increase in the daily 1-h max O₃ concentration and the
36 percent change in hospitalizations among all 10 cities was 2.3 (95% CI: 0.11, 4.50) in an
37 all-year analysis. The authors reported no evidence of effect modification by sex,

1 neighborhood-level education, or neighborhood-level income. A similar multicity time-
2 series study was conducted using nearly 400,000 ED visits to 14 hospitals in seven
3 Canadian cities from 1992 to 2003 ([Stieb et al., 2009](#)). Primary analyses considered daily
4 O₃ single day lags of 0-2 days; in addition, sub-daily lags of 3-h avg concentrations up to
5 12 hours before presentation to the ED were considered. Seasonal variation was assessed
6 by stratifying analyses by warm and cold seasons. No evidence of associations between
7 short-term O₃ exposure and CVD ED visits was observed. One negative, statistically
8 significant association was reported between a 1-day lag of O₃ concentration and visits
9 for angina/myocardial infarction. Ozone concentration was negatively correlated with
10 many of the other pollutants, particularly during the cold season.

11 The effect of air pollution on daily ED visits for ischemic stroke (n = 10,881 visits) in
12 Edmonton, Canada was assessed from April 1992 through March 2002 ([Szyszkowicz,
13 2008](#)). A 26.4% (95% CI: 3.16-54.5) increase in stroke ED visits was associated with a
14 20 ppb increase in 24-hour average O₃ concentration at lag 1 among men aged 20-
15 64 years in the warm season. No associations were present among women or among men
16 age 65 and older. In addition, no associations were observed for the cold season or for
17 other lags (lag 0 or lag 2). A similar investigation over the same time period in
18 Edmonton, Canada, assessed the relationship between air pollutants and ED visits for
19 stroke (ischemic stroke, hemorrhagic stroke, and transient ischemic attack) among those
20 65 years of age and older using a case-crossover framework ([Villeneuve et al., 2006a](#)).
21 No evidence of association was reported for O₃ concentration and stroke hospitalization
22 in single or co-pollutant models ([Villeneuve et al., 2006a](#)).

23 Additional studies in the U.S. reported no evidence of an association between O₃
24 concentrations and ED visits, hospitalizations, or symptoms leading to hospitalization
25 ([Symons et al., 2006](#); [Zanobetti and Schwartz, 2006](#); [Wellenius et al., 2005](#)). [Symons et
26 al. \(2006\)](#) used a case-crossover framework to assess the relationship between air
27 pollutants and the onset of symptoms (dyspnea) severe enough to lead to hospitalization
28 (through the ED) for congestive heart failure. The study was conducted from April to
29 December of 2002 in Baltimore, Maryland. Exposures were assigned using 3 index times:
30 8-hour and 24-hour periods prior to symptom onset and date of hospital admission. No
31 evidence of association was reported for O₃ concentrations. Although seasonal variation
32 was not assessed, the time frame for the study did not involve an entire year (April to
33 December). [Wellenius et al. \(2005\)](#) investigated the association between air pollutants
34 and congestive heart failure hospitalization among Medicare beneficiaries in Pittsburgh,
35 Pennsylvania from 1987 to 1999 utilizing a case-crossover framework. A total of 55,019
36 admissions from the emergency room with a primary discharge diagnosis of CHF were
37 collected. No evidence of an association was reported for O₃ concentration and CHF
38 hospitalization ([Wellenius et al., 2005](#)). Finally, [Zanobetti and Schwartz \(2006\)](#) assessed

1 the relationship between air pollutants and hospital admissions through the ED for MI
2 and pneumonia among patients aged 65 and older residing in the greater Boston area
3 (1995-1999) using a case-crossover framework with control days in the same month
4 matched on temperature. Pollution exposures were assigned for the same day and for the
5 mean of the exposure the day of and the day before the admission. Ozone concentration
6 was not associated with MI admissions in all-year and seasonal analyses.

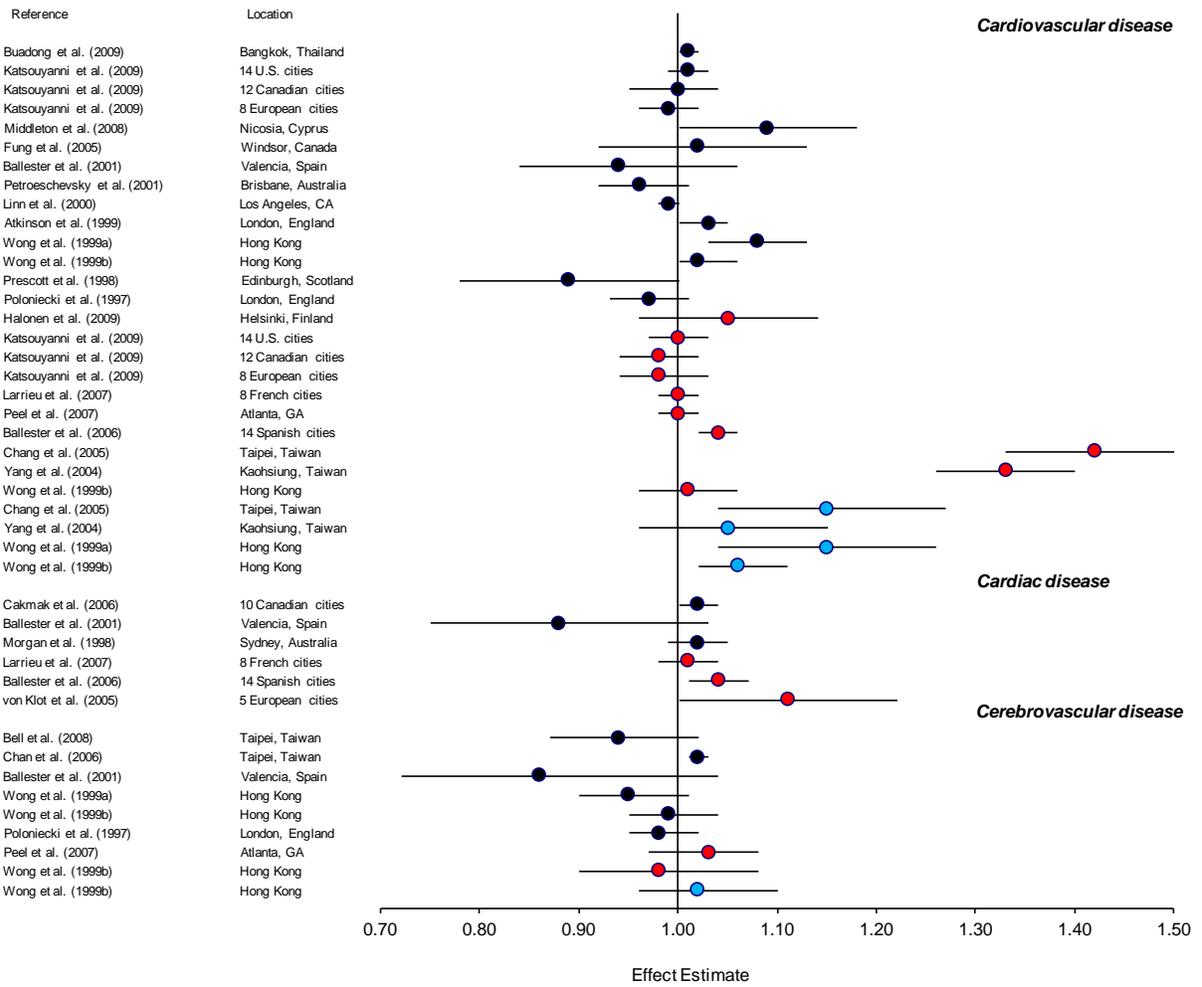
7 Several recent studies have examined the relationship between air pollution and CVD
8 hospital admissions and/or emergency department visits in Asia. Of note, some areas of
9 Asia have a more tropical climate than the U.S. and do not experience similar seasonal
10 changes. In Taiwan, fairly consistent positive associations have been reported for O₃
11 concentration and congestive heart failure hospital admissions (for single- and
12 copollutant models) in Taipei on warm days ([Yang, 2008](#)) and in Kaohsiung ([Lee et al.,
2007](#)); cerebrovascular disease ED visits (for lag 0 single- and two-pollutant models but
13 not other lags) in Taipei ([Chan et al., 2006](#)); and arrhythmia ED visits in Taipei among
14 those without comorbid conditions ([Chiu et al., 2009](#); [Lee et al., 2008a](#)) and in Taipei on
15 warm days among those with and without comorbid conditions ([Lee et al., 2008a](#)).
16 However, one study in Taiwan did not show an association. [Bell et al. \(2008\)](#) reported no
17 evidence of an association between O₃ concentration and hospital admissions for
18 ischemic heart disease or cerebrovascular disease. Studies based in Asia but outside
19 Taiwan were also performed. A Hong Kong-based investigation ([Wong et al., 2009](#))
20 reported no consistent evidence of a modifying effect of influenza on the relationship
21 between O₃ concentration and CVD admissions. Among elderly populations in Thailand,
22 O₃ concentration was associated with CVD visits, but this association was not detected
23 among younger age groups (15-64) ([Buadong et al., 2009](#)). Also, a study performed in
24 Seoul, Korea reported a positive association between O₃ concentration and hospital
25 admissions for ischemic heart disease; the association was slightly greater among those
26 over 64 years of age ([Lee et al., 2003b](#)).
27

28 Positive associations between short-term O₃ exposure and CVD hospital admissions
29 and/or ED visits have been reported in other areas of the world as well ([Azevedo et al.,
2011](#); [Linares and Diaz, 2010](#); [Middleton et al., 2008](#); [Turner et al., 2007](#); [Ballester et al.,
2006](#); [DePablo et al., 2006](#); [VonKlot et al., 2005](#)), although not consistently as some
30 studies reported no association ([Oudin et al., 2010](#); [Halonen et al., 2009](#); [Larrieu et al.,
2007](#); [Barnett et al., 2006](#); [Hinwood et al., 2006](#); [Lanki et al., 2006](#); [Hosseinpoor et al.,
2005](#); [Simpson et al., 2005](#)).
31
32
33
34

35 A couple of studies (U.S. and Australia) have examined cardiac arrests where emergency
36 services attempted treatment/resuscitation. No evidence of an association between O₃

1 concentration and out-of-hospital cardiac arrest was observed ([Dennekamp et al., 2010](#);
2 [Silverman et al., 2010](#)).

3 An increasing number of air pollution studies have investigated the relationship between
4 O₃ concentrations and CVD hospital admissions and/or ED visits. As summarized in the
5 2006 O₃ AQCD, some, especially those reporting results stratified by season (or
6 temperature) or comorbid conditions have reported positive associations. However, even
7 studies performing these stratified analyses are not consistent and the overall evidence
8 remains inconclusive regarding the association between short-term O₃ exposure and CVD
9 hospital admissions and ED visits. The Hospital Admission (HA) and ED visit studies
10 evaluated in this section are summarized in [Figure 6-21](#) through [Figure 6-25](#), which
11 depict the associations for studies in which quantitative data were presented. [Table 6-35](#)
12 through [Table 6-39](#) provide the numerical results displayed in the figures.



Note: Change in O₃ standardized to 20 ppb for 24-h avg period, 30 ppb for 8-h avg period, and 40 ppb for 1-h avg period (see Section 2.2). Ozone concentrations in ppb. Seasons depicted by colors – black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of [Katsouyanni et al. \(2009\)](#), [Fung et al. \(2005\)](#), [Wong et al. \(1999b\)](#), and [Prescott et al. \(1998\)](#), which included only individuals aged 65+. Studies organized by outcome and season and then listed in descending order of publication date.

Figure 6-21 Effect estimate (95% CI) per increment ppb increase in ozone for over all cardiovascular ED visits or hospital admissions.

Table 6-35 Effect estimate (95% CI) per increment ppb increase in ozone for overall cardiovascular ED visits or hospital admissions in studies presented in Figure 6-21.

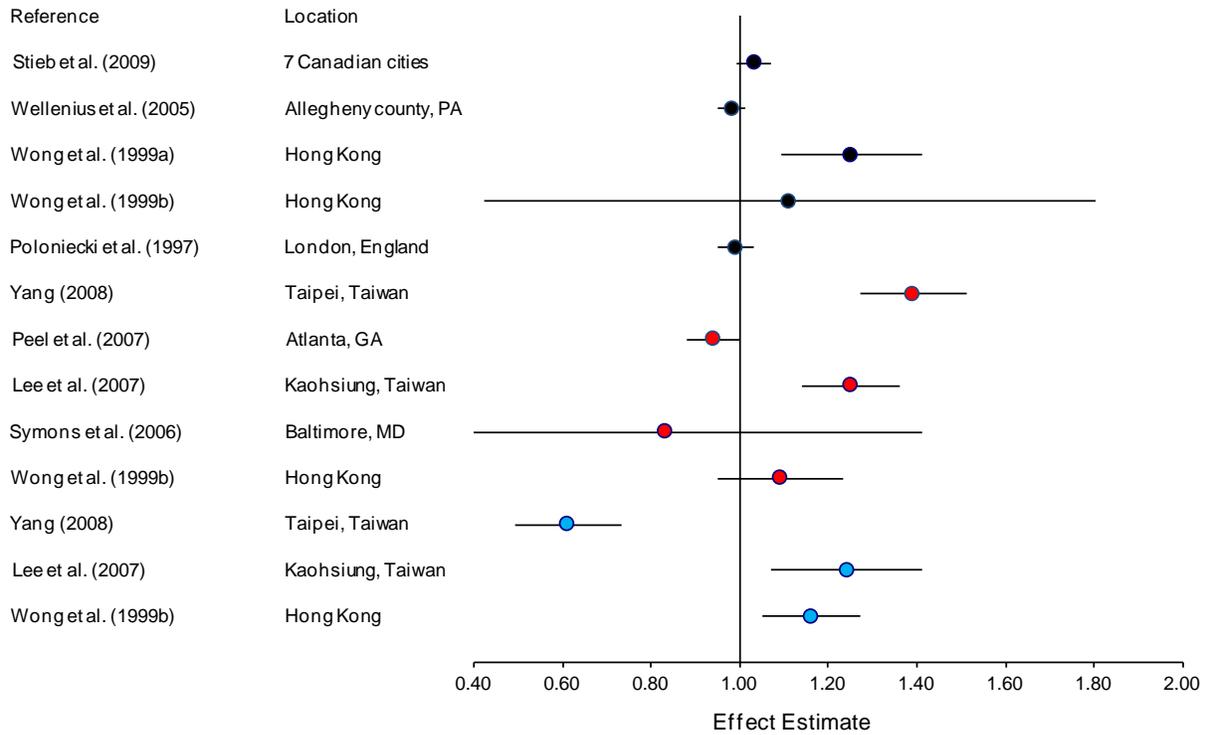
| Study* | Location | Outcome | Averaging Time | Effect Estimate (95% CI) |
|---|-------------------------|-------------------------|---------------------|--------------------------|
| Atkinson et al. (1999) | London, England | Cardiovascular disease | 8-h | 1.03 (1.00, 1.05) |
| Ballester et al. (2006) | 14 Spanish cities | Cardiovascular disease | 8-h warm season | 1.04 (1.02, 1.06) |
| | | Cardiac disease | 8-h warm season | 1.04 (1.01, 1.07) |
| Ballester et al. (2006) | Valencia, Spain | Cardiovascular disease | 8-h | 0.94 (0.84, 1.06) |
| | | Cardiac disease | 8-h | 0.88 (0.75, 1.03) |
| | | Cerebrovascular disease | 8-h | 0.86 (0.72, 1.04) |
| Bell et al. (2008) | Taipei, Taiwan | Cerebrovascular disease | 24-h | 0.94 (0.87, 1.02) |
| Buadong et al. (2009) | Bangkok, Thailand | Cardiovascular disease | 1-h | 1.01 (1.00, 1.02) |
| Cakmak et al. (2006a) | 10 Canadian cities | Cardiac disease | 1-h max | 1.02 (1.00, 1.04) |
| Chan et al. (2006) | Taipei, Taiwan | Cerebrovascular disease | 1-h max | 1.02 (1.01, 1.03) |
| Chang et al. (2005) | Taipei, Taiwan | Cardiovascular disease | 24-h warm season | 1.42 (1.33, 1.50) |
| | | | 24-h cold season | 1.15 (1.04, 1.27) |
| Fung et al. (2005) | Windsor, Canada | Cardiovascular disease | 1-h | 1.02 (0.92, 1.13) |
| Halonen et al. (2009) | Helsinki, Finland | Cardiovascular disease | 8-h max warm season | 1.05 (0.96, 1.14) |
| Katsouyanni et al. (2009) | 14 U.S. cities | Cardiovascular disease | 1-h max | 1.01 (0.99, 1.03) |
| | | | 1-h max warm season | 1.00 (0.97, 1.03) |
| | 12 Canadian cities | Cardiovascular disease | 1-h max | 1.00 (0.95, 1.04) |
| | | | 1-h max warm season | 0.98 (0.94, 1.02) |
| | 8 European cities | Cardiovascular disease | 1-h max | 0.99 (0.96, 1.02) |
| | | | 1-h max warm season | 0.98 (0.94, 1.03) |
| Larrieu et al. (2007) | 8 French cities | Cardiac disease | 8-h max warm season | 1.01 (0.98, 1.04) |
| Linn et al. (2000) | Los Angeles, California | Cardiovascular disease | 24-h | 0.99 (0.98, 1.00) |
| Middleton et al. (2008) | Nicosia, Cyprus | Cardiovascular disease | 8-h max | 1.09 (1.00, 1.18) |

| Study* | Location | Outcome | Averaging Time | Effect Estimate (95% CI) |
|--|---------------------|-------------------------|---------------------|--------------------------|
| Morgan et al. (1998) | Sydney, Australia | Cardiac disease | 1-h max | 1.02 (0.99, 1.05) |
| Peel et al. (2007) | Atlanta, GA | Cardiovascular disease | 8-h warm season | 1.00 (0.98, 1.02) |
| | | Cerebrovascular disease | 8-h warm season | 1.03 (0.97, 1.08) |
| Petroeschevsky et al. (2001) | Brisbane, Australia | Cardiovascular disease | 8-h | 0.96 (0.92, 1.01) |
| Poloniecki et al. (1997) | London, England | Cardiovascular disease | 8-h | 0.97 (0.93, 1.01) |
| | | Cerebrovascular disease | 8-h | 0.98 (0.95, 1.02) |
| Prescott et al. (1998) | Edinburgh, Scotland | Cardiovascular disease | 24-h | 0.89 (0.78, 1.00) |
| VonKlot et al. (2005) | 5 European cities | Cardiac disease | 8-h max warm season | 1.11 (1.00, 1.22) |
| Wong et al. (1999b) | Hong Kong | Cardiovascular disease | 24-h | 1.08 (1.03, 1.13) |
| | | | 24-h cold season | 1.15 (1.04, 1.26) |
| | | Cerebrovascular disease | 24-h | 0.95 (0.90, 1.01) |
| Wong et al. (1999a) | Hong Kong | Cardiovascular disease | 24-h | 1.02 (1.03, 1.06) |
| | | | 24-h warm season | 1.01 (0.96, 1.06) |
| | | | 24-h cold season | 1.06 (1.02, 1.11) |
| | | Cerebrovascular disease | 24-h | 0.99 (0.95, 1.04) |
| | | | 24-h warm season | 0.98 (0.90, 1.08) |
| | | | 24-h cold season | 1.02 (0.96, 1.10) |
| Yang et al. (2004) | Kaohsiung, Taiwan | Cardiovascular disease | 24-h warm season | 1.33 (1.26, 1.40) |
| | | | 24-h cold season | 1.05 (0.96, 1.15) |

*Studies included in [Figure 6-21](#)..

Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of [Katsouyanni et al. \(2009\)](#), [Fung et al. \(2005\)](#), [Wong et al. \(1999a\)](#), and [Prescott et al. \(1998\)](#), which included only individuals aged 65+. Studies listed in alphabetical order.

Warm season defined as: March-October ([Peel et al., 2007](#)), May-October ([Ballester et al., 2005](#); [Wong et al., 1999a](#)), May-September ([Halonen et al., 2009](#)), April-September ([Larrieu et al., 2007](#); [VonKlot et al., 2005](#)) [Katsouyanni et al. \(2009\)](#), $\geq 20^{\circ}\text{C}$ ([Chang et al., 2005](#)) and $\geq 25^{\circ}\text{C}$ ([Yang et al., 2004](#)). Cold season defined as: November-April ([Wong et al., 1999a](#)), $<20^{\circ}\text{C}$ ([Chang et al., 2005](#)) and $<25^{\circ}\text{C}$ ([Yang et al., 2004](#)), December-March ([Wong et al., 1999b](#))



Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Outcomes were all congestive heart failure, with the exception of [Symons et al. \(2006\)](#), which examined onset of congestive heart failure symptoms leading to a heart attack. Age groups of study populations were not specified or were adults with the exception of [Wellenius et al. \(2005\)](#) and [Wong et al. \(1999a\)](#), which included only individuals aged 65+. Studies organized by outcome and season and then listed in descending order of publication date.

Figure 6-22 Effect estimate (95% CI) per increment ppb increase in ozone for congestive heart failure ED visits or hospital admissions.

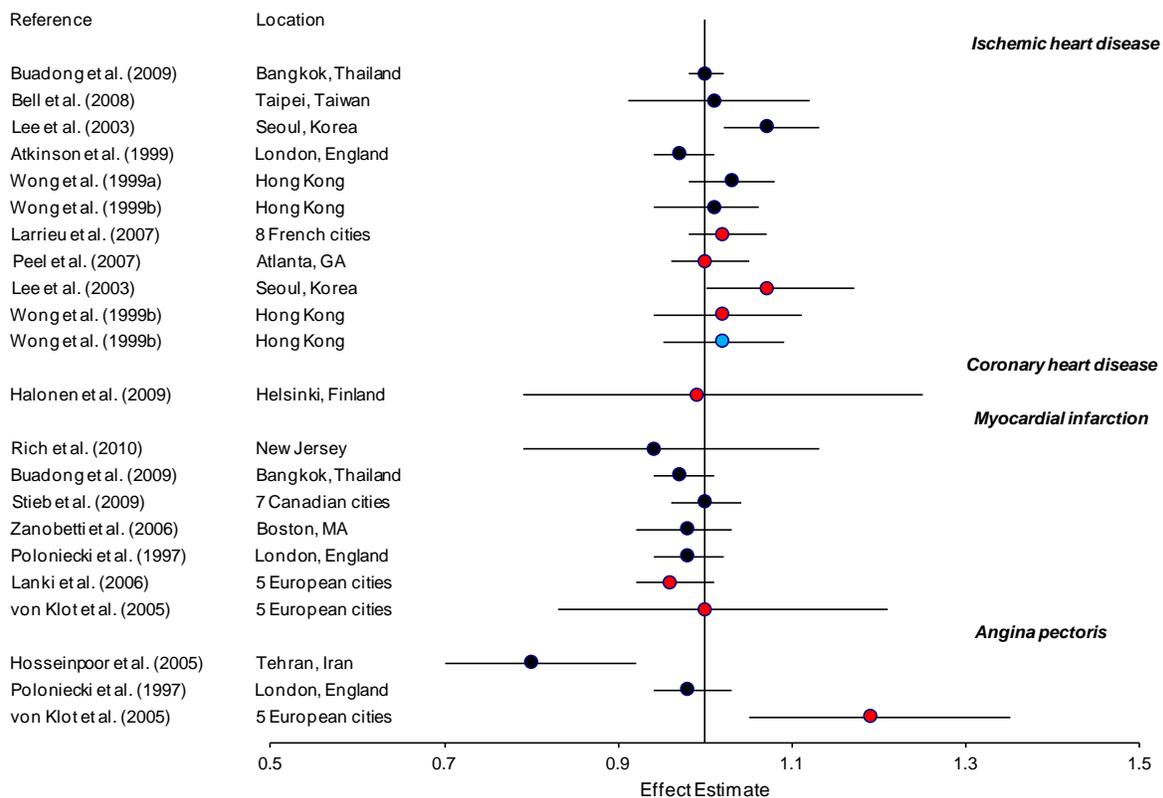
Table 6-36 Effect estimate (95% CI) per increment ppb increase in ozone for congestive heart failure ED visits or hospital admissions for studies in Figure 6-22.

| Study* | Location | Outcome | Averaging Time | Effect Estimate (95% CI) |
|--|----------------------|--|------------------|--------------------------|
| Lee et al. (2007) | Kaohsiung, Taiwan | Congestive heart failure | 24-h warm season | 1.25 (1.15, 1.36) |
| | | Congestive heart failure | 24-h cold season | 1.24 (1.09, 1.41) |
| Peel et al. (2007) | Atlanta, GA | Congestive heart failure | 8-h warm season | 0.94 (0.89, 1.00) |
| Poloniecki et al. (1997) | London, England | Congestive heart failure | 8-h | 0.99 (0.95, 1.03) |
| Stieb et al. (2009) | 7 Canadian cities | Congestive heart failure | 24-h | 1.03 (0.98, 1.07) |
| Symons et al. (2006) | Baltimore, MD | Onset of congestive heart failure symptoms leading to heart attack | 8-h warm season | 0.83 (0.49, 1.41) |
| Wellenius et al. (2005) | Allegheny county, PA | Congestive heart failure | 24-h | 0.98 (0.96, 1.01) |
| Wong et al. (1999a) | Hong Kong | Congestive heart failure | 24-h | 1.11 (1.04, 1.80) |
| | | Congestive heart failure | 24-h warm season | 1.09 (0.96, 1.23) |
| | | Congestive heart failure | 24-h cold season | 1.16 (1.06, 1.27) |
| Yang (2008) | Taipei, Taiwan | Congestive heart failure | 24-h warm season | 1.39 (1.27, 1.51) |
| | | Congestive heart failure | 24-h cold season | 0.61 (0.52, 0.73) |
| Wong et al. (1999b) | Hong Kong | Congestive heart failure | 24-h | 1.25 (1.11, 1.41) |

*Studies include those from [Figure 6-22](#).

Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Outcomes were all congestive heart failure, with the exception of [Symons et al. \(2006\)](#), which examined onset of congestive heart failure symptoms leading to a heart attack. Age groups of study populations were not specified or were adults with the exception of [Wellenius et al. \(2005\)](#) and [Wong et al. \(1999a\)](#), which included only individuals aged 65+. Studies listed in alphabetical order.

Warm season defined as: March-October ([Peel et al., 2007](#)), April-November ([Symons et al., 2006](#)), May-October ([Wong et al., 1999a](#)) ≥ 20°C ([Yang, 2008](#)), and >25°C ([Lee et al., 2007](#)). Cold season defined as: November-April ([Wong et al., 1999a](#)), <20°C ([Yang, 2008](#)), and <25°C ([Lee et al., 2007](#)).



Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of [Wong et al. \(1999a\)](#) and [Atkinson et al. \(1999\)](#), which included only individuals aged 65+. Studies organized by outcome and season and then listed in descending order of publication date.

Figure 6-23 Effect estimate (95% CI) per increment ppb increase in ozone for ischemic heart disease, coronary heart disease, myocardial infarction, and angina pectoris ED visits or hospital admissions.

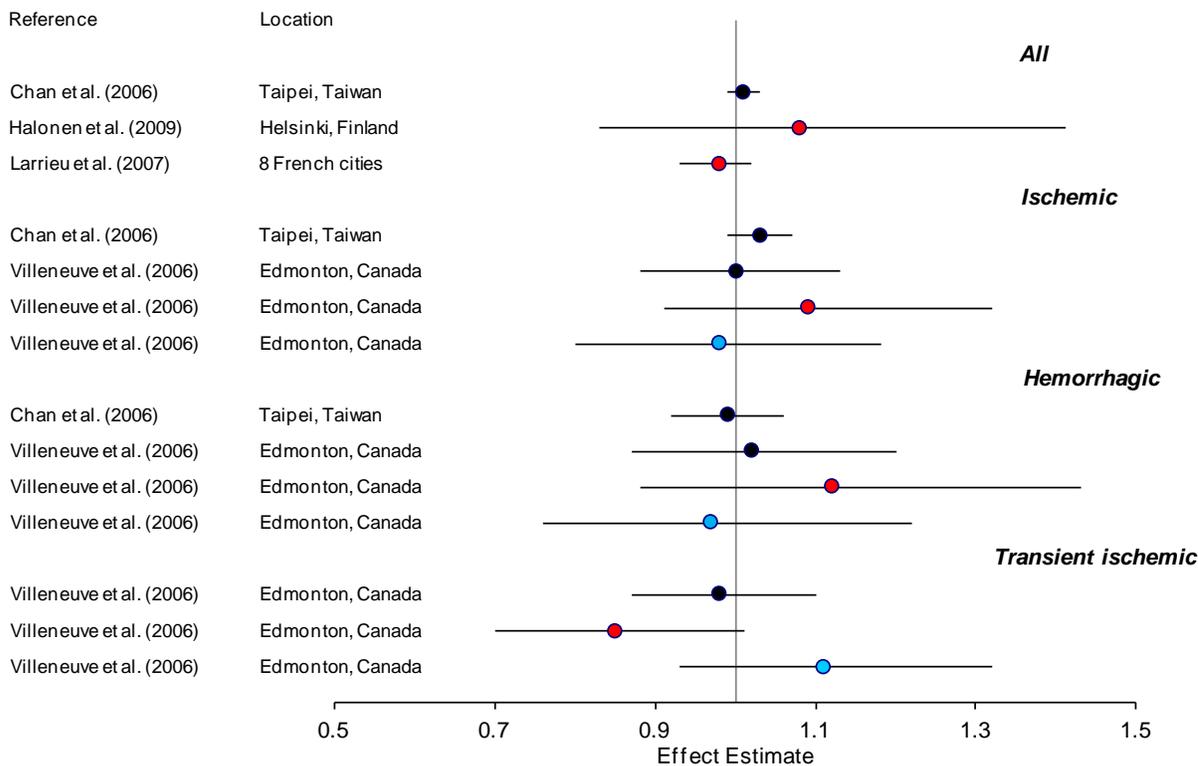
Table 6-37 Effect estimate (95% CI) per increment ppb increase in ozone for ischemic heart disease, coronary heart disease, myocardial infarction, and angina pectoris Evisits or hospital admissions for studies presented in Figure 6-23.

| Study* | Location | Outcome | Averaging Time | Effect Estimate (95% CI) |
|---|-------------------|------------------------|---------------------|--------------------------|
| Atkinson et al. (1999) | London, England | Ischemic heart disease | 8-h | 0.97 (0.94, 1.01) |
| Bell et al. (2008) | Taipei, Taiwan | Ischemic heart disease | 24-h | 1.01 (0.91, 1.12) |
| Buadong et al. (2009) | Bangkok, Thailand | Ischemic heart disease | 1-h | 1.00 (0.98, 1.02) |
| | | Myocardial infarction | 1-h | 0.97 (0.94, 1.01) |
| Halonen et al. (2009) | Helsinki, Finland | Coronary heart disease | 8-h max warm season | 0.99 (0.79, 1.25) |
| Hosseinpoor et al. (2005) | Tehran, Iran | Angina | 8-h max | 0.80 (0.70, 0.92) |
| Lanki et al. (2006) | 5 European cities | Myocardial infarction | 8-h max warm season | 0.96 (0.92, 1.01) |
| Larrieu et al. (2007) | 8 French cities | Ischemic heart disease | 8-h max warm season | 1.02 (0.98, 1.07) |
| Lee et al. (2003b) | Seoul, Korea | Ischemic heart disease | 1-h max | 1.07 (1.02, 1.13) |
| | | Ischemic heart disease | 1-h max warm season | 1.07 (1.00, 1.17) |
| Peel et al. (2007) | Atlanta, GA | Ischemic heart disease | 8-h warm season | 1.00 (0.96, 1.05) |
| Poloniecki et al. (1997) | London, England | Myocardial infarction | 8-h | 0.98 (0.94, 1.02) |
| | | Angina | 8-h | 0.98 (0.94, 1.03) |
| Rich et al. (2010) | New Jersey | Myocardial infarction | 24-h | 0.94 (0.79, 1.13) |
| Stieb et al. (2009) | 7 Canadian cities | Myocardial infarction | 2-h | 1.00 (0.96, 1.04) |
| VonKlot et al. (2005) | 5 European cities | Myocardial infarction | 8-h max warm season | 1.00 (0.83, 1.21) |
| | | Angina | 8-h max warm season | 1.19 (1.05, 1.35) |
| Wong et al. (1999a) | Hong Kong | Ischemic heart disease | 24-h | 1.01 (0.94, 1.06) |
| | | | 24-h warm season | 1.02 (0.94, 1.11) |
| | | | 24-h cold season | 1.02 (0.95, 1.09) |
| Wong et al. (1999b) | Hong Kong | Ischemic heart disease | 24-h | 1.03 (0.98, 1.08) |
| Zanobetti and Schwartz (2006) | Boston, MA | Myocardial infarction | 24-h | 0.98 (0.92, 1.03) |

*Studies included from [Figure 6-23](#).

Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of [Wong et al. \(1999a\)](#) and [Atkinson et al. \(1999\)](#), which included only individuals aged 65+. Studies listed in alphabetical order.

Warm season defined as: March-October ([Peel et al., 2007](#)), June-August ([Lee et al., 2003b](#)), May-September ([Halonen et al., 2009](#)), May-October ([Buadong et al., 2009](#)), and April-September ([Larrieu et al., 2007](#); [Lanki et al., 2006](#); [VonKlot et al., 2005](#)). Cold season defined as: November-April ([Buadong et al., 2009](#)).



Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of [Villeneuve et al. \(2006a\)](#), which included only individuals aged 65+, and [Chan et al. \(2006\)](#), which included only individuals aged 50+. Studies organized by outcome and season and then listed in descending order of publication date.

Figure 6-24 Effect estimate (95% CI) per increment ppb increase in ozone for stroke ED visits or hospital admissions.

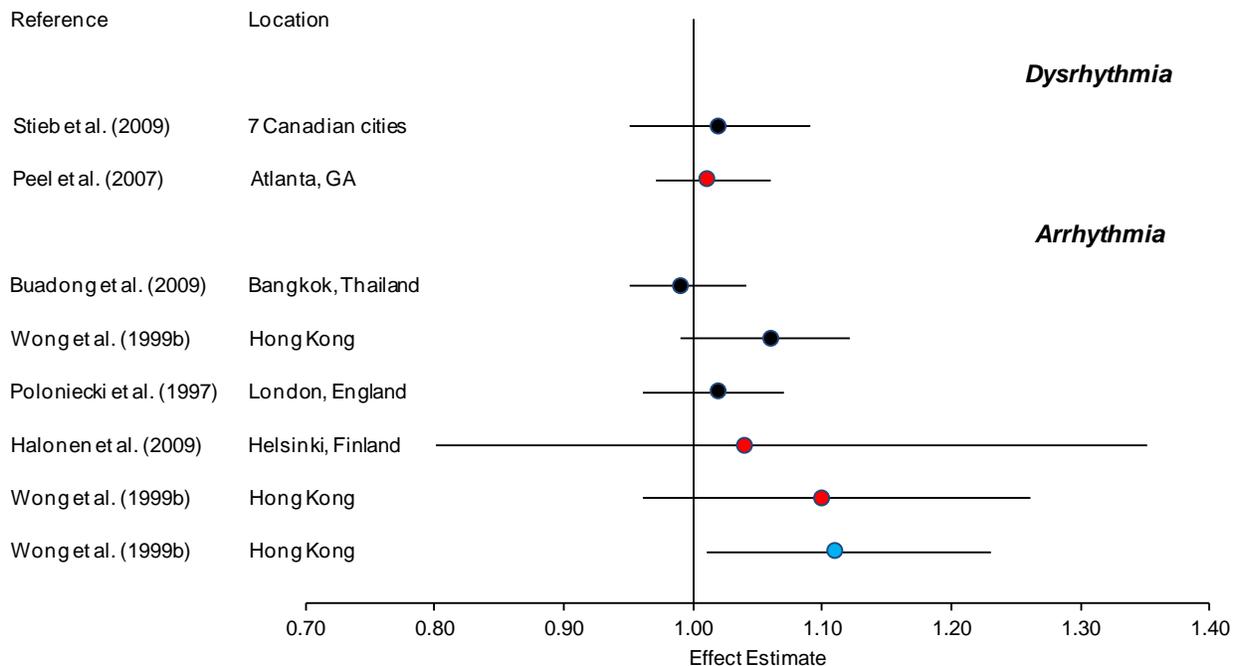
Table 6-38 Effect estimate (95% CI) per increment ppb increase in ozone for stroke ED visits or hospital admissions for studies presented in Figure 6-24.

| Study* | Location | Outcome | Averaging Time | Effect Estimate (95% CI) |
|---|-------------------|---------------------------|---------------------|--------------------------|
| Chan et al. (2006) | Taipei, Taiwan | All/non-specified stroke | 1-h max | 1.01 (0.99, 1.03) |
| | | Ischemic stroke | 1-h max | 1.03 (0.99, 1.07) |
| | | Hemorrhagic stroke | 1-h max | 0.99 (0.92, 1.06) |
| Halonen et al. (2009) | Helsinki, Finland | All/non-specified stroke | 8-h max warm season | 1.08 (0.83, 1.41) |
| Larrieu et al. (2007) | 8 French cities | All/non-specified stroke | 8-h max warm season | 0.98 (0.93, 1.02) |
| Villeneuve et al. (2006a) | Edmonton, Canada | Ischemic stroke | 24-h | 1.00 (0.88, 1.13) |
| | | Ischemic stroke | 24-h warm season | 1.09 (0.91, 1.32) |
| | | Ischemic stroke | 24-h cold season | 0.98 (0.80, 1.18) |
| | | Hemorrhagic stroke | 24-h | 1.02 (0.87, 1.20) |
| | | Hemorrhagic stroke | 24-h warm season | 1.12 (0.88, 1.43) |
| | | Hemorrhagic stroke | 24-h cold season | 0.97 (0.76, 1.22) |
| | | Transient ischemic stroke | 24-h | 0.98 (0.87, 1.10) |
| | | Transient ischemic stroke | 24-h warm season | 0.85 (0.70, 1.01) |
| | | Transient ischemic stroke | 24-h cold season | 1.11 (0.93, 1.32) |

*Studies included from [Figure 6-24](#).

Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of [Villeneuve et al. \(2006a\)](#), which included only individuals aged 65+, and [Chan et al. \(2006\)](#), which included only individuals aged 50+. Studies listed in alphabetical order.

Warm season defined as: May-September ([Halonen et al., 2009](#)), and April-September ([Larrieu et al., 2007](#); [Villeneuve et al., 2006a](#)). Cold season defined as: October-March ([Villeneuve et al., 2006a](#)).



Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of [Wong et al. \(1999a\)](#), which included only individuals aged 65+. Studies organized by outcome and season and then listed in descending order of publication date.

Figure 6-25 Effect estimate (95% CI) per increment ppb increase in ozone for arrhythmia and dysrhythmia ED visits or hospital admissions.

Table 6-39 Effect estimate (95% CI) per increment ppb increase in ozone for arrhythmia and dysrhythmia ED visits or hospital admissions for studies presented in Figure 6-25.

| Study | Location | Outcome | Averaging Time | Effect Estimate (95% CI) |
|--|-------------------|-------------|---------------------|--------------------------|
| Buadong et al. (2009) | Bangkok, Thailand | Arrhythmia | 1-h | 0.99 (0.95, 1.04) |
| Halonen et al. (2009) | Helsinki, Finland | Arrhythmia | 8-h max warm season | 1.04 (0.80, 1.35) |
| Peel et al. (2007) | Atlanta, GA | Dysrhythmia | 8-h warm season | 1.01 (0.97, 1.06) |
| Poloniecki et al. (1997) | London, England | Arrhythmia | 8-h | 1.02 (0.96, 1.07) |
| Stieb et al. (2009) | 7 Canadian cities | Dysrhythmia | 24-h | 1.02 (0.95, 1.09) |
| Wong et al. (1999a) | Hong Kong | Arrhythmia | 24-h | 1.06 (0.99, 1.12) |
| | | | 24-h warm season | 1.10 (0.96, 1.26) |
| | | | 24-h cold season | 1.11 (1.01, 1.23) |

*Studies included from [Figure 6-25](#).

Note: Change in O₃ standardized to 20 ppb for 24-hour averaging period, 30 ppb for 8-hour averaging period, and 40 ppb for 1-hour averaging period (see Section 2.2). Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of ([Wong et al., 1999a](#)), which included only individuals aged 65+. Studies listed in alphabetical order. Warm season defined as: March-October ([Peel et al., 2007](#)), May-October ([Wong et al., 1999a](#)) and May-September ([Halonen et al., 2009](#)). Cold season defined as: November-April ([Wong et al., 1999a](#)).

6.3.2.8 Cardiovascular Mortality

1 As discussed within this section (Section [6.3](#)), epidemiologic studies provide inconsistent
2 evidence of an association between short-term O₃ exposure and cardiovascular effects.
3 However, toxicological studies have demonstrated O₃-induced cardiovascular effects,
4 specifically enhanced atherosclerosis and ischemia, which could lead to death. The 2006
5 O₃ AQCD provided evidence, primarily from single-city studies, of consistent positive
6 associations between short-term O₃ exposure and cardiovascular mortality. Recent
7 multicity studies conducted in the U.S., Canada, and Europe further support the
8 association between short-term O₃ exposure and cardiovascular mortality.

9 As discussed in Section [6.2.7.2](#), the APHENA study ([Katsouyanni et al., 2009](#)) also
10 examined associations between short-term O₃ exposure and mortality and found
11 consistent positive associations for cardiovascular mortality in all-year analyses.
12 However, in analyses restricted to the summer season, results were more variable with no
13 evidence of an association in the Canadian dataset in the population <75 years of age, and
14 evidence of associations persisting or increasing in magnitude in the Canadian
15 (population ≥ 75 years of age), U.S., and European datasets. Additional multicity studies
16 from the U.S. ([Zanobetti and Schwartz, 2008b](#)), Europe ([Samoli et al., 2009](#)), Italy
17 ([Stafoggia et al., 2010](#)), and Asia ([Wong et al., 2010](#)) that conducted summer season

1 and/or all-year analyses provide additional support for an association between short-term
2 O₃ exposure and cardiovascular mortality ([Figure 6-36](#)).

3 Of the studies evaluated, only the APHENA study ([Katsouyanni et al., 2009](#)) and the
4 Italian multicity study ([Stafoggia et al., 2010](#)) conducted an analysis of the potential for
5 copollutant confounding of the O₃-cardiovascular mortality relationship. In the European
6 dataset, when focusing on the natural spline model with 8 df/year (Section [6.2.7.2](#)) and
7 lag 1 results in order to compare results across study locations (Section [6.6.2.1](#)),
8 cardiovascular mortality risk estimates were robust to the inclusion of PM₁₀ in
9 copollutant models in all-year analyses with more variability in the Canadian and U.S.
10 datasets (i.e., cardiovascular O₃ mortality risk estimates were reduced or increased in
11 copollutant models). In summer season analyses, cardiovascular O₃ mortality risk
12 estimates were robust in the European dataset and attenuated but remained positive in the
13 U.S. dataset. Similarly, in the Italian multicity study ([Stafoggia et al., 2010](#)), which was
14 limited to the summer season, cardiovascular mortality risk estimates were robust to the
15 inclusion of PM₁₀ in copollutant models. Based on the APHENA and Italian multicity
16 results, O₃ cardiovascular mortality risk estimates appear to be robust to inclusion of
17 PM₁₀ in copollutant models. However, in the U.S. and Canadian datasets there was
18 evidence that O₃ cardiovascular mortality risk estimates are moderately to substantially
19 sensitive (e.g., increased or attenuated) to PM₁₀. The mostly every-6th-day sampling
20 schedule for PM₁₀ in the Canadian and U.S. datasets greatly reduced their sample size
21 and limits the interpretation of these results.

6.3.2.9 Summary of Epidemiologic Studies

22 Overall, the available body of evidence examining the relationship between short-term
23 exposures to O₃ concentrations and cardiovascular morbidity is inconsistent. Across
24 studies, different definitions, i.e., ICD-9 diagnostic codes were used for both all-cause and
25 cause-specific cardiovascular morbidity ([Table 6-35](#), [Table 6-36](#), [Table 6-37](#), [Table 6-38](#),
26 and [Table 6-39](#)), which may contribute to inconsistency in results. However, within
27 diagnostic categories, no consistent pattern of association was found with O₃. Generally,
28 the studies summarized in this section used nearest air monitors to assess O₃
29 concentrations, with a few exceptions that used modeling or personal exposure monitors
30 (these exceptions were noted throughout the previous sections). The inconsistencies in
31 the associations observed between short-term O₃ and CVD morbidities are unlikely to be
32 explained by the different exposure assignment methods used (see Section [4.6](#)). The wide
33 variety of biomarkers considered and the lack of consistency among definitions used for
34 specific cardiovascular disease endpoints (e.g., arrhythmias, HRV) make comparisons
35 across studies difficult. Despite the inconsistent evidence for an association between O₃

1 concentration and CVD morbidity, mortality studies indicate a consistent positive
2 association between short-term O₃ exposure and cardiovascular mortality in multicity
3 studies and a multicontinent study.

6.3.3 Toxicology: Cardiovascular Effects

4 In the previous O₃ AQCDs ([U.S. EPA, 2006b](#), [1996a](#)) experimental animal studies have
5 reported relatively few cardiovascular system alterations after exposure to O₃ and other
6 photochemical oxidants. The limited amount of research directed at examining
7 O₃-induced cardiovascular effects has primarily found alterations in heart rate (HR), heart
8 rhythm, and BP after O₃ exposure. Although O₃ induced changes in HR and core
9 temperature (T_{CO}) in a number of rat studies, these responses have not been reported or
10 extensively studied in humans exposed to O₃ and may be unique to rodents.

11 According to recent animal toxicology studies, short-term O₃ exposure induces vascular
12 oxidative stress and proinflammatory mediators, alters HR and HRV, and disrupts the
13 regulation of the pulmonary endothelin system (study details are provided in [Table 6-40](#)).
14 A number of these effects were variable between strains examined, suggesting a genetic
15 component to development of O₃ induced cardiovascular effects. Further, recent studies
16 provide evidence that extended O₃ exposure enhances the risk of ischemia-reperfusion
17 (I/R) injury and atherosclerotic lesion development. Still, few studies have investigated
18 the role of O₃ reaction products in these processes, but more evidence is provided for
19 elevated inflammatory and reduction-oxidation (redox) cascades known to initiate these
20 cardiovascular pathologies.

Heart Rate, Rhythm, and Heart Rate Variability

21 Studies ([Arito et al., 1992](#); [Arito et al., 1990](#); [Uchiyama and Yokoyama, 1989](#);
22 [Yokoyama et al., 1989](#); [Uchiyama et al., 1986](#)) report O₃ exposure (0.2-1.0 ppm, 3 hours
23 to 3 days) in rats decreased T_{CO}, HR, and mean arterial pressure (MAP). In addition, O₃
24 exposure (0.1 – 1.0 ppm, 3 hours to 3 days) in rats induced arrhythmias, including
25 increased PR interval and QRS complex, premature atrial contraction, and incomplete
26 A-V block ([Arito et al., 1990](#); [Yokoyama et al., 1989](#); [Uchiyama et al., 1986](#)). The effects
27 were more pronounced in adult and awake rats than in younger or sleeping animals,
28 whereas no sex-related differences were noted in these O₃ induced outcomes ([Uchiyama
29 et al., 1986](#)). However, these cardiovascular responses to O₃, including decreased T_{CO} and
30 HR, could be attenuated by increased ambient temperatures and environmental stress and
31 exhibited adaptation ([Watkinson et al., 2003](#); [Watkinson et al., 1993](#)). These studies
32 suggest that these responses to O₃ were the result of the rodent hypothermic response,

1 which serves as a physiological and behavioral defense mechanism to minimize the
2 irritant effects of O₃ inhalation, ([Iwasaki et al., 1998](#); [Arito et al., 1997](#)). As humans do
3 not appear to exhibit decreased HR, MAP, and T_{CO} with routine environmental
4 (Section [6.3.2](#)) or controlled laboratory (Section [6.3.1](#)) exposures to O₃, caution must be
5 used in extrapolating the results of these animal studies to humans.

6 Other studies have shown that O₃ can increase BP in animal models. Rats exposed to
7 0.6 ppm O₃ for 33 days had increased systolic pressure and HR ([Revis et al., 1981](#)).
8 Increased BP triggers the release of atrial natriuretic factor (ANF), which has been found
9 in increased levels in the heart, lungs, and circulation of O₃ exposed (0.5 ppm) rats
10 ([Vesely et al., 1994a, b, c](#)). Exposures to high concentrations of O₃ (1.0 ppm) have also
11 been found to lead to heart and lung edema ([Friedman et al., 1983](#)), which could be the
12 result of increased ANF levels. Thus, O₃ may increase blood pressure and HR, leading to
13 increased ANF and tissue edema.

14 Recent studies report strain differences in HR and HRV in response to a 2-hour O₃
15 pretreatment followed by exposure to carbon black (CB) in mice (C3H/HeJ [HeJ],
16 C57BL/6J [B6], and C3H/HeOuJ [OuJ]) ([Hamade and Tankersley, 2009](#); [Hamade et al.,
17 2008](#)). These mice strains were chosen from prior studies on lung inflammatory and
18 hyperpermeability responses to be at increased risk (B6 and OuJ) or resistant (HeJ) to
19 O₃-induced health effects ([Kleeberger et al., 2000](#)). HR decreased during O₃ pre-exposure
20 for all strains, but recovered during the CB exposure ([Hamade et al., 2008](#)). Percent
21 change in HRV parameters, SDNN (indicating total HRV) and rMSSD (indicating beat-
22 to-beat HRV), were increased in both C3H mice strains, but not B6 mice, during O₃
23 pre-exposure and recovered during CB exposure when compared to the filtered air group.
24 The two C3H strains differ by a mutation in the Toll-like receptor 4 (TLR4) gene, but
25 these effects did not seem to be related to this mutation since similar responses were
26 observed. [Hamade et al. \(2008\)](#) speculate that the B6 and C3H strains differ in
27 mechanisms of HR response after O₃ exposure between withdrawal of sympathetic tone
28 and increase of parasympathetic tone; however, no direct evidence for this conclusion
29 was reported. The strain differences observed in HR and HRV suggest that genetic
30 variability affects cardiac responses after acute air pollutant exposures.

31 [Hamade and Tankersley \(2009\)](#) continued this investigation of gene-environment
32 interactions on cardiopulmonary adaptation of O₃ and CB induced changes in HR and
33 HRV using the previously described ([Hamade et al., 2008](#)) daily exposure scheme for 3
34 consecutive days. By comparing day-1 interim values it is possible to observe that O₃
35 exposure increased SDNN and rMSSD, but decreased HR in all strains. Measures of HR
36 and HRV in B6 and HeJ mice recovered to levels consistent with filtered air treated mice
37 by day 3; however, these responses in OuJ mice remained suppressed. B6 mice had no

1 change in respiratory rate (RR) after O₃ treatment, whereas HeJ mice on days 1 and 2 had
2 increased RR and OuJ mice on days 2 and 3 exhibited increased RR. V_T did not change
3 with treatment among the strains. Overall, B6 mice were mildly responsive with rapid
4 adaptation, whereas C3 mice were highly responsive with adaptation only in HeJ mice
5 with regards to changes in cardiac and respiratory responses. HR and HRV parameters
6 were not equally correlated with V_T and RR between the three mice strains, which
7 suggest that strains vary in the integration of the cardiac and respiratory systems. These
8 complex interactions could help explain variability in interindividual responses to air
9 pollution.

10 [Hamade et al. \(2010\)](#) expanded their investigation to explore the variation of these strain
11 dependent cardiopulmonary responses with age. As was observed previously, all
12 experimental mouse strains (B6, HeJ, and OuJ) exhibited decreased HR and increased
13 HRV after O₃ exposure. Younger O₃-exposed mice had a significantly lower HR
14 compared to older exposed mice, indicating an attenuation of the bradycardic effect of O₃
15 with age. Younger mice also had a greater increase in rMSSD in HeJ and OuJ strains and
16 SDNN in HeJ mice. Conversely, B6 mice had a slightly greater increase in SDNN in
17 aged mice compared to the young mice. No change was observed in the magnitude of the
18 O₃ induced increase of SDNN in OuJ mice or rMSSD in B6 mice. The B6 and HeJ mice
19 genetically vary in respect to the nuclear factor erythroid 2-related factor 2 (Nrf-2). The
20 authors propose that the genetic differences between the mice strains could be altering the
21 formation of ROS, which tends to increase with age, thus modulating the changes in
22 cardiopulmonary physiology after O₃ exposure.

23 Strain and age differences in HR and heart function were further investigated in B6 and
24 129S1/SvImJ (129) mice in response to a sequential O₃ and filtered air or CB exposure
25 ([Tankersley et al., 2010](#)). Young 129 mice showed a decrease in HR after O₃ or O₃ and
26 CB exposure. This bradycardia was not observed in B6 or older animals in this study,
27 suggesting a possible alteration or adaptation of the autonomic nervous system activity
28 with age. However, these authors did previously report bradycardia in similarly aged
29 young B6 mice ([Hamade et al., 2010](#); [Hamade and Tankersley, 2009](#); [Hamade et al.,
30 2008](#)). Ozone exposure in 129 mice also resulted in an increase in left ventricular
31 chamber dimensions at end diastole (LVEDD) in young and old mice and a decrease in
32 left ventricular posterior wall thickness at end systole (PWTES) in older mice. The
33 increase in LVEDD caused a decrease in fractional shortening, which can be used as a
34 rough indicator of left ventricular function. Regression analysis revealed a significant
35 interaction between age and strain on HR and PWTES, which implies that aging affects
36 HR and heart function in response to O₃ differently between mouse strains.

Vascular Disease and Injury

1 A recent study in young mice (C57Bl/6) and rhesus monkeys examined the effects of
2 short-term O₃ exposure (0.5 ppm, 1 or 5 days) on a number of cardiovascular endpoints
3 ([Chuang et al., 2009](#)). Mice exposed to O₃ for 5 days had increased HR as well as mean
4 and diastolic blood pressure. This is in contrast to the bradycardia that was reported in
5 18-20 week-old B6 mice treated with O₃, as described above ([Hamade and Tankersley,
6 2009](#); [Hamade et al., 2008](#)). Increased blood pressure could be explained by the inhibition
7 in endothelial-dependent (acetylcholine) vasorelaxation from decreased bioavailability of
8 aortic nitric oxide ($\cdot\text{NO}$). Ozone caused a decrease in aortic NO_x (nitrite and nitrate
9 levels) and a decrease in total, but not phosphorylated, endothelial nitric oxide synthase
10 (eNOS). Ozone also increased vascular oxidative stress in the form of increased aortic
11 and lung lipid peroxidation (F₂-isoprostane), increased aortic protein nitration (3-
12 nitrotyrosine), decreased aortic superoxide dismutase (SOD2) protein and activity, and
13 decreased aortic aconitase activity, indicating specific inactivation by O₂⁻ and ONOO⁻.
14 Mitochondrial DNA (mtDNA) damage was also used as a measure of oxidative and
15 nitrative stress in mice and infant rhesus monkeys exposed to O₃. [Chuang et al. \(2009\)](#)
16 observed that mtDNA damage accumulated in the lung and aorta of mice after 1 and
17 5 days of O₃ exposure and in the proximal and distal aorta of O₃ treated nonhuman
18 primates. Additionally, genetically hyperlipidemic mice exposed to O₃ (0.5 ppm) for
19 8 weeks had increased aortic atherosclerotic lesion area (Section [7.3.1](#)), which may be
20 associated with the short-term exposure changes discussed. Overall, this study suggests
21 that O₃ initiates an oxidative environment by increasing O₂⁻ production, which leads to
22 mtDNA damage and $\cdot\text{NO}$ consumption, known to perturb endothelial function ([Chuang
23 et al., 2009](#)). Endothelial dysfunction is characteristic of early and advanced
24 atherosclerosis and coincides with impaired vasodilation and blood pressure regulation.

25 Vascular occlusion resulting from atherosclerosis can block blood flow causing ischemia.
26 The restoration of blood flow in the vessel or reperfusion can cause injury to the tissue
27 from subsequent inflammation and oxidative damage. [Perepu et al. \(2010\)](#) observed that
28 O₃ exposure (0.8 ppm, 28 or 56 days) enhanced the sensitivity to myocardial I/R injury in
29 Sprague-Dawley rats while increasing oxidative stress levels and pro-inflammatory
30 mediators and decreasing production of anti-inflammatory proteins. Ozone was also
31 found to decrease the left ventricular developed pressure, rate of change of pressure
32 development, and rate of change of pressure decay while increasing left ventricular end
33 diastolic pressure in isolated perfused hearts. In this ex vivo heart model, O₃ induced
34 oxidative stress by decreasing SOD enzyme activity and increasing malondialdehyde
35 levels. Ozone also elicited a proinflammatory state which was evident by an increase in
36 TNF- α and a decrease in the anti-inflammatory cytokine IL-10. [Perepu et al. \(2010\)](#)
37 concluded that O₃ exposure may result in a greater I/R injury.

Effects on Cardiovascular-Related Proteins

1 Increased BP, changes in HRV, and increased atherosclerosis may be related to increases
2 in the vasoconstrictor peptide, endothelin-1 (amino acids 1-21, ET-1_[1-21]). Regulation of
3 the pulmonary endothelin system can be affected in rats by inhalation of PM (0, 5,
4 50 mg/m³, EHC-93) and O₃ ([Thomson et al., 2006](#); [Thomson et al., 2005](#)). Exposure to
5 either O₃ (0.8 ppm) or PM increased plasma ET-1_[1-21], ET-3_[1-21], and the ET-1 precursor
6 peptide, bigET-1. Increases in circulating ET-1_[1-21] could be a result of a transient
7 increase in the gene expression of lung preproET-1 and endothelin converting enzyme-1
8 (ECE-1) immediately following inhalation of O₃ or PM. These latter gene expression
9 changes (e.g., preproET-1 and ECE-1) were additive with co-exposure to O₃ and PM.
10 Conversely, preproET-3 decreased immediately after O₃ exposure, suggesting the
11 increase in ET-3_[1-21] was not through de novo production. A recent study also found
12 increased ET-1 gene expression in the aorta of O₃-exposed rats ([Kodavanti et al., 2011](#)).
13 These rats also exhibited an increase in ET_BR after O₃ exposure; however, they did not
14 demonstrate increased biomarkers for vascular inflammation, thrombosis, or oxidation.

15 O₃ can oxidize protein functional groups and disturb the affected protein. For example,
16 the soluble plasma protein fibrinogen is oxidized by O₃ (0.01-0.03 ppm) in vitro, creating
17 fibrinogen and fibrin aggregates, characteristically similar to defective fibrinogen
18 ([Rosenfeld et al., 2009](#); [Rozenfeld et al., 2008](#)). In these studies, oxidized fibrinogen
19 retained the ability to form fibrin gels that are involved in coagulation, however the
20 aggregation time increased and the gels were rougher than normal with thicker fibers.
21 Oxidized fibrinogen also developed the ability to self assemble creating fibrinogen
22 aggregates that may play a role in thrombosis. Since O₃ does not readily translocate past
23 the ELF and pulmonary epithelium and fibrinogen is primarily a plasma protein, it is
24 uncertain if O₃ would have the opportunity to react with plasma fibrinogen. However,
25 fibrinogen can be released from the basolateral face of pulmonary epithelial cells during
26 inflammation, where the deposition of fibrinogen could lead to lung injury ([Lawrence
27 and Simpson-Haidaris, 2004](#)).

Studies on Ozone Reaction Products

28 Although toxicological studies have demonstrated O₃-induced effects on the
29 cardiovascular system, it remains unclear if the mechanism is through a reflex response
30 or the result of effects from O₃ reaction products ([U.S. EPA, 2006b, 1996a](#)). Oxysterols
31 derived from cholesterol ozonation, such as β -epoxide and 5 β ,6 β -epoxycholesterol (and
32 its metabolite cholestan-6-oxo-3,5-diol), have been implicated in inflammation associated
33 with cardiovascular disease ([Pulfer et al., 2005](#); [Pulfer and Murphy, 2004](#)). Two other
34 cholesterol ozonolysis products, atheronal-A and -B (e.g., cholesterol secoaldehyde),

1 have been found in human atherosclerotic plaques and shown in vitro to induce foam cell
2 formation and induce cardiomyocyte apoptosis and necrosis ([Sathishkumar et al., 2005](#);
3 [Wentworth et al., 2003](#)); however, these products have not been found in the lung
4 compartment or systemically after O₃ exposure. The ability to form these cholesterol
5 ozonation products in the circulation in the absence of O₃ exposure complicates their
6 implication in O₃ induced cardiovascular disease.

7 Although it has been proposed that O₃ reaction products released after the interaction of
8 O₃ with ELF constituents (see Section [5.2.3](#)) on O₃ interaction with ELF) are responsible
9 for systemic effects, it is not known whether they gain access to the vascular space.
10 Alternatively, extrapulmonary release of diffusible mediators, such as cytokines or
11 endothelins, may initiate or propagate inflammatory responses in the vascular or systemic
12 compartments ([Cole and Freeman, 2009](#)) (Section [5.3.8](#)). Ozone reacts within the lung to
13 amplify ROS production, induce pulmonary inflammation, and activate inflammatory
14 cells, resulting in a cascading proinflammatory state and extrapulmonary release of
15 diffusible mediators that could lead to cardiovascular injury.

16 A recent study that examined O₃ reaction byproducts has shown that cholesterol
17 secoaldehyde (e.g., atheronal A) induces apoptosis in vitro in mouse macrophages ([Gao](#)
18 [et al., 2009b](#)) and cardiomyocytes ([Sathishkumar et al., 2009](#)). Additionally, atheronal-A
19 and -B has been found to induce in vitro macrophage and endothelial cell
20 proinflammatory events involved in the initiation of atherosclerosis ([Takeuchi et al.,](#)
21 [2006](#)). These O₃ reaction products when complexed with low density lipoprotein
22 upregulate scavenger receptor class A and induce dose-dependent macrophage
23 chemotaxis. Atheronal-A increases expression of the adhesion molecule, E-selectin, in
24 endothelial cells, while atheronal-B induces monocyte differentiation. These events
25 contribute to both monocyte recruitment and foam cell formation in atherosclerotic
26 vessels. It is unknown whether these O₃ reaction products gain access to the vascular
27 space from the lungs. Alternative explanations include the extrapulmonary release of
28 diffusible mediators that may initiate or propagate inflammatory responses in the vascular
29 or systemic compartments.

Table 6-40 Characterization of study details for Section 6.3.3.

| Study ^{a*} | Model | O ₃ (ppm) | Exposure Duration | Effects |
|--|---|--|--|--|
| Chuang et al. (2009) | Mice; C57Bl/6; M; 6 weeks | 0.5 | 1 or 5 days, 8-h/day | Increased HR and blood pressure. Initiated an oxidative environment by increasing vascular O ₂ ⁻ production, which lead to mtDNA damage and ·NO consumption, known to perturb endothelial function. |
| | Monkey; rhesus <i>Macaca mulatta</i> ; M; Infant (180 days old) | 0.5 | 5 days, 8-h/day | Increased aortic mtDNA damage. |
| Perepu et al. (2010) | Rat; Sprague-Dawley; 50-75 g | 0.8 | 28 days, 8-h/day | Enhanced the sensitivity to myocardial I/R injury while increasing oxidative stress and pro-inflammatory mediators and decreasing production of anti-inflammatory proteins. |
| Hamade et al. (2008) | Mice; C57Bl/6J, C3H/HeJ, and C3H/HeOuj; M; 18-20 weeks | 0.6 (subsequent CB exposure, 536 µg/m ³) | 2-h followed by 3 h of CB | Decreased HR. Strain differences observed in HRV suggest that genetic variability affects cardiac responses. |
| Hamade and Tankersley (2009) | Mice; C57Bl/6J, C3H/HeJ, and C3H/HeOuj; M; 18-20 weeks | 0.6 (subsequent CB exposure, 536 µg/m ³) | 3 days, 2-h/day followed by 3-h of CB | Strains varied in integration of the cardiac and respiratory systems, implications in interindividual variability. B6 mice were mildly responsive with rapid adaptation, whereas C3 mice were highly responsive with adaptation only in HeJ mice with regards to changes in cardiac and respiratory responses. |
| Hamade et al. (2010) | Mice; C57Bl/6J, C3H/HeJ, and C3H/HeOuj; M; 5 or 12 mo old | 0.6 (subsequent CB exposure, 536 µg/m ³) | 2-h followed by 3-h of CB | Aged mice exhibited attenuated changes in cardiopulmonary physiology after O ₃ exposure. Genetic differences between mice strains could be altering formation of ROS, which tends to increase with age, thus modulating O ₃ induced effects. |
| Tankersley et al. (2010) | Mice; C57Bl/6J, 129S1/SvImJ; M/F; 5 or 18 mo old | 0.6 (subsequent CB exposure, 556 µg/m ³) | 2-h followed by 3-h of CB | Significant interaction between age and strain on HR and PWTES, which implies that aging affects the HR and function in response to O ₃ differently between mouse strains. |
| Thomson et al. (2005) | Rat; Fischer-344; M; 200-250 g | 0.4 or 0.8 | 4-h | Activation of the vasoconstricting ET system. Increased plasma ET-1 through higher production and slower clearance. |
| Thomson et al. (2006) | Rat; Fischer-344; M; 200-250 g | 0.8 | 4-h | Increased plasma ET-3 not due to de novo synthesis, unlike ET-1. |
| Kodavanti et al. (2011) | Rat; Wistar; M; 10-12 weeks | 0.5 or 1.0 | 2 days, 5-h/day | No changes to aortic genes of thrombosis, inflammation, or proteolysis, except ET-1 and ETBR (1.0 ppm). |

^aResults from previous studies are presented in Table AX5-14 of the 2006 O₃ AQCD and Table 6-23 of the 1996 O₃ AQCD.

*Study details for Section [6.3.3](#)^a

Summary of Toxicological Studies

1 Overall, animal studies suggest that O₃ exposure may result in O₃ induced cardiovascular
2 effects. Studies provide evidence for both increased and decreased HR, however it is
3 uncertain if O₃-induced bradycardia would also occur in humans or if it is due solely to a
4 rodent hypothermic response. Animal studies also provide evidence for increased HRV,
5 arrhythmias, vascular disease, and injury following short-term O₃ exposure. In addition, a
6 series of studies highlight the role of gene-environment interactions and age in the
7 induction of effects and attenuation of responses to O₃ exposure.

8 Biologically plausible mechanisms are present for the cardiovascular effects observed in
9 animal exposure studies, however there is a lack of coherence with controlled human
10 exposure and epidemiologic studies. Further discussion of the modes of action that may
11 lead to cardiovascular effects can be found in Section [5.3.8](#). Recent studies suggest that
12 O₃ exposure may disrupt both the NO[•] and endothelin systems, which can result in an
13 increase in HR, HRV, and ANF. The observed bradycardia following O₃ exposure may
14 be the result of reflex reactions, including the trigeminocardiac reflex, evoked following
15 the stimulation of sensory receptors lining the nose and RT. These mechanisms of
16 parasympathetically-derived cardiac effects are described in more detail in Section [5.3.2](#).
17 Additionally, O₃ may increase oxidative stress and vascular inflammation promoting the
18 progression of atherosclerosis and leading to increased susceptibility to I/R injury. As O₃
19 reacts quickly with the ELF and does not translocate to the heart and large vessels,
20 studies suggest that the cardiovascular effects exhibited could be caused by reaction
21 byproducts of O₃ exposure. However, direct evidence of translocation of O₃ reaction
22 products to the cardiovascular system has not been demonstrated in vivo. Alternatively,
23 extrapulmonary release of diffusible mediators, such as cytokines or endothelins, may
24 initiate or propagate inflammatory responses in the vascular or systemic compartments
25 leading to the reported cardiovascular pathologies.

6.3.4 Summary and Causal Determination

26 In previous O₃ reviews ([U.S. EPA, 2006b](#), [1996a](#)) very few studies examined the effect of
27 short-term O₃ exposure on the cardiovascular system. More recently, the body of
28 scientific evidence available that has examined the effect of O₃ on the cardiovascular
29 system has advanced, but overall still remains small.

30 Although limited in number, toxicological studies have provided evidence of O₃-induced
31 cardiovascular effects. Animal toxicological studies have reported enhanced I/R injury,
32 disrupted NO-induced vascular reactivity, decreased cardiac function, increased vascular
33 disease, and increased HRV following short-term O₃ exposure. The observed increase in

1 HRV is supported by a recent controlled human exposure study that also found increased
2 high frequency HRV, but not altered blood pressure, following O₃ exposure ([Fakhri et al.,
3 2009](#)). Toxicological studies investigating the role of O₃ in heart rate regulation are
4 mixed with both bradycardic and tachycardic responses observed. However, these
5 changes in cardiac function provide preliminary evidence for O₃-induced modulation of
6 the autonomic nervous system leading to cardiovascular complications. It is still
7 uncertain how O₃ inhalation may cause systemic toxicity; however the cardiovascular
8 effects of O₃ found in animals correspond to the development and maintenance of an
9 extrapulmonary oxidative, proinflammatory environment that may result from pulmonary
10 inflammation.

11 The epidemiologic studies evaluated do not support the evidence of O₃-induced
12 cardiovascular effects observed in the toxicological studies. This is highlighted by the
13 multiple studies that examined the association between short-term O₃ exposure and
14 cardiovascular-related hospital admissions and ED visits and other various cardiovascular
15 effects and found no evidence of a consistent relationship with O₃ exposure. Although
16 there is inconsistent evidence for O₃-induced cardiovascular morbidity in the
17 epidemiologic literature, single-city studies reviewed in the 2006 O₃ AQCD, and recent
18 multicity studies, and a multicontinent study demonstrate consistent positive associations
19 between short-term O₃ exposure and cardiovascular mortality. Additionally, O₃ mortality
20 associations were found to remain robust in copollutant models with PM. However, the
21 lack of coherence between the results from studies that examined associations between
22 short-term O₃ exposure and cardiovascular morbidity and subsequently cardiovascular
23 mortality complicate the interpretation of the overall evidence for O₃-induced
24 cardiovascular effects.

25 In conclusion, animal toxicological studies provide some evidence for O₃-induced
26 cardiovascular effects, but the effects observed were not consistently supported by
27 controlled human exposure studies or epidemiologic studies. Although the toxicological
28 evidence provides initial support to the relatively strong body of evidence indicating
29 O₃-induced cardiovascular mortality, there is a lack of coherence with controlled human
30 exposure and epidemiologic studies of cardiovascular morbidity which together do not
31 support O₃-induced cardiovascular effects. Thus, the overall body of evidence across
32 disciplines **is suggestive of a causal relationship between relevant short-term**
33 **exposures to O₃ and cardiovascular effects.**

6.4 Central Nervous System Effects

1 The 2006 O₃ AQCD included toxicological evidence that acute exposures to O₃ are
2 associated with alterations in neurotransmitters, motor activity, short and long term
3 memory, and sleep patterns. Additionally, histological signs of neurodegeneration have
4 been observed. Reports of headache, dizziness, and irritation of the nose with O₃
5 exposure are common complaints in humans, and some behavioral changes in animals
6 may be related to these symptoms rather than indicative of neurotoxicity. [Peterson and](#)
7 [Andrews \(1963\)](#) and [Tepper et al. \(1983\)](#) showed that mice would alter their behavior to
8 avoid O₃ exposure. [Murphy et al. \(1964\)](#) and [Tepper et al. \(1982\)](#) showed that running-
9 wheel behavior was suppressed, and [Tepper et al. \(1985\)](#) subsequently demonstrated the
10 effects of a 6-hour exposure to O₃ on the suppression of running-wheel behavior in rats
11 and mice, with the lowest effective concentration being about 0.12 ppm O₃ in the rat and
12 about 0.2 ppm in the mouse. The suppression of active behavior by 6 hours of exposure
13 to 0.12 ppm O₃ has recently been confirmed by [Martrette et al. \(2011\)](#) in juvenile female
14 rats, and the suppression of three different active behavior parameters was found to
15 become more pronounced after 15 days of exposure. A table of studies examining the
16 effects of O₃ on behavior can be found on p 6-128 of the 1996 O₃ AQCD. Generally
17 speaking, transient changes in behavior in rodent models appear to be dependent on a
18 complex interaction of factors such as (1) the type of behavior being measured, with
19 some behaviors increased and others suppressed; (2) the factors motivating that behavior
20 (differences in reinforcement); and (3) the sensitivity of the particular behavior
21 (e.g., active behaviors are more affected than more sedentary behaviors). Many
22 behavioral changes are likely to result from avoidance of irritation, but more recent
23 studies indicate that O₃ also directly affects the CNS.

24 Research in the area of O₃-induced neurotoxicity has notably increased over the past few
25 years, with the majority of the evidence coming from toxicological studies that examined
26 the association between O₃ exposure, neuropathology, and neurobehavioral effects, and
27 more limited evidence from epidemiologic studies. In an epidemiologic study conducted
28 by [Chen and Schwartz \(2009\)](#), data from the NHANES III cohort was utilized to study
29 the relationship between long-term O₃ exposure (mean annual O₃ concentration of
30 26.5 ppb) and neurobehavioral effects among adults aged 20-59 years. The authors
31 observed an association between annual exposure to O₃ and tests measuring coding
32 ability and attention/short-term memory. Each 10-ppb increase in annual O₃ levels
33 corresponded to an aging-related cognitive performance decline of 3.5 years for coding
34 ability and 5.3 years for attention/short-term memory. These associations persisted in
35 both crude and adjusted models. There was no association between annual O₃
36 concentrations and reaction time tests. The authors conclude that overall there is a
37 positive association between O₃ exposure and reduced performance on neurobehavioral

1 tests. Although [Chen and Schwartz \(2009\)](#) is a long-term exposure study, it is included in
2 this section because it is the first epidemiologic study to demonstrate that exposure to
3 ambient O₃ is associated with decrements in neurocognitive tests related to memory and
4 attention in humans. This epidemiologic evidence of an effect on the CNS due to
5 exposure to ambient concentrations of O₃ is coherent with animal studies demonstrating
6 that exposure to O₃ can produce a variety of CNS effects including behavioral deficits,
7 morphological changes, and oxidative stress in the brains of rodents. In these rodent
8 studies, interestingly, CNS effects were reported at O₃ concentrations that were generally
9 lower than those concentrations commonly observed to produce pulmonary or cardiac
10 effects in rats.

11 A number of new studies demonstrate various perturbations in neurologic function or
12 histology, including changes similar to those observed with Parkinson's and Alzheimer's
13 disease pathologies occurring in similar regions of the brain ([Table 6-41](#)). Many of these
14 include exposure durations ranging from short-term to long-term, and as such are
15 discussed here and in [Chapter 7](#) with emphasis on the effects resulting from exposure
16 durations relevant to the respective chapter. Several studies assess short- and long-term
17 memory acquisition via passive avoidance behavioral testing and find decrements in test
18 performance after O₃ exposure, consistent with the aforementioned observation made in
19 humans by [Chen and Schwartz \(2009\)](#). Impairment of long-term memory has been
20 previously described in rats exposed to 0.2 ppm O₃ for 4 hours ([Rivas-Arancibia et al.,
21 1998](#)) and in other studies of 4-hour exposures at concentrations of 0.7 to 1 ppm ([Dorado-
22 Martinez et al., 2001](#); [Rivas-Arancibia et al., 2000](#); [Avila-Costa et al., 1999](#)). More
23 recently, statistically significant decreases in both short and long-term memory were
24 observed in rats after 15 days of exposure to 0.25 ppm O₃ ([Rivas-Arancibia et al., 2010](#)).

25 The central nervous system is very sensitive to oxidative stress, due in part to its high
26 content of polyunsaturated fatty acids, high rate of oxygen consumption, and low
27 antioxidant enzyme capacity. Oxidative stress has been identified as one of the
28 pathophysiological mechanisms underlying neurodegenerative disorders such as
29 Parkinson's and Alzheimer's disease, among others ([Simonian and Coyle, 1996](#)). It is
30 also believed to play a role in altering hippocampal function, which causes cognitive
31 deficits with aging ([Vanguilder and Freeman, 2011](#)). A particularly common finding in
32 studies of O₃-exposed rats is lipid peroxidation in the brain, especially in the
33 hippocampus, which is important for higher cognitive function including contextual
34 memory acquisition. Performance in passive avoidance learning tests is impaired when
35 the hippocampus is injured, and the observed behavioral effects are well correlated with
36 histological and biochemical changes in the hippocampus, including reduction in spine
37 density in the pyramidal neurons ([Avila-Costa et al., 1999](#)), lipoperoxidation ([Rivas-
38 Arancibia et al., 2010](#); [Dorado-Martinez et al., 2001](#)), progressive neurodegeneration, and

1 activated and phagocytic microglia ([Rivas-Arancibia et al., 2010](#)). The hippocampus is
2 also one of the main regions affected by age-related neurodegenerative diseases,
3 including Alzheimer's disease, and it may be more sensitive to oxidative damage in aged
4 rats. In a study of young (47 days) and aged (900 days) rats exposed to 1 ppm O₃ for 4 h,
5 O₃-induced lipid peroxidation occurred to a greater extent in the striatum of young rats,
6 whereas it was highest in the hippocampus in aged rats ([Rivas-Arancibia et al., 2000](#)).
7 [Martínez-Canabal and Angora-Perez \(2008\)](#) showed exposure of rats to 0.25 ppm,
8 4h/day, for 7, 15, or 30 days increased lipoperoxides in the hippocampus. This effect was
9 observed at day 7 and continued to increase with time, indicating cumulative oxidative
10 damage. O₃-induced changes in lipid peroxidation, neuronal death, and COX-2 positive
11 cells in the hippocampus could be significantly inhibited by daily treatment with growth
12 hormone (GH), which declines with age in most species. The protective effect of GH on
13 -induced oxidative stress was greatest at 15 days of exposure and was non-significant at
14 day 30. Consistent with these findings, lipid peroxidation in the hippocampus of rats was
15 observed to increase significantly after a 30-day exposure to 0.25 ppm , but not after a
16 single 4-hour exposure to the same concentration ([Mokoena et al., 2010](#)). However,
17 4 hours of exposure was sufficient to cause significant increases in lipid peroxidation
18 when the concentration was increased to 0.7 ppm, and another study observed lipid
19 peroxidation after a 4-hour exposure to 0.4 ppm ([Dorado-Martinez et al., 2001](#)).

20 Other commonly affected areas of the brain include the striatum, substantia nigra,
21 cerebellum, olfactory bulb, and frontal/prefrontal cortex. The striatum and substantia
22 nigra are particularly sensitive to oxidative stress because the metabolism of dopamine,
23 central to their function, is an oxidative process perturbed by redox imbalance. Oxidative
24 stress has been implicated in the premature death of substantia nigra dopamine neurons in
25 Parkinson's disease. [Angoa-Pérez et al. \(2006\)](#) have shown progressive lipoperoxidation
26 in the substantia nigra and a decrease in nigral dopamine neurons in ovariectomized
27 female rats exposed to 0.25 ppm O₃, 4h/day, for 7, 15, or 30 days. Estradiol, an
28 antioxidant, attenuated O₃-induced oxidative stress and nigral neuronal death, and the
29 authors note that in humans, estrogen therapy can ameliorate symptoms of Parkinson's
30 disease, which is more prevalent in men. Progressive oxidative stress has also been
31 observed in the striatum and substantia nigra of rats after 15 and 30 days of exposure to
32 0.25 ppm O₃ for 4 h/day, along with a loss of dopaminergic neurons from the substantia
33 nigra ([Pereyra-Muñoz et al., 2006](#)). Decreases in motor activity were also observed at 15
34 and 30 days of exposure, consistent with other reports ([Martrette et al., 2011](#); [Dorado-](#)
35 [Martinez et al., 2001](#)). Using a similar O₃ exposure protocol, [Santiago-López et al. \(2010\)](#)
36 also observed a progressive loss of dopaminergic neurons within the substantia nigra,
37 accompanied by alterations in the morphology of remaining cells and an increase in p53
38 levels and nuclear translocation.

1 The olfactory bulb also undergoes oxidative damage in O₃ exposed animals, in some
2 cases altering olfactory-dependent behavior. Lipid peroxidation was observed in the
3 olfactory bulbs of ovariectomized female rats exposed to 0.25 ppm O₃ (4 h/day) for 30 or
4 60 days ([Guevara-Guzmán et al., 2009](#)). O₃ also induced decrements in a selective
5 olfactory recognition memory test, and the authors note that early deficits in odor
6 perception and memory are components of human neurodegenerative diseases. The
7 decrements in olfactory memory were not due to damaged olfactory perception based on
8 other tests. However, deficits in olfactory perception emerged with longer exposures
9 (discussed in Chapter 7). As with the study by [Angoa-Pérez et al. \(2006\)](#) described
10 above, a protective effect for estradiol was demonstrated for both lipid peroxidation and
11 olfactory memory defects. The role of oxidative stress in memory deficits and associated
12 morphological changes has also been demonstrated via attenuation by other antioxidants
13 as well, such as α -tocopherol ([Guerrero et al., 1999](#)) and taurine ([Rivas-Arancibia et al.,](#)
14 [2000](#)). It is unclear how persistent these effects might be. One study of acute exposure,
15 using 1 ppm O₃ for 4 hours, observed morphological changes in the olfactory bulb of rats
16 at 2 hours, and 1 and 10 days, but not 15 days, after exposure ([Colín-Barenque et al.,](#)
17 [2005](#)).

18 Other acute studies also report changes in the CNS. Lipid peroxidation was observed in
19 multiple regions of the brain after a 1- to 9-hour exposure to 1 ppm O₃ ([Escalante-](#)
20 [Membrillo et al., 2005](#)). Ozone has also been shown to alter gene expression of
21 endothelin-1 (pituitary) and inducible nitric oxide synthase (cerebral hemisphere) after a
22 single 4-hour exposure to 0.8 ppm O₃, indicating potential cerebrovascular effects. This
23 concentration-dependent effect was not observed at 0.4 ppm O₃ ([Thomson et al., 2007](#)).
24 Vascular endothelial growth factor was upregulated in astroglial cells in the central
25 respiratory areas of the brain of rats exposed to 0.5 ppm O₃ for 3 hours ([Araneda et al.,](#)
26 [2008](#)). The persistence of CNS changes after a single exposure was also examined and
27 the increase in vascular endothelial growth factor was present after a short (3 hours)
28 recovery period. Thus, there is evidence that O₃-induced CNS effects are both
29 concentration- and time-dependent.

30 Because O₃ can produce a disruption of the sleep-wake cycle ([U.S. EPA, 2006b](#)), [Alfaro-](#)
31 [Rodríguez and González-Piña \(2005\)](#) examined whether acetylcholine in a region of the
32 brain involved in sleep regulation was altered by O₃. After a 24-hour exposure to 0.5 ppm
33 O₃, the acetylcholine concentration in the medial preoptic area was decreased by 58% and
34 strongly correlated with a disruption in paradoxical sleep. Such behavioral-biochemical
35 effects of O₃ are confirmed by a number of studies which have demonstrated
36 morphological and biochemical changes in rats.

1 CNS effects have also been demonstrated in newborn and adult rats whose only exposure
2 to O₃ occurred in utero. Several neurotransmitters were assessed in male offspring of
3 dams exposed to 1 ppm O₃ during the entire pregnancy ([Gonzalez-Pina et al., 2008](#)). The
4 data showed that catecholamine neurotransmitters were affected to a greater degree than
5 indole-amine neurotransmitters in the cerebellum. CNS changes, including behavioral,
6 cellular, and biochemical effects, have also been observed after in utero exposure to
7 0.5 ppm O₃ for 12 h/day from gestational days 5-20 ([Boussouar et al., 2009](#)). Tyrosine
8 hydroxylase labeling in the nucleus tractus solatarius was increased after in utero
9 exposure to O₃ whereas Fos protein labeling did not change. When these offspring were
10 challenged by immobilization stress, neuroplasticity pathways, which were activated in
11 air-exposed offspring, were inhibited in O₃-exposed offspring. Although an O₃ exposure
12 C-R was not studied in these two in utero studies, it has been examined in one study.
13 [Santucci et al. \(2006\)](#) investigated behavioral effects and gene expression after in utero
14 exposure of mice to as little as 0.3 ppm O₃. Increased defensive/submissive behavior and
15 reduced social investigation were observed in both the 0.3 and 0.6 ppm O₃ groups.
16 Changes in gene expression of brain-derived neurotrophic factor (BDNF, increased in
17 striatum) and nerve growth factor (NGF, decreased in hippocampus) accompanied these
18 behavioral changes. Thus, these three studies demonstrate that CNS effects can occur as a
19 result of in utero exposure to O₃, and although the mode of action of these effects is not
20 known, it has been suggested that circulating lipid peroxidation products may play a role
21 ([Boussouar et al., 2009](#)). Importantly, these CNS effects occurred in rodent models after
22 in utero only exposure to relevant concentrations of O₃.

Table 6-41 Central nervous system and behavioral effects of short-term ozone exposure in rats

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|---|--|----------------------|--|---|
| Martrette et al. (2011) | Rat; Wistar; F; Weight: 152g; 7 weeks old | 0.12 | 1-15 days, 6 h/day | Significant decrease in rearing, locomotor activity, and jumping activity at day 1, with a further decrease in these activities by day 15. |
| Anqoa-Pérez et al. (2006) | Rat; Wistar; F; Weight: 300g; ovariectomized | 0.25 | 7 to 60 days, 4-h/day, 5 days/week | Progressive lipid peroxidation and loss of tyrosine hydrolase-immunopositive neurons in the substantia nigra starting at 7 days. |
| Guevara-Guzmán et al. (2009) | Rat; Wistar; F; 264g; ovariectomized | 0.25 | 30 and 60 days, 4h/day | Estradiol treatment protected against lipid peroxidation and decreases in estrogen receptors and dopamine β-hydroxylase in olfactory bulbs along with deficits in olfactory recognition memory. |
| Martínez-Canabal and Anqora-Perez (2008) | Rat; Wistar; M; Weight: 300g | 0.25 | 7 to 30 days, 4-h/day | Growth hormone inhibited O ₃ -induced increases in lipoperoxidation and COX-2 positive cells in the hippocampus. |
| Pereyra-Muñoz et al. (2006) | Rat; Wistar; M; 250-300g | 0.25 | 15 and 30 days, 4-h/day | Decreased motor activity, increased lipid peroxidation, altered morphology, and loss of dopamine neurons in substantia nigra and striatum, increased expression of DARPP-32, iNOS, and SOD. |
| Rivas-Arancibia et al. (2010) | Rat; Wistar; M; 250-300g | 0.25 | 15 to 90 days, 4-h/ day | Ozone produced significant increases in lipid peroxidation in the hippocampus, and altered the number of p53 positive immunoreactive cells, activated and phagocytic microglia cells, GFAP immunoreactive cells, and doublecortine cells, and short- and long-term memory-retention latency. |
| Santiago-López et al. (2010) | Rat; Wistar; M; 250-300g | 0.25 | 15, 30, and 60 days, 4-h/day | Progressive loss of dopamine reactivity in the substantia nigra, along with morphological changes. Increased p53 levels and nuclear translocation. |
| Thomson et al. (2007) | Rat; Fischer-344; M; 200-250g | 0.4; 0.8 | 4-h; assays at 0 and 24 h postexposure | At 0.8 ppm, O ₃ produced rapid perturbations in the ET-NO pathway gene expression in the brain. Ozone induced a small but significant time- and concentration-dependent increase in prepro-endothelin-1 mRNA levels in the cerebral hemisphere and pituitary, whereas TNFα and iNOS mRNA levels were decreased at 0 h and unchanged or increased, respectively, at 24 h. |
| Alfaro-Rodríguez and González-Piña (2005) | Rat; Wistar; M; 292g | 0.5 | 24-h | During the light phase, O ₃ caused a significant decrease in paradoxical sleep accompanied by a significant decrease in Ach levels in the hypothalamic medial preoptic area. The same effects occurred during the dark phase exposure to O ₃ in addition to a significant increase in slow-wave sleep and decrease in wakefulness. |
| Araneda et al. (2008) | Rats; Sprague-Dawley; M; 280-320g | 0.5 | 3-h (measurements taken at 0 h and 3 h after exposure) | Ozone upregulated VEGF in astroglial cells located in the respiratory center of the brain. VEGF co-located with IL-6 and TNF in cells near blood vessel walls, and blood vessel area was markedly increased. |

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|---|--|----------------------|---|--|
| Boussouar et al. (2009) | Rat; Sprague-Dawley; M; adult offspring of prenatally exposed dams; 403-414g | 0.5 | From embryonic day E5 to E20 for 1-h/day; immobilization stress | Prenatal O ₃ exposure had a long term impact on the nucleus tractus solitarius of adult rats, as revealed during immobilization stress. |
| Soulage et al. (2004) | Rat; Sprague-Dawley; M; Approx. 7 weeks old | 0.7 | 5-h | Ozone produced differential effects on peripheral and central components of the sympatho-adrenal system. While catecholamine biosynthesis was increased in portions of the brain, the catecholamine turnover rate was significantly increased in the heart and cerebral cortex and inhibited in the lung and striatum. |
| Calderón Guzmán et al. (2006); (2005) | Rat; Wistar; M; 21 days old; well-nourished and malnourished groups | 0.75 | 15 successive days for 4-h/day | A significant decrease in body weight was observed in both well nourished (WN) and malnourished (MN) rats after O ₃ exposure. Localized ATPase, TBARS, and GSH levels changed in response to O ₃ in certain brain areas and the O ₃ -induced changes were dependent on nutritional condition. |
| Colín-Barenque et al. (2005) | Rats; Wistar; M; 250-300g | 1.0 | 4-h; assays at 2-h, 24-h, 10 days, and 15 days after exposure | A significant loss of dendritic spines in granule cells of the olfactory bulb occurred at 2 hrs to 10 days after exposure. Cytological and ultrastructural changes returned towards normal morphology by 15 days. |
| Escalante-Membrillo et al. (2005) | Rats; Wistar; M; 280-320g | 1.0 | 1-, 3-, 6-, or 9-h | Significant increases in TBARS occurred in hypothalamus, cortex, striatum, midbrain, thalamus, and pons. Partial but significant recovery was observed by 3 h after the 9 h exposure. |
| Gonzalez-Pina et al. (2008) | Rat; Wistar; M; | 1 | 12-h/day, 21 days of gestation; assays at 0, 5, & 10 days postnatal | Prenatal O ₃ exposure produced significant decreases in cerebellar monoamine but not indolamine content at 0 and 5 days after birth with a partial recovery by 10 days. 5-hydroxy-indole-acetic acid levels were significantly increased at 10 days. |

6.4.1 Neuroendocrine Effects

1 According to the 2006 O₃ AQCD, early studies suggested an interaction of O₃ with the
2 pituitary-thyroid-adrenal axis, because thyroidectomy, hypophysectomy, and
3 adrenalectomy protected against the lethal effects of O₃. Concentrations of 0.7-1.0 ppm
4 O₃ for a 1-day exposure in male rats caused changes in the parathyroid, thymic atrophy,
5 decreased serum levels of thyroid hormones and protein binding, and increased prolactin.
6 Increased toxicity to O₃ was reported in hyperthyroid rats and T3 supplementation was
7 shown to increase metabolic rate and pulmonary injury in the lungs of O₃-treated animals.
8 The mechanisms by which O₃ affects neuroendocrine function are not well understood,
9 but previous work suggests that high ambient levels of O₃ can produce marked neural
10 disturbances in structures involved in the integration of chemosensory inputs, arousal,

1 and motor control, effects that may be responsible for some of the behavioral effects seen
2 with O₃ exposure. A more recent study exposing immature female rats to 0.12 ppm O₃
3 demonstrated significantly increased serum levels of the thyroid hormone free T₃ after
4 15 days of exposure, whereas free T₄ was unchanged ([Martrette et al., 2011](#)). These
5 results are in contrast to those previously presented whereby 1 ppm O₃ for 1 day
6 significantly decreased T₃ and T₄ ([Clemons and Garcia, 1980](#)), although comparisons are
7 made difficult by highly disparate exposure regimens along with sex differences.
8 [Martrette et al. \(2011\)](#) also demonstrated significantly increased corticosterone levels
9 after 15 days of exposure, suggesting a stress related response.

6.4.2 Summary and Causal Determination

10 In rodents, O₃ exposure has been shown to cause physicochemical changes in the brain
11 indicative of oxidative stress and inflammation. Newer toxicological studies add to earlier
12 evidence that acute exposures to O₃ can produce a range of effects on the central nervous
13 system and behavior. Previously observed effects, including neurodegeneration,
14 alterations in neurotransmitters, short and long term memory, and sleep patterns, have
15 been further supported by recent studies. In instances where pathology and behavior are
16 both examined, animals exhibit decrements in behaviors tied to the brain regions or
17 chemicals found to be affected or damaged. For example, damage in the hippocampus,
18 which is important for memory acquisition, was correlated with impaired performance in
19 tests designed to assess memory. Thus the brain is functionally affected by O₃ exposure.
20 The single epidemiologic study conducted showed an association between O₃ exposure
21 and memory deficits in humans as well, albeit on a long-term exposure basis. Notably,
22 exposure to O₃ levels as low as 0.25 ppm for 7 days has resulted in progressive
23 neurodegeneration and deficits in both short and long-term memory in rodents.
24 Examination of changes in the brain at lower exposure concentrations or at 0.25 ppm for
25 shorter durations has not been reported, but 0.12 ppm O₃ has been shown to alter
26 behavior. It is possible that some behavioral changes may reflect avoidance of irritation
27 as opposed to functional changes in brain morphology or chemistry, but in many cases
28 functional changes are related to oxidative stress and damage. In some instances, changes
29 were dependent on the nutritional status of the rats (high versus low protein diet). For
30 example, O₃ produced an increase in glutathione in the brains of rats fed the high protein
31 diet but decreases in glutathione in rats fed low protein chow ([Calderón Guzmán et al.,
32 2006](#)). The hippocampus, one of the main regions affected by age-related
33 neurodegenerative diseases, appears to be more sensitive to oxidative damage in aged rats
34 ([Rivas-Arancibia et al., 2000](#)), and growth hormone, which declines with age in most
35 species, may be protective ([Martínez-Canabal and Angora-Perez, 2008](#)). Developing

1 animals may also be sensitive, as changes in the CNS, including biochemical, cellular,
2 and behavioral effects, have been observed in juvenile and adult animals whose sole
3 exposure occurred in utero, at levels as low as 0.3 ppm. A number of studies
4 demonstrate O₃-induced changes that are also observed in human neurodegenerative
5 disorders such as Alzheimer's and Parkinson's disease, including signs of oxidative
6 stress, loss of neurons/neuronal death, reductions in dopamine levels, increased COX-2
7 expression, and increases in activated microglia in important regions of the brain
8 (hippocampus, substantia nigra).

9 Thus, evidence for neurological effects from epidemiologic and controlled human
10 exposure studies is lacking. However, the toxicological evidence for the impact of O₃ on
11 the brain and behavior is strong, and **suggestive of a causal relationship between O₃**
12 **exposure and effects on the central nervous system.**

6.5 Effects on Other Organ Systems

6.5.1 Effects on the Liver and Xenobiotic Metabolism

13 Early investigations of the effects of O₃ on the liver centered on xenobiotic metabolism,
14 and the prolongation of drug-induced sleeping time, which was observed at 0.1 ppm O₃
15 ([Graham et al., 1981](#)). In some species, only adults and especially females were affected.
16 In rats, high (1.0-2.0 ppm for 3 hours) acute O₃ exposures caused increased production of
17 NO by hepatocytes and enhanced protein synthesis ([Laskin et al., 1996](#); [Laskin et al.,](#)
18 [1994](#)). Except for the earlier work on xenobiotic metabolism, the responses occurred only
19 after very high acute O₃ exposures. One study, conducted at 1 ppm O₃ exposure, has been
20 identified ([Last et al., 2005](#)) in which alterations in gene expression underlying
21 O₃-induced cachexia and downregulation of xenobiotic metabolism were examined. A
22 number of the downregulated genes are known to be interferon (IFN) dependent,
23 suggesting a role for circulating IFN. A more recent study by [Aibo et al. \(2010\)](#)
24 demonstrates exacerbation of acetaminophen-induced liver injury in mice after a single
25 6-hour exposure to 0.25 or 0.5 ppm O₃. Data indicate that O₃ may worsen drug-induced
26 liver injury by inhibiting hepatic repair. The O₃-associated effects shown in the liver are
27 thought to be mediated by inflammatory cytokines or other cytotoxic mediators released
28 by activated macrophages or other cells in the lungs ([Laskin and Laskin, 2001](#); [Laskin et](#)
29 [al., 1998](#); [Vincent et al., 1996a](#)). Recently, increased peroxidated lipids were detected in
30 the plasma of O₃ exposed animals ([Santiago-López et al., 2010](#)).

31 In summary, mediators generated by O₃ exposure may cause effects on the liver in
32 laboratory rodents. Ozone exposures as low as 0.1 ppm have been shown to affect

1 drug-induced sleeping time, and exposure to 0.25 ppm can exacerbate liver injury
2 induced by a common analgesic. However, very few studies at relevant concentrations
3 have been conducted, and no data from controlled human exposure or epidemiologic
4 studies are currently available. Therefore the collective evidence **is inadequate to**
5 **determine if a causal relationship exists between short-term O₃ exposure and**
6 **effects on the liver and metabolism.**

6.5.2 Effects on Cutaneous and Ocular Tissues

7 In addition to the lungs, the skin is highly exposed to O₃ and contains O₃ reactive targets
8 (polyunsaturated fatty acids) that can produce lipid peroxides. The 2006 O₃ AQCD ([U.S.](#)
9 [EPA, 2006b](#)) reported that although there is evidence of oxidative stress at near ambient
10 O₃ concentrations, skin and eyes are only affected at high concentrations (greater than
11 1-5 ppm). Ozone exposure (0.8 ppm for 7 days) induces oxidative stress in the skin of
12 hairless mice, along with proinflammatory cytokines ([Valacchi et al., 2009](#)). A recent
13 study demonstrated that 0.25 ppm O₃ differentially alters expression of
14 metalloproteinases in the skin of young and aged mice, indicating that age may
15 potentially increase risk of oxidative stress ([Fortino et al., 2007](#)). In young mice, healing
16 of skin wounds is not significantly affected by O₃ exposure ([Lim et al., 2006](#)). However,
17 exposure to 0.5 ppm O₃ for 6 h/day significantly delays wound closure in aged mice. As
18 with effects on the liver described above, the effects of O₃ on the skin and eyes have not
19 been widely studied, and information from controlled human exposure or epidemiologic
20 studies is not currently available. Therefore **the collective evidence is inadequate to**
21 **determine if a causal relationship exists between short-term O₃ exposure and**
22 **effects on cutaneous and ocular tissues.**

6.6 Mortality

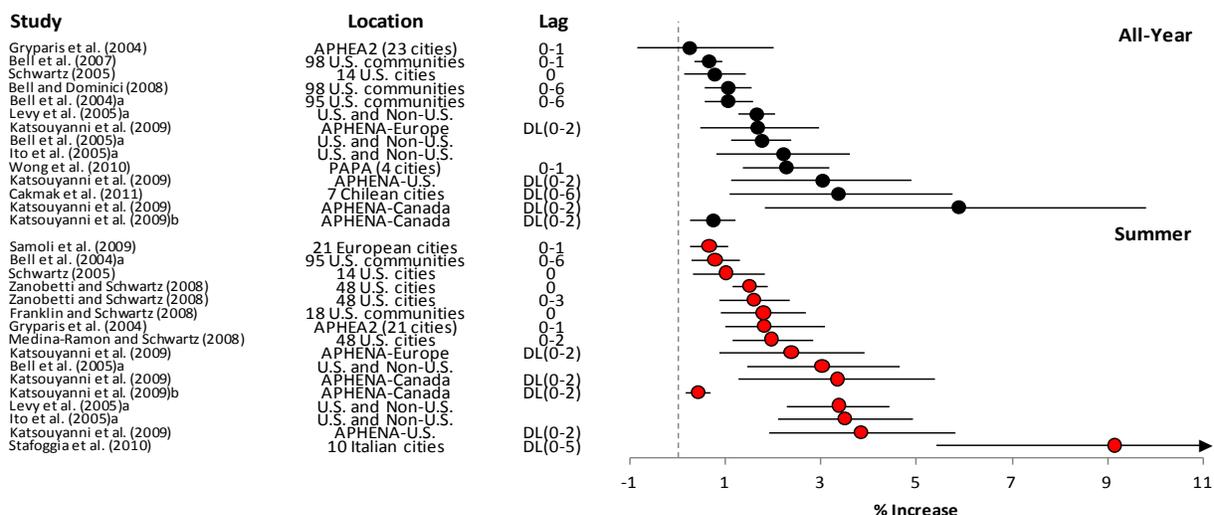
6.6.1 Summary of Findings from 2006 Ozone AQCD

23 The 2006 O₃ AQCD reviewed a large number of time-series studies consisting of single-
24 and multicity studies, and meta-analyses. In the large U.S. multicity studies that
25 examined all-year data, summary effect estimates corresponding to single-day lags
26 ranged from a 0.5-1% increase in all-cause (nonaccidental) mortality per a standardized
27 unit increase in O₃ of 20 ppb for 24-h avg, 30 ppb for 8-h max, and 40 ppb for 1-h max as
28 discussed in Section [2.2](#). The association between short-term O₃ exposure and mortality
29 was substantiated by a collection of meta-analyses and international multicity studies.

1 The studies evaluated found some evidence for heterogeneity in O₃ mortality risk
2 estimates across cities and studies. Studies that conducted seasonal analyses, although
3 more limited in number, reported larger O₃ mortality risk estimates during the warm or
4 summer season. Overall, the 2006 O₃ AQCD identified robust associations between
5 various measures of daily ambient O₃ concentrations and all-cause mortality, with
6 additional evidence for associations with cardiovascular mortality, which could not be
7 readily explained by confounding due to time, weather, or copollutants. However, it was
8 noted that multiple uncertainties remain regarding the O₃-mortality relationship
9 including: the extent of residual confounding by copollutants; factors that modify the
10 O₃-mortality association; the appropriate lag structure for identifying O₃-mortality effects
11 (e.g., single-day lags versus distributed lag model); the shape of the O₃-mortality C-R
12 function and whether a threshold exists; and the identification of susceptible populations.
13 Collectively, the 2006 O₃ AQCD concluded that “the overall body of evidence is highly
14 suggestive that O₃ directly or indirectly contributes to non-accidental and
15 cardiopulmonary-related mortality.”

6.6.2 Associations of Mortality and Short-Term Ozone Exposure

16 Recent studies that examined the association between short-term O₃ exposure and
17 mortality further confirmed the associations reported in the 2006 O₃ AQCD. New
18 multicontinent and multicity studies reported consistent positive associations between
19 short-term O₃ exposure and all-cause mortality in all-year analyses, with additional
20 evidence for larger mortality risk estimates during the warm or summer months
21 ([Figure 6-26](#); [Table 6-42](#)). These associations were reported across a range of ambient O₃
22 concentrations that were in some cases quite low ([Table 6-43](#)).



Note: Effect estimates are for a 40 ppb increase in 1-h max, 30 ppb increase in 8-h max, and 20 ppb increase in 24-h avg O₃ concentrations. An “a” represent multicity studies and meta-analyses from the 2006 O₃ AQCD. [Bell et al. \(2005\)](#), [Ito et al. \(2005\)](#), and [Levy et al. \(2005\)](#) used a range of lag days in the meta-analysis: Lag 0, 1, 2, or average 0-1 or 1-2; single-day lags from 0 to 3; and lag 0 and 1-2; respectively. A “b” represents risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations (see explanation in Section [6.2.7.2](#)).

Figure 6-26 Summary of mortality risk estimates for short-term ozone exposure and all-cause (nonaccidental) mortality from all-year and summer season analyses.

Table 6-42 Corresponding effect estimates for Figure 6-26.

| Study* | Location | Lag | Avg Time | % Increase (95% CI) |
|---|---------------------|---------|----------|---------------------|
| All-year | | | | |
| Gryparis et al. (2004) | APHEA2 (23 cities) | 0-1 | 1-h max | 0.24 (-0.86, 1.98) |
| Bell et al. (2007) | 98 U.S. communities | 0-1 | 24-h avg | 0.64 (0.34, 0.92) |
| Schwartz (2005a) | 14 U.S. cities | 0 | 1-h max | 0.76 (0.13, 1.40) |
| Bell and Dominici (2008) | 98 U.S. communities | 0-6 | 24-h avg | 1.04 (0.56, 1.55) |
| Bell et al. (2004)^a | 95 U.S. communities | 0-6 | 24-h avg | 1.04 (0.54, 1.55) |
| Levy et al. (2005)^a | U.S. and Non-U.S. | --- | 24-h avg | 1.64 (1.25, 2.03) |
| Katsouyanni et al. (2009) | APHENA-europe | DL(0-2) | 1-h max | 1.66 (0.47, 2.94) |
| Bell et al. (2005)^a | U.S. and Non-U.S. | --- | 24-h avg | 1.75 (1.10, 2.37) |
| (Ito et al., 2005)^a | U.S. and Non-U.S. | --- | 24-h avg | 2.20 (0.80, 3.60) |
| (Wong et al., 2010) | PAPA (4 cities) | 0-1 | 8-h avg | 2.26 (1.36, 3.16) |
| Katsouyanni et al. (2009) | APHENA-U.S. | DL(0-2) | 1-h max | 3.02 (1.10, 4.89) |
| Cakmak et al. (2011) | 7 Chilean cities | DL(0-6) | 8-h max | 3.35 (1.07, 5.75) |
| Katsouyanni et al. (2009) | APHENA-Canada | DL(0-2) | 1-h max | 5.87 (1.82, 9.81) |
| Katsouyanni et al. (2009)^b | APHENA-Canada | DL(0-2) | 1-h max | 0.73 (0.23, 1.20) |
| Summer | | | | |
| Samoli et al. (2009) | 21 European cities | 0-1 | 8-h max | 0.66 (0.24, 1.05) |
| Bell et al. (2004)^a | 95 U.S. communities | 0-6 | 24-h avg | 0.78 (0.26, 1.30) |
| Schwartz (2005a) | 14 U.S. cities | 0 | 1-h max | 1.00 (0.30, 1.80) |
| Zanobetti and Schwartz (2008a) | 48 U.S. cities | 0 | 8-h max | 1.51 (1.14, 1.87) |
| Zanobetti and Schwartz (2008b) | 48 U.S. cities | 0-3 | 8-h max | 1.60 (0.84, 2.33) |
| Franklin and Schwartz (2008) | 18 U.S. communities | 0 | 24-h avg | 1.79 (0.90, 2.68) |
| Gryparis et al. (2004) | APHEA2 (21 cities) | 0-1 | 8-h max | 1.80 (0.99, 3.06) |
| Medina-Ramón and Schwartz (2008) | 48 U.S. cities | 0-2 | 8-h max | 1.96 (1.14, 2.82) |
| Katsouyanni et al. (2009) | APHENA-europe | DL(0-2) | 1-h max | 2.38 (0.87, 3.91) |
| Bell et al. (2005)^a | U.S. and Non-U.S. | --- | 24-h avg | 3.02 (1.45, 4.63) |
| Katsouyanni et al. (2009) | APHENA-Canada | DL(0-2) | 1-h max | 3.34 (1.26, 5.38) |
| Katsouyanni et al. (2009) | APHENA-Canada | DL(0-2) | 1-h max | 0.42 (0.16, 0.67) |
| Levy et al. (2005)^a | U.S. and Non-U.S. | --- | 24-h avg | 3.38 (2.27, 4.42) |
| Ito et al. (2005)^a | U.S. and Non-U.S. | --- | 24-h avg | 3.50 (2.10, 4.90) |
| Katsouyanni et al. (2009) | APHENA-U.S. | DL(0-2) | 1-h max | 3.83 (1.90, 5.79) |
| Stafoggia et al. (2010) | 10 Italian cities | DL(0-5) | 8-h max | 9.15 (5.41, 13.0) |

*Studies included from [Figure 6-26](#).

^aMulticity studies and meta-analyses from the 2006 O₃ AQCD. [Bell et al. \(2005\)^a](#), [Ito et al. \(2005\)^a](#), and [Levy et al. \(2005\)^a](#) used a range of lag days in the meta-analysis: Lag 0, 1, 2, or average 0-1 or 1-2; Single-day lags from 0-3; and Lag 0 and 1-2; respectively.

^bRisk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations (see explanation in Section [6.2.7.2](#)).

Table 6-43 Range of mean and upper percentile ozone concentrations in previous and recent multicity studies.

| Study | Location | Years | Averaging Time | Mean Concentration (ppb) ^a | Upper Percentile Concentrations (ppb) ^a |
|--|---------------------------------------|---|--------------------|--|--|
| Gryparis et al. (2004)^b | 23 European cities (APHEA2) | 1990-1997 | 1-h max 8-h max | Summer: 1-h max: 44-117 8-h max: 30-99 Winter: 1-h max: 11-57 8-h max: 8-49 | Summer: 1-h max: 62-173 8-h max: 57-154 Winter: 1-h max: 40-88 8-h max: 25-78 |
| Schwartz (2005a)^b | 14 U.S. cities | 1986-1993 | 1-h max | 35.1-60 | 25th: 26.5-52 75th: 46.3-69 |
| Bell et al. (2004) | 95 U.S. communities (NMMAPS) | 1987-2000 | 24-h avg | 26.0 | NR |
| Bell et al. (2007) | 98 U.S. communities (NMMAPS) | 1987-2000 | 24-h avg | 26.0 ^d | NR |
| Bell and Dominici (2008) | 98 U.S. communities (NMMAPS) | 1987-2000 (All year and May-September) | 24-h avg | All year: 26.8 May-September: 30.0 | Maximum: All year: 37.3 May-September: 47.2 |
| Franklin and Schwartz (2008) | 18 U.S. communities | 2000-2005 (May-September) | 24-h avg | 21.4-48.7 | NR |
| Katsouyanni et al. (2009)^{b,e} | NMMAPS 12 Canadian cities (APHEA2) | 1987-1996 (Canada and U.S.) varied by city for Europe | 1-h max | U.S.: 13.3-38.4 Canada: 6.7-8.4 Europe: 18.3-41.9 | 75th: U.S.: 21.0-52.0 Canada: 8.7-12.5 Europe: 24.0-65.8 |
| Medina-Ramón and Schwartz (2008)^b | 48 U.S. cities | 1989-2000 (May-September) | 8-h max | 16.1-58.8 | NR |
| Samoli et al. (2009)^b | 21 European cities (APHEA2) | 1990-1997 (June-August) | 8-h max | 20.0-62.8 | 75th: 27.2-74.8 |
| Stafoggia et al. (2010) | 10 Italian cities | 2001-2005 (April-September) | 8-h max | 41.2-58.9 | 75th: 47.0-71.6 |
| Cakmak et al. (2011) | 7 Chilean cities | 1997-2007 | 8-h max | 59.0-87.6 | NR |
| Wong et al. (2010) | PAPA (4 cities) | 1999-2003 (Bangkok) 1996-2002 (Hong Kong) 2001-2004 (Shanghai) 2001-2004 (Wuhan) | 8-h avg | 18.7-43.7 | 75th: 38.4 - 60.4 Max: 92.1 - 131.8 |
| Zanobetti and Schwartz (2008b) | 48 U.S. cities | 1989-2000 (June-August) | 8-h max | 15.1-62.8 | Max: 34.3-146.2 75th: 19.8-75.9 |

| Study | Location | Years | Averaging Time | Mean Concentration (ppb) ^a | Upper Percentile Concentrations (ppb) ^a |
|--|-----------------------------|---|----------------|--|---|
| Zanobetti and Schwartz (2008a) | 48 U.S. cities ^c | 1989-2000 (Winter: Dec-Feb) (Spring: March-May) (Summer: June-Aug) (Autumn: Sept-Nov) | 8-h max | Winter: 16.5 Spring: 41.6 Summer: 47.8 Autumn: 33.5 | Max: Winter: 40.6 Spring: 91.4 Summer: 103.0 Autumn: 91.2 |

^aO₃ concentrations were converted to ppb if the study presented them as µg/m³ by using the conversion factor of 0.51 assuming standard temperature (25° C) and pressure (1 atm).

^bStudy only reported median O₃ concentrations.

^cCities with less than 75% observations in a season excluded. As a result, 29 cities examined in winter, 32 in spring, 33 in autumn, and all 48 in the summer.

^d[Bell et al. \(2007\)](#) did not report mean O₃ concentrations, however, it used a similar dataset as [Bell et al. \(2004\)](#) which consisted of 95 U.S. communities for 1987-2000. For comparison purposes the 24-h avg O₃ concentrations for the 95 communities from [Bell et al. \(2004\)](#) are reported here.

^eStudy did not present air quality data for the summer months.

1 In addition to examining the relationship between short-term O₃ exposure and all-cause
2 mortality, recent studies attempted to address the uncertainties that remained upon the
3 completion of the 2006 O₃ AQCD. As a result, given the robust associations between
4 short-term O₃ exposure and mortality presented across studies in the 2006 O₃ AQCD and
5 supported in the new multicity studies ([Figure 6-26](#)), the following sections primarily
6 focus on the examination of previously identified uncertainties in the O₃-mortality
7 relationship, specifically: O₃ associations with cause-specific mortality, confounding, lag
8 structure (e.g., multiday effects and mortality displacement), effect modification
9 (i.e., sources of heterogeneity in risk estimates across cities); and the O₃-mortality C-R
10 relationship. Focusing specifically on these uncertainties allows for a more detailed
11 characterization of the relationship between short-term O₃ exposure and mortality.

6.6.2.1 Confounding

12 Recent epidemiologic studies examined potential confounders of the O₃-mortality
13 relationship. These studies specifically focused on whether PM and its constituents or
14 seasonal trends confounded the association between short-term O₃ exposure and
15 mortality.

Confounding by PM and PM Constituents

16 An important question in the evaluation of the association between short-term O₃
17 exposure and mortality is whether the relationship is confounded by particulate matter,
18 particularly the PM chemical components that are found in the “summer haze” mixture
19 which also contains O₃. However, because of the temporal correlation among these PM
20 components and O₃, and their possible interactions, the interpretation of results from

1 copollutant models that attempt to disentangle the health effects associated with each
2 pollutant is challenging. Further complicating the interpretation of copollutant results, at
3 times, is the every-3rd or -6th day PM sampling schedule employed in most locations,
4 which limits the number of days where both PM and O₃ data is available.

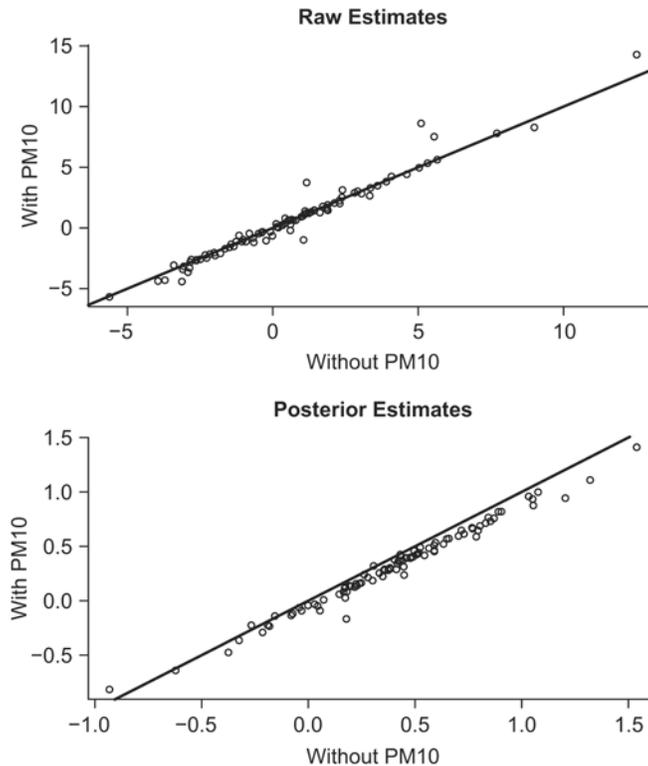
5 The potential confounding effects of PM₁₀ and PM_{2.5} on the O₃-mortality relationship
6 were examined by [Bell et al. \(2007\)](#) using data on 98 U.S. urban communities for the
7 years 1987-2000 from the National Morbidity, Mortality, and Air Pollution Study
8 (NMMAPS). In this analysis the authors included PM as a covariate in time-series
9 models, and also examined O₃-mortality associations on days when O₃ concentrations
10 were below a specified value. This analysis was limited by the small fraction of days
11 when both PM and O₃ data were available, due to the every-3rd - or 6th -day sampling
12 schedule for the PM indices, and the limited amount of city-specific data for PM_{2.5}
13 because it was only collected in most cities since 1999. As a result, of the 91
14 communities with PM_{2.5} data, only 9.2% of days in the study period had data for both O₃
15 and PM_{2.5}, resulting in the use of only 62 communities in the PM_{2.5} analysis. An
16 examination of the correlation between PM (PM₁₀ and PM_{2.5}) and O₃ across various strata
17 of daily PM₁₀ and PM_{2.5} concentrations found that neither PM size fraction was highly
18 correlated with daily O₃ concentrations across any of the strata examined. These results
19 were also observed when using 8-h max and 1-h max O₃ exposure metrics. National and
20 community-specific effect estimates of the association between short-term O₃ exposure
21 and mortality were robust to inclusion of PM₁₀ or PM_{2.5} in time-series models through the
22 range of O₃ concentrations (i.e., <10 ppb, 10-20, 20-40, 40-60, 60-80, and >80 ppb).
23 Even with the small number of days in which both PM_{2.5} and O₃ data was available, the
24 percent increases in nonaccidental deaths per 10 ppb increase 24-h avg O₃ concentrations
25 at lag 0-1 day were 0.22% (95% CI: -0.22, 0.65) without PM_{2.5} and 0.21% (95% CI:
26 -0.22, 0.64) with PM_{2.5} in 62 communities.

27 Although strong correlations between PM and O₃ were not reported by [Bell et al. \(2007\)](#)
28 the patterns observed suggest regional differences in their correlation ([Table 6-44](#)). Both
29 PM₁₀ and PM_{2.5} show positive correlations with O₃ in the Industrial Midwest, Northeast,
30 Urban Midwest, and Southeast, especially in the summer months, presumably, because of
31 the summer peaking sulfate. However, the mostly negative or weak correlations between
32 PM and O₃ in the summer in the Southwest, Northwest, and southern California could be
33 due to winter-peaking nitrate. Thus, the potential confounding effect of PM on the
34 O₃-mortality relationship could be influenced by the relative contribution of sulfate and
35 nitrate, which varies regionally and seasonally.

Table 6-44 Correlations between PM and ozone by season and region.

| | No. of Communities | Winter | Spring | Summer | Fall | Yearly |
|-------------------------|--------------------|--------|--------|--------|-------|--------|
| PM₁₀ | | | | | | |
| Industrial Midwest | 19 | 0.37 | 0.44 | 0.44 | 0.39 | 0.41 |
| Northeast | 15 | 0.34 | 0.44 | 0.36 | 0.44 | 0.40 |
| Urban Midwest | 6 | 0.24 | 0.25 | 0.22 | 0.26 | 0.24 |
| Southwest | 9 | 0.00 | 0.02 | -0.02 | 0.10 | 0.03 |
| Northwest | 11 | -0.17 | -0.20 | -0.13 | -0.11 | -0.16 |
| Southern California | 7 | 0.19 | 0.08 | 0.12 | 0.19 | 0.14 |
| Southeast | 25 | 0.33 | 0.35 | 0.31 | 0.31 | 0.32 |
| U.S. | 93 | 0.23 | 0.26 | 0.24 | 0.26 | 0.25 |
| PM_{2.5} | | | | | | |
| Industrial Midwest | 19 | 0.18 | 0.39 | 0.43 | 0.44 | 0.36 |
| Northeast | 13 | 0.05 | 0.26 | 0.16 | 0.43 | 0.25 |
| Urban Midwest | 4 | 0.22 | 0.31 | 0.15 | 0.32 | 0.20 |
| Southwest | 9 | -0.15 | -0.08 | -0.17 | -0.15 | -0.14 |
| Northwest | 11 | -0.32 | -0.34 | -0.39 | -0.24 | -0.31 |
| Southern California | 7 | -0.25 | -0.22 | -0.25 | -0.15 | -0.23 |
| Southeast | 26 | 0.38 | 0.47 | 0.30 | 0.37 | 0.39 |
| U.S. | 90 | 0.09 | 0.21 | 0.12 | 0.22 | 0.16 |

Source: [Bell et al. \(2007\)](#).



Note: The diagonal line indicates 1:1 ratio.

Source: Reprinted with permission of Informa UK Ltd, ([Smith et al., 2009b](#)).

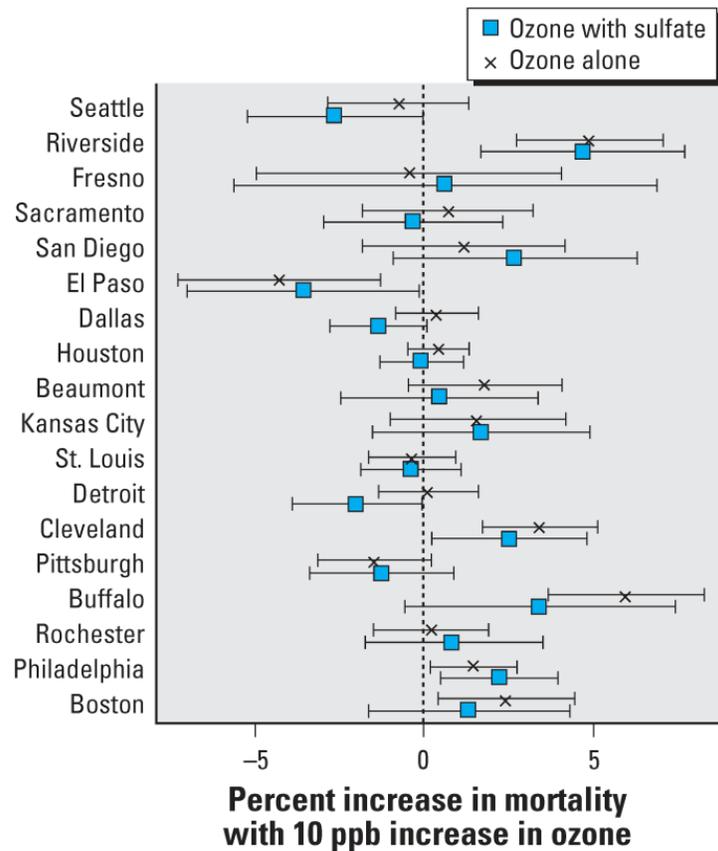
Figure 6-27 Scatter plots of ozone mortality risk estimates with versus without adjustment for PM₁₀ in NMMAPS cities.

1 In an attempt to reassess a number of issues associated with the O₃-mortality relationship,
 2 including confounding, [Smith et al. \(2009b\)](#) re-analyzed the publicly available NMMAPS
 3 database for the years 1987-2000. Similar to [Bell et al. \(2007\)](#), the PM₁₀ data used in the
 4 [Smith et al. \(2009b\)](#) analysis consisted primarily of every-6th day data. In analyses
 5 conducted to examine the potential confounding effects of PM₁₀, the authors reported
 6 that, in most cases, O₃ mortality risk estimates were reduced by between 22% and 33% in
 7 copollutant models. This is further highlighted in [Figure 6-27](#), which shows scatter plots
 8 of O₃-mortality risk estimates with adjustment for PM₁₀ versus without adjustment for
 9 PM₁₀. [Smith et al. \(2009b\)](#) point out that a larger fraction (89 out of 93) of the posterior
 10 estimates lie below the diagonal line (i.e., estimates are smaller with PM₁₀ adjustment)
 11 compared to the raw estimates (56 out of 93). This observation could be attributed to both
 12 sets of posterior estimates being calculated by “shrinking towards the mean” along with
 13 the small number of days where both PM₁₀ and O₃ data was available. However, the most

1 prominent feature of these plots is that the variation of O₃-mortality risk estimates across
2 cities is much larger than the impact of PM₁₀ adjustment on the O₃-mortality relationship.

3 [Franklin and Schwartz \(2008\)](#) examined the sensitivity of O₃ mortality risk estimates to
4 the inclusion of PM_{2.5} or PM chemical components associated with secondary aerosols
5 (e.g., sulfate [SO₄²⁻], organic carbon [OC], and nitrate [NO₃⁻]) in copollutant models.
6 This analysis consisted of between 3 and 6 years of data from May through September
7 2000-2005 from 18 U.S. communities. The association between O₃ and non-accidental
8 mortality was examined in single-pollutant models and after adjustment for PM_{2.5},
9 sulfate, organic carbon, or nitrate concentrations. The single-city effect estimates were
10 combined into an overall estimate using a random-effects model. In the single-pollutant
11 model, the authors found a 0.89% (95% CI: 0.45, 1.33%) increase in nonaccidental
12 mortality with a 10 ppb increase in same-day 24-hour summertime O₃ concentrations
13 across the 18 U.S. communities. Adjustment for PM_{2.5} mass, which was available for
14 84% of the days, decreased the O₃-mortality risk estimate only slightly (from 0.88% to
15 0.79%), but the inclusion of sulfate in the model reduced the risk estimate by 31% (from
16 0.85% to 0.58%). However, sulfate data were only available for 18% of the days.
17 Therefore, a limitation of this study is the limited amount of data for PM_{2.5} chemical
18 components due to the every-3rd-day or every-6th-day sampling schedule. For example,
19 when using a subset of days when organic carbon measurements were available (i.e., 17%
20 of the available days), O₃ mortality risk estimates were reduced to 0.51% (95% CI: -0.36
21 to 1.36) in a single-pollutant model.

22 Consistent with the studies previously discussed, the results from [Franklin and Schwartz](#)
23 [\(2008\)](#) also demonstrate that the interpretation of the potential confounding effects of
24 copollutants on O₃ mortality risk estimates is not straightforward as a result of the PM
25 sampling schedule employed in most cities. However, [Franklin and Schwartz \(2008\)](#) find
26 that O₃-mortality risk estimates, although attenuated in some cases (i.e., sulfate), remain
27 positive. As presented in [Figure 6-28](#), the regional and city-to-city variations in O₃
28 mortality risk estimates appear greater than the impact of adjusting for copollutants. In
29 addition, in some cases, a negative O₃ mortality risk estimate becomes even more
30 negative with the inclusion of sulfate (e.g., Seattle) in a copollutant model, or a null O₃
31 mortality risk estimate becomes negative when sulfate is included (e.g., Dallas and
32 Detroit). Thus, the reduction in the overall O₃ mortality risk estimate (i.e., across cities)
33 needs to be assessed in the context of the heterogeneity in the single-city estimates.



Source: [Franklin and Schwartz \(2008\)](#).

Figure 6-28 Community-specific ozone-mortality risk estimates for nonaccidental mortality per 10 ppb increase in same-day 24-h average summertime ozone concentrations in single-pollutant models and copollutant models with sulfate.

1 In the APHENA study, the investigators from the U.S. (NMMAPS), Canadian, and
 2 European (APHEA2) multicity studies collaborated and conducted a joint analysis of
 3 PM₁₀ and O₃ using each of these datasets ([Katsouyanni et al., 2009](#)). For mortality, each
 4 dataset consisted of a different number of cities and years of air quality data: U.S.
 5 encompassed 90 cities with daily O₃ data from 1987-1996 of which 36 cities had summer
 6 only O₃ measurements; Europe included 23 cities with 3-7 years of daily O₃ data during
 7 1990-1997; and Canada consisted of 12 cities with daily O₃ data from 1987 to 1996. As
 8 discussed in Section [6.2.7.2](#), the APHENA study conducted extensive sensitivity
 9 analyses, of which the 8 df/year results for both the penalized spline (PS) and natural
 10 spline (NS) models are presented in the text for comparison purposes, but only the NS

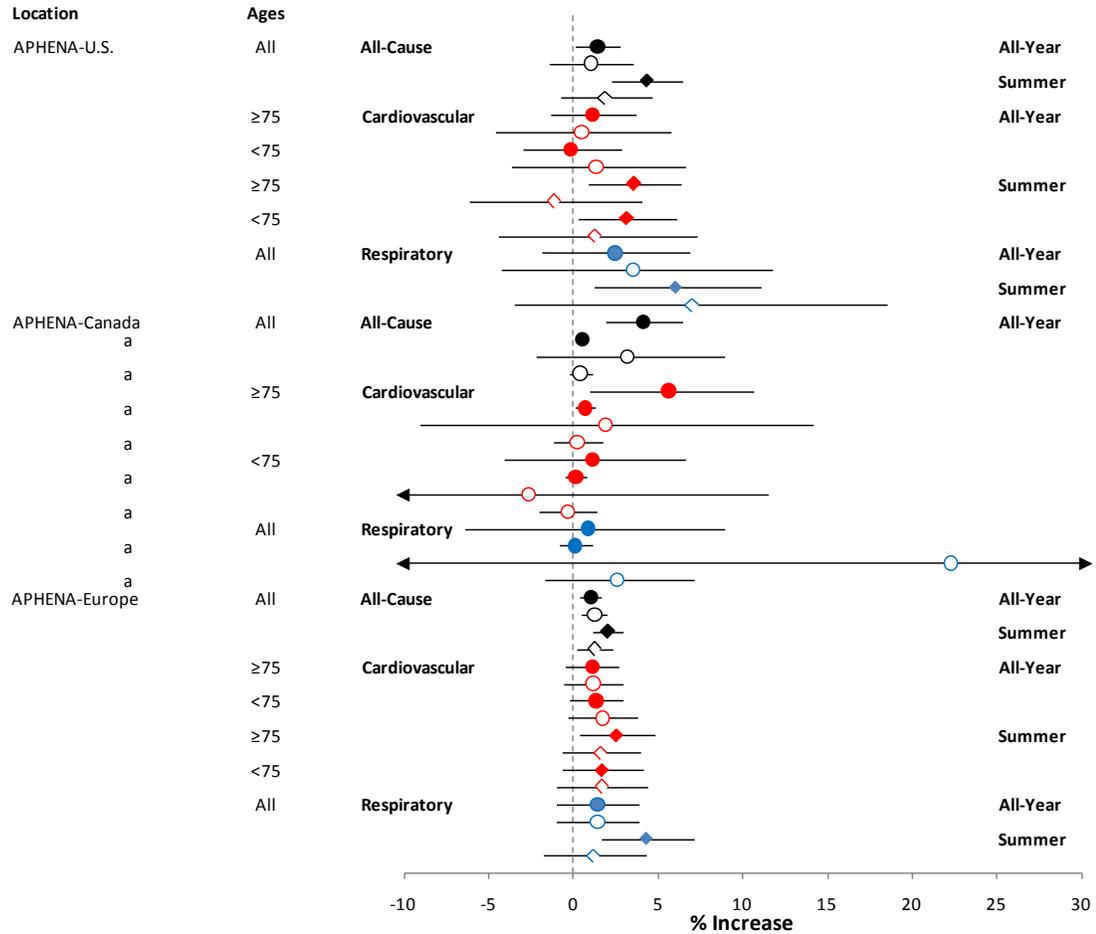
1 results are presented in figures because alternative spline models have previously been
2 shown to result in similar effect estimates (HEI, 2003). Additionally, for the Canadian
3 results, figures contain risk estimates standardized to both a 40 ppb increment for
4 1-h max O₃ concentrations, consistent with the rest of the ISA, but also the approximate
5 IQR across the Canadian cities as discussed previously (Section 6.2.7.2).

6 In the three datasets, the authors found generally positive associations between short-term
7 O₃ exposure and all-cause, cardiovascular, and respiratory mortality. The estimated
8 excess risks for O₃ were larger for the Canadian cities than for the U.S. and European
9 cities. When examining the potential confounding effects of PM₁₀ on O₃ mortality risk
10 estimates, the sensitivity of the estimates varied across the data sets and age groups. In
11 the Canadian dataset, O₃ risk estimates were modestly reduced, but remained positive,
12 when adjusting for PM₁₀ for all-cause mortality for all ages in the PS (4.5% [95% CI: 2.2,
13 6.7%]) and NS (4.2% [95% CI: 1.9, 6.5%]) models to 3.8% (95% CI: -1.4, 9.8%) and
14 3.2% (95% CI: -2.2, 9.0%), respectively, at lag 1 for a 40 ppb increase in 1-h max O₃
15 concentrations (Figure 6-29; Table 6-45). However, adjusting for PM₁₀ reduced O₃
16 mortality risk estimates in the ≥ 75-year age group, but increased the risk estimates in the
17 <75-year age group. For cardiovascular and respiratory mortality more variable results
18 were observed with O₃ risk estimates being reduced and increased, respectively, in
19 copollutant models with PM₁₀ (Figure 6-29; Table 6-45). Unlike the European and U.S.
20 datasets, the Canadian dataset only conducted copollutant analyses at lag 1; as a result, to
21 provide a comparison across study locations only the lag 1 results are presented for the
22 European and U.S. datasets in this section.

23 In the European data, O₃ risk estimates were robust when adjusting for PM₁₀ in the year-
24 round data for all-cause, cardiovascular and respiratory mortality. When restricting the
25 analysis to the summer months moderate reductions were observed in O₃ risk estimates
26 for all-cause mortality with more pronounced reductions in respiratory mortality. In the
27 U.S. data, adjusting for PM₁₀ moderately reduced O₃ risk estimates for all-cause mortality
28 in a year-round analysis at lag 1 (e.g., both the PS and NS models were reduced from
29 0.18% to 0.13%) (Figure 6-29; Table 6-45). Similar to the European data, when
30 restricting the analysis to the summer months, in the U.S. O₃ mortality risk estimates
31 were moderately reduced, but remained positive, when adjusting for PM₁₀ for all-cause
32 mortality. However, when examining cause-specific mortality risk estimates, consistent
33 with the results from the Canadian dataset, which employed a similar PM sampling
34 strategy (i.e., every-6th-day sampling), O₃ risk estimates for cardiovascular and
35 respiratory mortality were more variable (i.e., reduced or increased in all-year and
36 summer analyses). Overall, the estimated O₃ risks appeared to be moderately to
37 substantially sensitive to inclusion of PM₁₀ in copollutant models. Despite the multicity

1
2

approach, the mostly every-6th-day sampling schedule for PM₁₀ in the Canadian and U.S. datasets greatly reduced the sample size and limits the interpretation of these results.



Note: Effect estimates are for a 40 ppb increase in 1-h max O₃ concentrations at lag 1. All estimates are for the 8 df/year model with natural splines. Circles represent all-year analysis results while diamonds represent summer season analysis results. Open circles and diamonds represent copollutant models with PM₁₀. Black = all-cause mortality; red = cardiovascular mortality; and blue = respiratory mortality.

^aRisk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations (see explanation in Section 6.2.7.2).

Figure 6-29 Percent increase in all-cause (nonaccidental) and cause-specific mortality from natural spline models with 8 df/yr from the APHENA study for single- and copollutant models.

Table 6-45 Corresponding effect estimates for Figure 6-29.

| Location* | Mortality | Ages | Season | Copollutant | % Increase (95% CI) | |
|----------------|---------------------------------|-----------|------------------|----------------------------------|---------------------------------|---------------------------------|
| APHENA-U.S. | All-Cause | All | All-year | | 1.42 (0.08, 2.78) | |
| | | | | PM ₁₀ | 1.02 (-1.40, 3.50) | |
| | Cardiovascular | ≥ 75 | All-year | | 4.31 (2.22, 6.45) | |
| | | | | PM ₁₀ | 1.90 (-0.78, 4.64) | |
| | | | | | 1.10 (-1.33, 3.67) | |
| | | | | PM ₁₀ | 0.47 (-4.61, 5.79) | |
| | | <75 | All-year | | -0.16 (-3.02, 2.86) | |
| | | | | PM ₁₀ | 1.34 (-3.63, 6.61) | |
| | | | | | 3.58 (0.87, 6.37) | |
| | | | | PM ₁₀ | -1.17 (-6.18, 4.07) | |
| | <75 | Summer | | 3.18 (0.31, 6.12) | | |
| | | | PM ₁₀ | 1.26 (-4.46, 7.28) | | |
| | | | | 2.46 (-1.87, 6.86) | | |
| | | | PM ₁₀ | 3.50 (-4.23, 11.8) | | |
| Respiratory | All | All-year | | 6.04 (1.18, 11.1) | | |
| | | | PM ₁₀ | 7.03 (-3.48, 18.5) | | |
| | | | | 4.15 (1.90, 6.45) | | |
| | APHENA-Canada | All-Cause | All | All-year | | 0.52 (0.24, 0.80) ^a |
| | | | | | PM ₁₀ | 3.18 (-2.18, 8.96) |
| | | | | | PM ₁₀ | 0.40 (-0.28, 1.10) ^a |
| Cardiovascular | | ≥ 75 | All-year | | 5.62 (0.95, 10.7) | |
| | | | | PM ₁₀ | 0.70 (0.12, 1.30) ^a | |
| | | | | PM ₁₀ | 1.90 (-9.03, 14.1) | |
| | | <75 | All-year | | 0.24 (-1.20, 1.70) ^a | |
| | | | | PM ₁₀ | 1.10 (-4.08, 6.61) | |
| | | | | PM ₁₀ | 0.14 (-0.53, 0.82) ^a | |
| Respiratory | All | All-year | | -2.64 (-14.7, 11.5) | | |
| | | | PM ₁₀ | -0.34 (-2.00, 1.40) ^a | | |
| | | | | 0.87 (-6.40, 8.96) | | |
| | | | PM ₁₀ | 0.11 (-0.84, 1.10) ^a | | |
| | | | PM ₁₀ | 22.3 (-12.6, 71.3) | | |
| | 2.60 (-1.70, 7.10) ^a | | | | | |

| Location* | Mortality | Ages | Season | Copollutant | % Increase (95% CI) | |
|---------------|----------------|-------------|----------|------------------|---------------------|--------------------|
| APHENA-Europe | All-Cause | All | All-year | | 1.02 (0.39, 1.66) | |
| | | | | PM ₁₀ | 1.26 (0.47, 1.98) | |
| | | | Summer | | 2.06 (1.10, 2.94) | |
| | Cardiovascular | ≥ 75 | All-year | | 1.10 (-0.47, 2.70) | |
| | | | | PM ₁₀ | 1.18 (-0.55, 2.94) | |
| | | | <75 | All-year | | 1.34 (-0.24, 2.94) |
| | | ≥ 75 | Summer | | 2.54 (0.39, 4.80) | |
| | | | | PM ₁₀ | 1.58 (-0.70, 3.99) | |
| | | | <75 | Summer | | 1.66 (-0.70, 4.15) |
| | | Respiratory | All | All-year | | 1.42 (-1.02, 3.83) |
| | | | | | PM ₁₀ | 1.42 (-1.02, 3.83) |
| | | | | Summer | | 4.31 (1.66, 7.11) |
| | | | | PM ₁₀ | 1.18 (-1.79, 4.31) | |

*Effect estimates from [Figure 6-29](#).

^aRisk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations (see explanation in Section [6.2.7.2](#)).

1 [Stafoggia et al. \(2010\)](#) examined the potential confounding effects of PM₁₀ on the
2 O₃-mortality relationship in individuals 35 years of age and older in 10 Italian cities from
3 2001 to 2005. In a time-stratified case-crossover analysis, using data for the summer
4 months (i.e., April-September), the authors examined O₃-mortality associations across
5 each city, and then obtained a pooled estimate through a random-effects meta-analysis.
6 [Stafoggia et al. \(2010\)](#) found a strong association with nonaccidental mortality (9.2%
7 [95% CI: 5.4, 13.0%] for a 30 ppb increase in 8-h max O₃ concentrations) in an
8 unconstrained distributed lag model (lag 0-5) that persisted in copollutant models with
9 PM₁₀ (9.2% [95% CI: 5.4, 13.7%]). Additionally, when examining cause-specific
10 mortality, the authors found positive associations between short-term O₃ exposure and
11 cardiovascular (14.3% [95% CI: 6.7, 22.4%]), cerebrovascular (8.5% [95% CI: 0.1,
12 16.3%]), and respiratory (17.6% [95% CI: 1.8, 35.6%]) mortality in single-pollutant
13 models. In copollutant models, O₃-mortality effect estimates for cardiovascular and
14 cerebrovascular mortality were robust to the inclusion of PM₁₀ (9.2% [95% CI: 5.4,
15 13.7%]) and 7.3% [95% CI: -1.2, 16.3%], respectively), and attenuated, but remained
16 positive, for respiratory mortality (9.2% [95% CI: -6.9, 28.8%]). Of note, the correlations
17 between O₃ and PM₁₀ across cities were found to be generally low, ranging from (-0.03 to
18 0.49). The authors do not specify the sampling strategy used for PM₁₀ in this analysis.

Confounding by Seasonal Trend

1 The APHENA study ([Katsouyanni et al., 2009](#)), mentioned above, also conducted
2 extensive sensitivity analyses to identify the appropriate: (1) smoothing method and basis
3 functions to estimate smooth functions of time in city-specific models; and (2) degrees of
4 freedom to be used in the smooth functions of time, to adjust for seasonal trends. Because
5 O₃ peaks in the summer and mortality peaks in the winter, not adjusting or not
6 sufficiently adjusting for the seasonal trend would result in an apparent negative
7 association between the O₃ and mortality time-series. [Katsouyanni et al. \(2009\)](#) examined
8 the effect of the extent of smoothing for seasonal trends by using models with 3 df/year,
9 8 df/year (the choice for their main model), 12 df/year, and df/year selected using the sum
10 of absolute values of partial autocorrelation function of the model residuals (PACF)
11 (i.e., choosing the degrees of freedom that minimizes positive and negative
12 autocorrelations in the residuals). [Table 6-46](#) presents the results of the degrees of
13 freedom analysis using alternative methods to calculate a combined estimate: the [Berkey](#)
14 [et al. \(1998\)](#) meta-regression and the two-level normal independent sampling estimation
15 (TLNISE) hierarchical method. The results show that the methods used to combine
16 single-city estimates did not influence the overall results, and that neither 3 df/year nor
17 choosing the df/year by minimizing the sum of absolute values of PACF of regression
18 residuals was sufficient to adjust for the seasonal negative relationship between O₃ and
19 mortality. However, it should be noted, the majority of studies in the literature that
20 examined the mortality effects of short-term O₃ exposure, particularly the multicity
21 studies, used 7 or 8 df/year to adjust for seasonal trends, and in both methods a positive
22 association was observed between O₃ exposure and mortality.

Table 6-46 Sensitivity of ozone risk estimates per 10 µg/m³ increase in 24-h average ozone concentrations at lag 0-1 to alternative methods for adjustment of seasonal trend, for all-cause mortality using Berkey MLE and TLNISE Hierarchical Models.

| Seasonality Control | Berkey | TLNISE |
|---------------------|----------------------|----------------------|
| 3 df/year | -0.54 (-0.88, 0.20) | -0.55 (-0.88, -0.22) |
| 8 df/year | 0.30 (0.11, 0.50) | 0.31 (0.09, 0.52) |
| 12 df/year | 0.34 (0.15, 0.53) | 0.33 (0.12, 0.54) |
| PACF | -0.62 (-1.01, -0.22) | -0.62 (-0.98, -0.27) |

Source: Reprinted with permission of Health Effects Institute ([Katsouyanni et al., 2009](#)).

6.6.2.2 Effect Modification

1 There have been several multicity studies that examined potential effect modifiers, or
 2 time-invariant factors, which may modify O₃ mortality risk estimates. These effect
 3 modifiers can be categorized into either individual-level or community-level
 4 characteristics, which are traditionally examined in second stage regression models. The
 5 results from these analyses also inform upon whether certain populations are greater risk
 6 of an O₃-related health effects (Chapter 8). In addition to potentially modifying the
 7 association between short-term O₃ exposure and mortality, both individual-level and
 8 community-level characteristics may contribute to the geographic pattern of spatial
 9 heterogeneity in O₃ mortality risk estimates. As a result, the geographic pattern of O₃
 10 mortality risk estimates is also evaluated in this section.

Individual-Level Characteristics

11 [Medina-Ramón and Schwartz \(2008\)](#) conducted a case-only study in 48 U.S. cities to
 12 identify populations potentially at increased risk to O₃-related mortality for the period
 13 1989-2000 (May through September of each year [i.e., warm season]). A case-only
 14 design predicts the occurrence of time-invariant characteristics among cases as a function
 15 of the exposure level ([Armstrong, 2003](#)). For each potential effect modifier
 16 (time-invariant individual-level characteristics), city-specific logistic regression models
 17 were fitted, and the estimates were pooled across all cities. Furthermore, the authors
 18 examined potential differences in individual effect modifiers according to several city
 19 characteristics (e.g., mean O₃ level, mean temperature, households with central air
 20 conditioning, and population density) in a meta-regression. Across cities, the authors
 21 found a 1.96% (95% CI: 1.14-2.82%) increase in mortality at lag 0-2 for a 30 ppb
 22 increase in 8-h max O₃ concentrations. Additionally, [Medina-Ramón and Schwartz](#)

1 [\(2008\)](#) examined a number of individual-level characteristics (e.g., age, race) and chronic
2 conditions (e.g., secondary causes of death) as effect modifiers of the association between
3 short-term O₃ exposure and mortality. The authors found that older adults (i.e., ≥ 65),
4 women >60 years of age, black race, and secondary atrial fibrillation showed the greatest
5 additional percent change in O₃-related mortality ([Table 6-47](#)). When examining city-
6 level characteristics, the authors found that older adults, black race, and secondary atrial
7 fibrillation had a larger effect on O₃ mortality risk estimates in cities with lower mean O₃
8 concentrations. Of note, a similar case-only study ([Schwartz, 2005b](#)) examined potential
9 effect modifiers of the association between temperature and mortality, which would be
10 expected to find results consistent with the [Medina-Ramón and Schwartz \(2008\)](#) study
11 due to the high correlation between temperature and O₃. However, when stratifying days
12 by temperature [Schwartz \(2005b\)](#) found strong evidence that diabetes modified the
13 temperature-mortality association on hot days, which was not as evident when examining
14 the O₃-mortality association in [Medina-Ramón and Schwartz \(2008\)](#). This difference
15 could be due to the study design and populations included in both studies, a multicity
16 study including all ages ([Medina-Ramón and Schwartz, 2008](#)) compared to a single-city
17 study of individuals ≥ 65 years of age ([Schwartz, 2005b](#)). However, when examining
18 results stratified by race, nonwhites were found to have higher mortality risks on both hot
19 and cold days, which provide some support for the additional risk found for black race in
20 [Medina-Ramón and Schwartz \(2008\)](#).

21 Individual-level factors that may result in increased risk of O₃-related mortality were also
22 examined by [Stafoggia et al. \(2010\)](#). As discussed above, using a time-stratified case-
23 crossover analysis, the authors found an association between short-term O₃ exposure and
24 nonaccidental mortality in an unconstrained distributed lag model in 10 Italian cities
25 (9.2% [95% CI: 5.4, 13.0%; lag 0-5 for a 30 ppb increase in 8-h max O₃ concentrations]).
26 [Stafoggia et al. \(2010\)](#) conducted additional analyses to examine whether age, sex,
27 income level, location of death, and underlying chronic conditions increased the risk of
28 O₃-related mortality, but data were only available for nine of the cities for these analyses.
29 Of the individual-level factors examined, the authors found the strongest evidence for
30 increased risk of O₃-related mortality in individuals ≥ 85 years of age (22.4% [95% CI:
31 15.0, 30.2%]), women (13.7% [95% CI: 8.5, 19.7%]), and out-of-hospital deaths (13.0%
32 [95% CI: 6.0, 20.4%]). When focusing specifically on out-of hospital deaths and the
33 subset of individuals with chronic conditions, [Stafoggia et al. \(2010\)](#) found the strongest
34 association for individuals with diabetes, which is consistent with the potentially
35 increased risk of diabetics on hot days observed in [Schwartz \(2005b\)](#).

Table 6-47 Additional percent change in ozone-related mortality for individual-level characteristics.

| | Percentage | (95% CI) |
|---|------------|-------------|
| Socio-demographic characteristics | | |
| Age 65 yr or older | 1.10 | 0.44, 1.77 |
| Women | 0.58 | 0.18, 0.98 |
| Women <60 yr old ^b | -0.09 | -0.76, 0.58 |
| Women ≥ 60 yr old ^b | 0.60 | 0.25, 0.96 |
| Black race | 0.53 | 0.19, 0.87 |
| Low education | -0.29 | -0.81, 0.23 |
| Chronic conditions (listed as secondary cause) | | |
| Respiratory system diseases | | |
| Asthma | 1.35 | -0.31, 3.03 |
| COPD | 0.01 | -0.49, 0.52 |
| Circulatory system diseases | | |
| Atherosclerosis | -0.72 | -1.89, 0.45 |
| Atherosclerotic CVD | 0.74 | -0.86, 2.37 |
| Atherosclerotic heart disease | -0.38 | -1.70, 0.96 |
| Congestive heart disease | -0.04 | -0.39, 0.30 |
| Atrial fibrillation | 1.66 | 0.03, 3.32 |
| Stroke | 0.17 | -0.28, 0.62 |
| Other diseases | | |
| Diabetes | 0.19 | -0.46, 0.84 |
| Inflammatory diseases | 0.18 | -1.09, 1.46 |

^aThese estimates represent the additional percent change in mortality for persons who had the characteristic being examined compared to persons who did not have the characteristic, when the mean O₃ level of the previous 3 days increased 10 ppb. These values were not standardized because they do not represent the actual effect estimate for the characteristic being evaluated, but instead, the difference between effect estimates for persons with versus without the condition.

^bCompared with males in the same age group.

Source: Reprinted with permission of Lippincott Williams & Wilkins ([Medina-Ramón and Schwartz, 2008](#)).

1 Additionally, [Cakmak et al. \(2011\)](#) examined the effect of individual-level characteristics
2 that may modify the O₃-mortality relationship in 7 Chilean cities. In a time-series analysis
3 using a constrained distributed lag of 0-6 days, [Cakmak et al. \(2011\)](#) found evidence for
4 larger O₃ mortality effects in individuals >75 years of age compared to younger ages,
5 which is similar to [Medina-Ramón and Schwartz \(2008\)](#) and [Stafoggia et al. \(2010\)](#).
6 Unlike the studies discussed above O₃-mortality risk estimates were found to be slightly
7 larger in males (3.71% [95% CI: 0.79, 6.66] for a 40 ppb increase in max 8-h avg O₃
8 concentrations), but were not significantly different than those observed for females
9 (3.00% [95% CI: 0.43, 5.68]). The major focus of [Cakmak et al. \(2011\)](#) is the

1 examination of the influence of SES indicators (i.e., educational attainment, income level,
2 and employment status) on the O₃-mortality relationship. The authors found the largest
3 risk estimates in the lowest SES categories for each of the indicators examined this
4 includes: primary school not completed when examining educational attainment; the
5 lowest quartile of income level; and unemployed individuals when comparing
6 employment status.

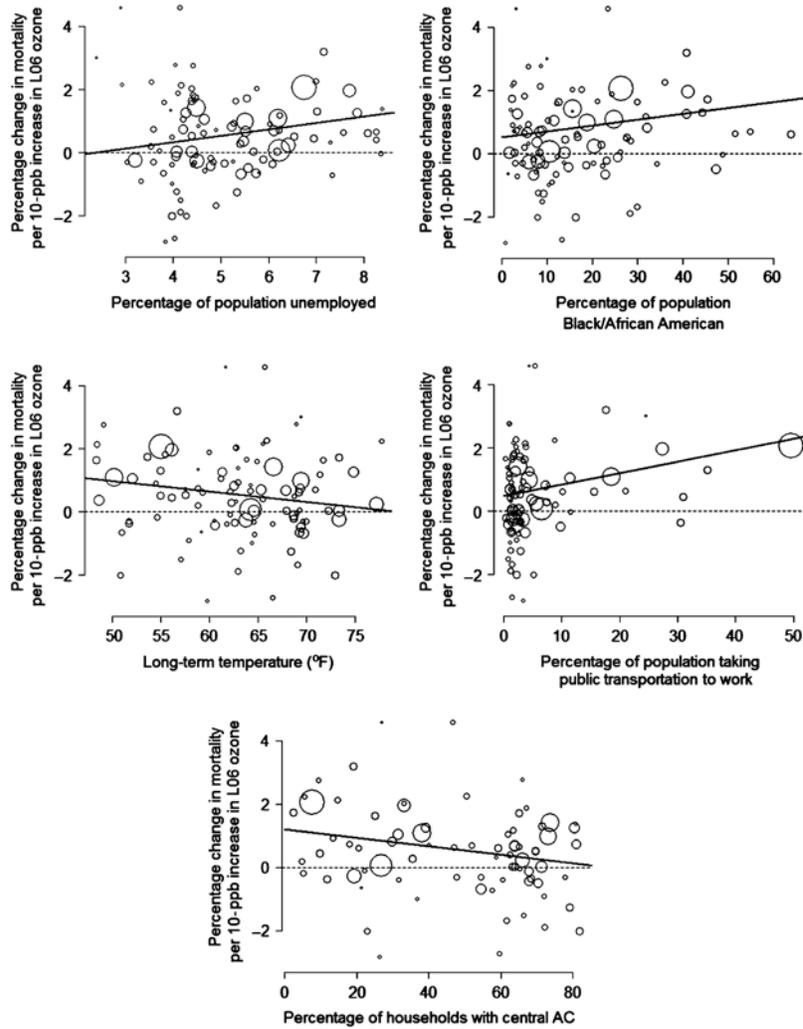
7 Overall, uncertainties exist in the interpretation of the potential effect modifiers identified
8 in [Medina-Ramón and Schwartz \(2008\)](#), [Stafoggia et al. \(2010\)](#), and [Cakmak et al. \(2011\)](#)
9 of the O₃-mortality relationship due to the heterogeneity in O₃-mortality risk estimates
10 across cities as highlighted in [Smith et al. \(2009b\)](#) ([Figure 6-27](#)) and [Franklin and](#)
11 [Schwartz \(2008\)](#) ([Figure 6-28](#)). In addition, it is likely that individual-level factors
12 identified in [Medina-Ramón and Schwartz \(2008\)](#), ([Stafoggia et al., 2010](#)), and [Cakmak](#)
13 [et al. \(2011\)](#) only modify the O₃-mortality relationship and do not entirely explain the
14 observed regional heterogeneity in O₃-mortality risk estimates.

Community-level Characteristics

15 Several studies also examined city-level (i.e., ecological) variables in an attempt to
16 explain the observed city-to-city variation in estimated O₃-mortality risk estimates. [Bell](#)
17 [and Dominici \(2008\)](#) investigated whether community-level characteristics, such as race,
18 income, education, urbanization, transportation use, PM and O₃ concentrations, number
19 of O₃ monitors, weather, and air conditioning use could explain the heterogeneity in
20 O₃-mortality risk estimates across cities. The authors analyzed 98 U.S. urban
21 communities from NMMAPS for the period 1987-2000. In the all-year regression model
22 that included no community-level variables, a 20 ppb increase in 24-h avg O₃
23 concentrations during the previous week was associated with a 1.04% (95% CI: 0.56,
24 1.55) increase in mortality. [Bell and Dominici \(2008\)](#) found that higher O₃-mortality
25 effect estimates were associated with an increase in: percent unemployment, fraction of
26 the population Black/African-American, percent of the population that take public
27 transportation to work; and with a reduction in: temperatures and percent of households
28 with central air conditioning ([Figure 6-30](#)). The modification of O₃-mortality risk
29 estimates reported for city-specific temperature and prevalence of central air conditioning
30 in this analysis confirm the result from the meta-analyses reviewed in the 2006 O₃
31 AQCD.

32 The APHENA project ([Katsouyanni et al., 2009](#)) examined potential effect modification
33 of O₃ risk estimates in the Canadian, European, and U.S. data sets using a consistent set
34 of city-specific variables. [Table 6-48](#) presents the results from all age analyses for all-
35 cause mortality using all-year O₃ data for the average of lag 0-1 day. While there are

1 several significant effect modifiers in the U.S. data, the results are mostly inconsistent
2 with the results from the Canadian and European data sets. The positive effect
3 modification by percentage unemployed and the negative effect modification by mean
4 temperature (i.e., a surrogate for air conditioning rate) are consistent with the results
5 reported by [Bell and Dominici \(2008\)](#) discussed above. However, the lack of consistency
6 across the data sets, even between the Canadian and U.S. data, makes it difficult to
7 interpret the results. Some of these associations may be due to coincidental correlations
8 with other unmeasured factors that vary regionally (e.g., mean SO₂ tend to be higher in
9 the eastern U.S.).



Note: The size of each circle corresponds to the inverse of the standard error of the community's maximum likelihood estimate. Risk estimates are for a 10 ppb increase in 24-h avg ozone concentrations during the previous week. Source: Reprinted with permission of Johns Hopkins Bloomberg School of Public Health ([Bell and Dominici, 2008](#)).

Figure 6-30 Ozone mortality risk estimates and community-specific characteristics, U.S., 1987-2000.

Table 6-48 Percent change in all-cause mortality, for all ages, associated with a 40ppb increase in 1-h max ozone concentrations at Lag 0–1 at the 25th and 75th percentile of the center-specific distribution of selected effect modifiers.

| Effect Modifier | Canada | | | Europe | | | U.S. | | |
|--|-----------------------------------|-----------------------------------|---------|-----------------------------------|-----------------------------------|---------|-----------------------------------|-----------------------------------|---------|
| | 25th Percentile Estimate (95% CI) | 75th Percentile Estimate (95% CI) | t Value | 25th Percentile Estimate (95% CI) | 75th Percentile Estimate (95% CI) | t Value | 25th Percentile Estimate (95% CI) | 75th Percentile Estimate (95% CI) | t Value |
| NO ₂ CV | 3.10 (1.90, 4.40) | 3.99 (2.38, 5.62) | 1.33 | 1.66 (0.71, 2.62) | 1.34 (-0.08, 2.78) | -0.49 | 1.26 (0.47, 1.98) | 0.08 (-0.78, 0.95) | -2.87 |
| Mean SO ₂ | 2.22 (0.71, 3.83) | 4.72 (2.94, 6.61) | 2.16 | 1.58 (0.47, 2.62) | 1.66 (0.39, 2.86) | 0.16 | 0.47 (-0.47, 1.42) | 1.98 (1.10, 2.94) | 2.79 |
| O ₃ CV | 2.86 (0.79, 5.05) | 3.50 (2.14, 4.89) | 0.60 | 2.62 (1.50, 3.75) | 1.10 (0.24, 1.98) | -2.65 | 0.16 (-0.70, 1.10) | 1.50 (0.71, 2.22) | 2.68 |
| Mean NO ₂ /PM ₁₀ | 3.91 (2.54, 5.29) | 2.54 (0.95, 4.15) | -1.58 | 1.74 (0.87, 2.70) | 1.50 (0.47, 2.62) | -0.43 | -0.08 (-1.02, 0.95) | 1.26 (0.47, 2.06) | 2.64 |
| Mean Temperature | 2.86 (0.95, 4.72) | 3.50 (2.22, 4.89) | 0.83 | 1.58 (0.39, 2.86) | 1.58 (0.31, 2.78) | -0.04 | 2.14 (1.34, 2.94) | 0.00 (-0.78, 0.79) | -4.40 |
| % ≥ 75 yr | 2.22 (0.79, 3.58) | 4.23 (3.02, 5.54) | 2.68 | 1.50 (0.55, 2.46) | 1.82 (0.55, 3.10) | 0.52 | 1.02 (0.24, 1.90) | 1.02 (0.31, 1.74) | -0.02 |
| Age-standardized Mortality | 2.62 (0.79, 4.48) | 4.07 (2.22, 5.87) | 1.14 | 1.10 (-0.16, 2.38) | 1.98 (0.79, 3.26) | 1.07 | 0.00 (-0.94, 0.87) | 1.58 (0.87, 2.38) | 3.81 |
| % Unemployed | 2.78 (1.42, 4.07) | 3.75 (2.54, 4.89) | 1.88 | 1.42 (-0.47, 3.34) | 1.34 (-0.47, 3.18) | -0.07 | 0.16 (-0.78, 1.18) | 1.50 (0.71, 2.30) | 2.45 |

Source: Adapted with permission of Health Effects Institute [Katsouyanni et al. \(2009\)](#).

Regional Pattern of Ozone-Mortality Risk Estimates

1 In addition to examining whether individual- and community-level factors modify the
2 O₃-mortality association, studies have also examined whether these associations varied
3 regionally within the U.S. [Bell and Dominici \(2008\)](#), in the study discussed above, also
4 noted that O₃-mortality risk estimates were higher in the Northeast (1.44% [95% CI: 0.78,
5 2.10%]) and Industrial Midwest (0.73% [95% CI: 0.11, 1.35%]), while null associations
6 were observed in the Southwest and Urban Midwest ([Table 6-49](#)). The regional
7 heterogeneity in O₃-mortality risk estimates was further reflected by [Bell and Dominici](#)
8 ([2008](#)) in a map of community-specific Bayesian O₃-mortality risk estimates

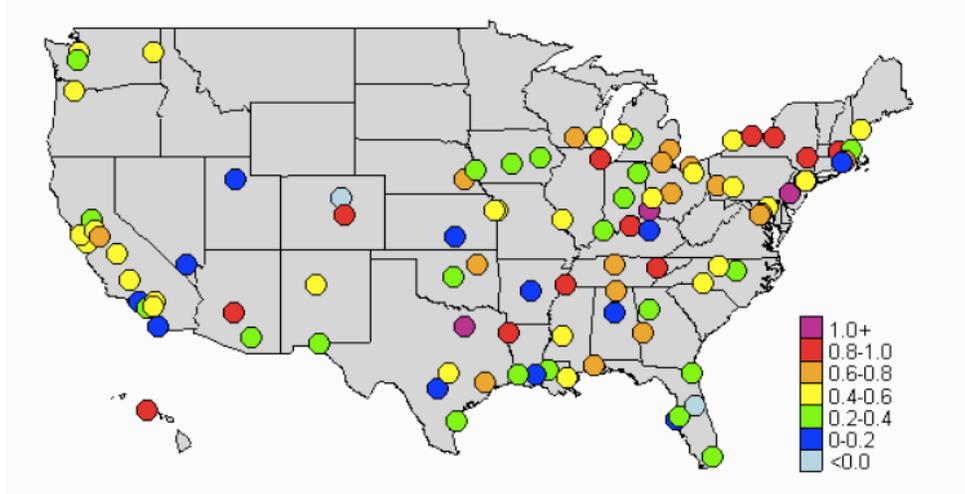
(Figure 6-31). It is worth noting that in the analysis of PM₁₀ using the same data set, Peng et al. (2005) also found that both the Northeast and Industrial Midwest showed particularly elevated effects, especially during the summer months. As mentioned above, although no evidence for confounding of O₃ mortality risk estimates by PM₁₀ was observed, Bell et al. (2007) did find regional differences in the correlation between O₃ and PM₁₀. Thus, the heterogeneity in O₃ mortality risk estimates may need to be examined as a function of the correlation between PM and O₃.

Smith et al. (2009b), as discussed earlier, also examined the regional difference in O₃ mortality risk estimates across the same seven regions and similarly found evidence for regional heterogeneity. In addition, Smith et al. (2009b) constructed spatial maps of the risk estimates by an extension of a hierarchical model that allows for spatial auto-correlation among the city-specific random effects. Figure 6-32 presents the spatial map of O₃ mortality coefficients from the Smith et al. (2009b) analysis that used 8-h max O₃ concentrations during the summer. The results from the Bell and Dominici (2008) analysis (Figure 6-31) shows much stronger apparent heterogeneity in O₃-mortality risk estimates across cities than the smoothed map from Smith et al. (2009b) (Figure 6-32), but both maps generally show larger risk estimates in the eastern region of the U.S.

Table 6-49 Percentage increase in daily mortality for a 10 ppb increase in 24-h average ozone concentrations during the previous week by geographic region in the U.S., 1987-2000.

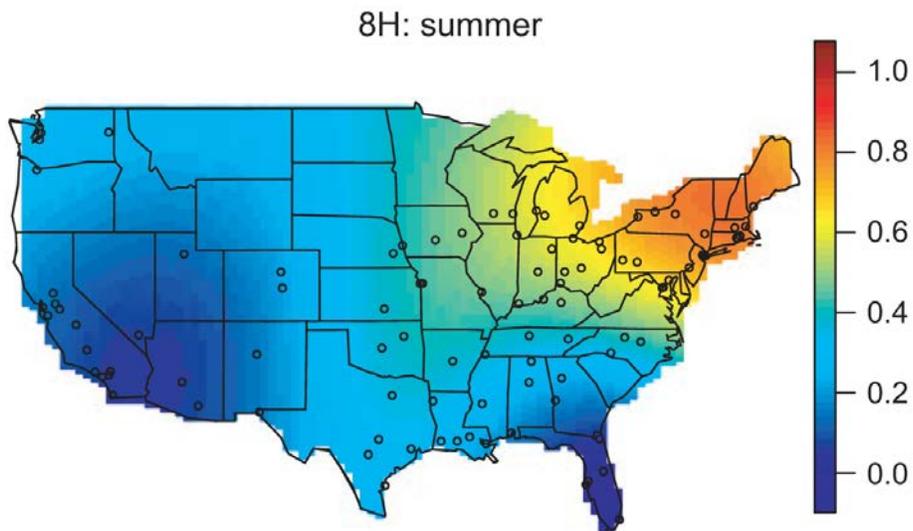
| | No. of Communities | Regional Estimate | 95% PI* |
|-----------------------------|--------------------|-------------------|-------------|
| Regional results | | | |
| Industrial Midwest | 20 | 0.73 | 0.11, 1.35 |
| Northeast | 16 | 1.44 | 0.78, 2.10 |
| Northwest | 12 | 0.08 | -0.92, 1.09 |
| Southern California | 7 | 0.21 | -0.46, 0.88 |
| Southeast | 26 | 0.38 | -0.07, 0.85 |
| Southwest | 9 | -0.06 | -0.92, 0.81 |
| Urban Midwest | 7 | -0.05 | -1.28, 1.19 |
| National results | | | |
| All continental communities | 97 | 0.51 | 0.27, 076 |
| All communities | 98 | 0.52 | 0.28, 0.77 |

Source: Reprinted with permission of Johns Hopkins Bloomberg School of Public Health (Bell and Dominici, 2008).



Source: Reprinted with permission of Johns Hopkins Bloomberg School of Public Health, ([Bell and Dominici, 2008](#)).

Figure 6-31 Community-specific Bayesian ozone-mortality risk estimates in 98 U.S. communities.



Source: Reprinted with permission of Informa UK Ltd. ([Smith et al., 2009b](#)).

Figure 6-32 Map of spatially dependent ozone-mortality coefficients for 8-h max ozone concentrations using summer data.

6.6.2.3 Interaction

1 Interactions can lead to either antagonistic or synergistic effects; however, most studies
2 attempt to identify potential factors that interact synergistically with O₃ to increase the
3 risk of mortality. Within this section, interactive effects are defined as time-varying
4 covariates, such as temperature and copollutants that are included in 1st stage time-series
5 regression models. To date, only a few time-series studies have investigated the potential
6 interaction between O₃ exposure and copollutants or weather variables. This can be
7 attributed to the moderate to high correlation between O₃ and these covariates, which
8 makes such investigations methodologically challenging.

9 [Ren et al. \(2008\)](#) examined the possible synergistic effect between O₃ and temperature on
10 mortality in the 60 largest eastern U.S. communities from the NMMAPS data during the
11 warm months (i.e., April to October) from 1987-2000. This analysis was restricted to the
12 eastern areas of the U.S. (i.e., Northeast, Industrial Midwest and Southeast) because a
13 previous study which focused specifically on the eastern U.S. found that
14 temperature-mortality patterns differ between the northeast and southeast regions
15 possibly due to climatic differences ([Curriero et al., 2002](#)). To examine possible
16 geographic differences in the interaction between temperature and O₃, [Ren et al. \(2008\)](#)
17 further divided the NMMAPS regions into the Northeast, which included the Northeast
18 and Industrial Midwest regions (34 cities), and the Southeast, which included the
19 Southeast region (26 cities). The potential synergistic effects between O₃ and temperature
20 were examined using two different models. Model 1 included an interaction term in a
21 Generalized Additive Model (GAM) for O₃ and maximum temperature (3-day avg values
22 were used for both terms) to examine the bivariate response surface and the pattern of
23 interaction between the two variables in each community. Model 2 consisted of a
24 Generalized Linear Model (GLM) that used interaction terms to stratify by “low,”
25 “moderate,” and “high” temperature days using the first and third quartiles of temperature
26 as cut-offs to examine the percent increase in mortality in each community. Furthermore,
27 a two-stage Bayesian hierarchical model was used to estimate the overall percent increase
28 in all-cause mortality associated with short-term O₃ exposure across temperature levels
29 and each region using model 2. The same covariates were used in both model 1 and 2.
30 The bivariate response surfaces from model 1 suggest possible interactive effects
31 between O₃ and temperature although the interpretation of these results is not
32 straightforward due to the high correlation between these terms. The apparent interaction
33 between temperature and O₃ as evaluated in model 2 varied across geographic regions. In
34 the northeast region, a 20 ppb increase in 24-h avg O₃ concentrations at lag 0-2 was
35 associated with an increase of 4.49% (95% posterior interval [PI]: 2.39, 6.36%), 6.21%
36 (95% PI: 4.47, 7.66%) and 12.8% (95% PI: 9.77, 15.7%) in mortality at low, moderate
37 and high temperature levels, respectively. The corresponding percent increases in

1 mortality in the southeast region were 2.27% (95% PI: -2.23, 6.46%) for low temperature,
2 3.02% (95% PI: 0.44, 5.70%) for moderate temperature, and 2.60% (95% PI: -0.66,
3 6.01%) for high temperature.

4 When examining the relationship between temperature and O₃-related mortality, the
5 results reported by [Ren et al. \(2008\)](#) (i.e., higher O₃-mortality risks on days with higher
6 temperatures) may appear to contradict the results of [Bell and Dominici \(2008\)](#) described
7 earlier (i.e., communities with higher temperature have lower O₃-mortality risk
8 estimates). However, the observed difference in results can be attributed to the
9 interpretation of effect modification in a second-stage regression which uses long-term
10 average temperatures, as was performed by [Bell and Dominici \(2008\)](#), compared to a
11 first-stage regression that examines the interaction between daily temperature and O₃-
12 related mortality. In this case, the second-stage regression results from [Bell and Dominici](#)
13 [\(2008\)](#) indicate that a city with lower temperatures, on average, tend to show a stronger
14 O₃ mortality effect, whereas, in the first-stage regression performed by [Ren et al. \(2008\)](#),
15 the days with higher temperature tend to show a larger O₃-mortality effect. This observed
16 difference may in part reflect the higher air conditioning use in communities with higher
17 long-term average temperatures. Therefore, the findings from [Ren et al. \(2008\)](#) indicating
18 generally lower O₃ risk estimates in the southeast region where the average temperature is
19 higher than in the northeast region is consistent with the regional results reported by [Bell](#)
20 [and Dominici \(2008\)](#). As demonstrated by the results from both [Ren et al. \(2008\)](#) and
21 [Bell and Dominici \(2008\)](#) caution is required when interpreting results from studies that
22 examined interactive effects using two different approaches because potential effect
23 modification as suggested in a second-stage regression generally does not provide
24 evidence for a short-term interaction examined in a first-stage regression. Overall, further
25 examination of the potential interactive (synergistic) effects of O₃ and covariates in time-
26 series regression models is required to more clearly understand the factors that may
27 influence O₃ mortality risk estimates.

6.6.2.4 Evaluation of the Ozone-Mortality C-R Relationship and Related Issues

28 Evaluation of the O₃-mortality C-R relationship is not straightforward because the
29 evidence from multicity studies (using log-linear models) suggests that O₃-mortality
30 associations are highly heterogeneous across regions. In addition, there are numerous
31 issues that may influence the shape of the O₃-mortality C-R relationship and the observed
32 association between short-term O₃ exposure and mortality that warrant examination
33 including: multi-day effects (distributed lags), mortality displacement (i.e., hastening of
34 death by a short period), potential adaptation, and the exposure metric used to compute

1 risks (e.g., 1-hour daily max versus 24-h avg). The following section presents the recent
2 studies identified that conducted an initial examination of these issues.

Multiday Effects, Mortality Displacement, and Adaptation

3 The pattern of positive lagged associations followed by negative associations in a
4 distributed lag model may be considered an indication of “mortality displacement”
5 (i.e., deaths are occurring in frail individuals and exposure is only moving the day of
6 death to a day slightly earlier). [Zanobetti and Schwartz \(2008b\)](#) examined this issue in 48
7 U.S. cities during the warm season (i.e., June-August) for the years 1989-2000. In an
8 initial analysis, the authors applied a GLM to examine same-day O₃-mortality effects, and
9 in the model included an unconstrained distributed lag for apparent temperature to take
10 into account the effect of temperature on the day death occurred and the previous 7 days.
11 To examine mortality displacement [Zanobetti and Schwartz \(2008b\)](#) refit models using
12 two approaches: an unconstrained and a smooth distributed lag each with 21-day lags for
13 O₃. In this study, all-cause mortality as well as cause-specific mortality
14 (i.e., cardiovascular, respiratory, and stroke) were examined for evidence of mortality
15 displacement. The authors found a 0.96% (95% CI: 0.60, 1.30%) increase in all-cause
16 mortality across all 48 cities for a 30 ppb increase in 8-h max O₃ concentrations at lag 0
17 whereas the combined estimate of the unconstrained distributed lag model (lag 0-20) was
18 1.54% (95% CI: 0.15, 2.91%). Similarly, when examining the cause-specific mortality
19 results ([Table 6-50](#)), larger risk estimates were observed for the distributed lag model
20 compared to the lag 0 day estimates. However, for stroke a slightly larger effect was
21 observed at lags 4-20 compared to lags 0-3 suggesting a larger window for O₃-induced
22 stroke mortality. This is further supported by the sum of lags 0 through 20 days showing
23 the greatest effect. Overall, these results suggest that estimating the mortality risk using a
24 single day of O₃ exposure may underestimate the public health impact, but the extent of
25 multi-day effects appear to be limited to a few days. This is further supported by the
26 shape of the combined smooth distributed lag ([Figure 6-33](#)). It should be noted that the
27 proportion of total variation in the effect estimates due to the between-cities
28 heterogeneity, as measured by I² statistic, was relatively low (4% for the lag 0 estimates
29 and 21% for the distributed lag), but 21 out of the 48 cities exhibited null or negative
30 estimates. As a result, the estimated shape of the distributed lag cannot be interpreted as a
31 general form of lag structure of associations applicable to all the cities included in this
32 analysis.

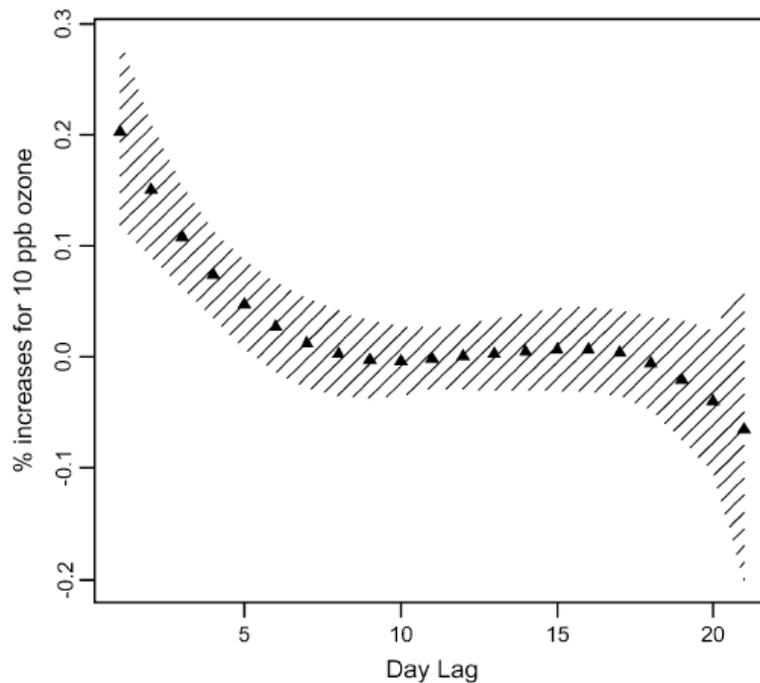
Table 6-50 Estimated effect of a 10 ppb increase in 8-h max ozone concentrations on mortality during the summer months for single-day and distributed lag models.

| | % (Percentage) | 95% CI |
|---------------------------------|----------------|-------------|
| Total mortality | | |
| Lag 0 | 0.32 | 0.20, 0.43 |
| Sum lags 0-20 | 0.51 | 0.05, 0.96 |
| Sum lags 0-3 | 0.53 | 0.28, 0.77 |
| Sum lags 4-20 | -0.02 | -0.35, 0.31 |
| Cardiovascular mortality | | |
| Lag 0 | 0.47 | 0.30, 0.64 |
| Sum lags 0-20 | 0.49 | -0.01, 1.00 |
| Sum lags 0-3 | 0.80 | 0.48, 1.13 |
| Sum lags 4-20 | -0.23 | -0.67, 0.22 |
| Respiratory mortality | | |
| Lag 0 | 0.54 | 0.26, 0.81 |
| Sum lags 0-20 | 0.61 | -0.41, 1.65 |
| Sum lags 0-3 | 0.83 | 0.38, 1.28 |
| Sum lags 4-20 | -0.24 | -1.08, 0.60 |
| Stroke | | |
| Lag 0 | 0.37 | 0.01, 0.74 |
| Sum lags 0-20 | 2.20 | 0.76, 3.67 |
| Sum lags 0-3 | 0.92 | 0.26, 1.59 |
| Sum lags 4-20 | 1.26 | 0.05, 2.49 |

Source: Reprinted with permission of American Thoracic Society, [Zanobetti and Schwartz \(2008b\)](#).

1 [Samoli et al. \(2009\)](#) also investigated the temporal pattern of mortality effects in response
2 to short-term exposure to O₃ in 21 European cities that were included in the APHEA2
3 project. Using a method similar to [Zanobetti and Schwartz \(2008b\)](#), the authors applied
4 unconstrained distributed lag models with lags up to 21 days in each city during the
5 summer months (i.e., June through August) to examine the effect of O₃ on all-cause,
6 cardiovascular, and respiratory mortality. They also applied a generalized additive
7 distributed lag model to obtain smoothed distributed lag coefficients. However, unlike
8 [Zanobetti and Schwartz \(2008b\)](#), [Samoli et al. \(2009\)](#) controlled for temperature using a
9 linear term for humidity and an unconstrained distributed lag model of temperature at
10 lags 0-3 days. The choice of 0- through 3-day lags of temperature was based on a
11 previous European multicity study ([Baccini et al., 2008](#)), which suggested that summer
12 temperature effects last only a few days. Upon combining the individual city estimates
13 across cities in a second stage regression, [Samoli et al. \(2009\)](#) found that the estimated

1 effects on respiratory mortality were extended for a period of two weeks. However, for
2 all-cause and cardiovascular mortality, the 21-day distributed lag models yielded null or
3 (non-significant) negative estimates (Table 6-51). Figure 6-34 shows the distributed lag
4 coefficients for all-cause mortality, which exhibit a declining trend and negative
5 coefficients beyond 5-day lags. The authors' interpretation of these results was that
6 "using single-day exposures may have overestimated the effects on all-cause and
7 cardiovascular mortality, but underestimated the effects on respiratory mortality." Thus,
8 the results in part suggest evidence of mortality displacement for all-cause and
9 cardiovascular mortality.



Source: Reprinted with permission of American Thoracic Society (Zanobetti and Schwartz, 2008b).

Note: The triangles represent the percent increase in all-cause mortality for a 10 ppb increase in 8-h max O₃ concentrations at each lag while the shaded areas are the 95% point-wise confidence intervals.

Figure 6-33 Estimated combined smooth distributed lag for 48 U.S. cities during the summer months.

Table 6-51 Estimated percent increase in cause-specific mortality (and 95% CIs) for a 10- $\mu\text{g}/\text{m}^3$ increase in maximum 8-hour ozone during June-August.

| | Fixed effects % (95% CI) | Random effects % (95% CI) |
|---|-----------------------------|------------------------------|
| Total mortality^a | | |
| Lag 0 | 0.28 (0.11, 0.45) | 0.28 (0.07, 0.48) |
| Average lags 0-1 | 0.24 (0.15, 0.34) | 0.22 (0.08, 0.35) |
| Sum lags 0-20, unconstrained | 0.01 (-0.40, 0.41) | -0.54 (-1.28, 0.20) |
| Sum lags 0-20, penalized | 0.01 (-0.41, 0.42) | -0.56 (-1.30, 0.19) |
| Cardiovascular mortality^a | | |
| Lag 0 | 0.43 (0.18, 0.69) | 0.37 (0.05, 0.69) |
| Average lags 0-1 | 0.33 (0.19, 0.48) | 0.25 (0.03, 0.47) |
| Sum lags 0-20, unconstrained | -0.33 (-0.93, 0.29) | -0.62 (-1.47, 0.24) |
| Sum lags 0-20, penalized | -0.32 (-0.92, 0.28) | -0.57 (-1.39, 0.26) |
| Respiratory mortality^a | | |
| Lag 0 | 0.36 (-0.21, 0.94) | 0.36 (-0.21, 0.94) |
| Average lags 0-1 | 0.40 (0.11, 0.70) | 0.40 (0.11, 0.70) |
| Sum lags 0-20, unconstrained | 3.35 (1.90, 4.83) | 3.35 (1.90, 4.83) |
| Sum lags 0-20, penalized | 3.66 (2.25, 5.08) | 3.66 (2.25, 5.08) |

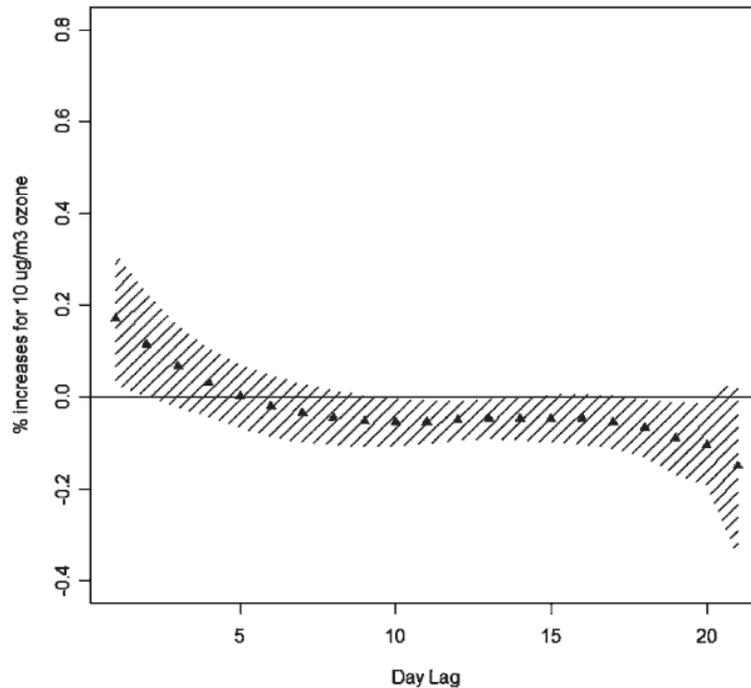
^aAnalysis for the same day (lag 0), the average of the same and previous day (lag 0-1), the unconstrained distributed lag model for the sum of 0-20 days and the penalized distributed lag model (lag 0-20)

Source: Used with permission of BMJ Group ([Samoli et al., 2009](#)).

1 Although the APHENA project ([Katsouyanni et al., 2009](#)) did not specifically investigate
2 mortality displacement and therefore did not consider longer lags (e.g., lag >3 days), the
3 study did present O₃ risk estimates for lag 0-1, lag 1, and a distributed lag model of 0-
4 2 days in the Canadian, European, and U.S. datasets. [Katsouyanni et al. \(2009\)](#) found that
5 the results vary somewhat across the regions, but, in general, there was no indication that
6 the distributed lag model with up to a 2-day lag yielded meaningfully larger O₃ mortality
7 risk estimates than the lag 0-1 and lag 1 results. For example, for all-cause mortality,
8 using the model with natural splines and 8 df/year to adjust for seasonal trends, the
9 reported percent excess risk for mortality for a 40 ppb increase in 1-h max O₃
10 concentrations for lag 0-1, lag 1, and the distributed lag model (lag 0-2) was 2.70%
11 (95% CI: 1.02, 4.40%), 1.42% (95% CI: 0.08, 2.78%), and 3.02% (95% CI: 1.10, 4.89%),
12 respectively. Thus, the observed associations appear to occur over a short time period,
13 (i.e., a few days). Similarly, the Public Health and Air Pollution in Asia (PAPA) study
14 ([Wong et al., 2010](#)) also examined multiple lag days (i.e., lag 0, lag 0-1, and lag 0-4), and
15 although it did not specifically examine mortality displacement it does provide additional
16 evidence regarding the timing of mortality effects proceeding O₃ exposure. In a combined

1 analysis using data from all four cities examined (Bangkok, Hong Kong, Shanghai, and
2 Wuhan), excess risk estimates at lag 0-4 were larger than those at lag 0 or lag 0-1 in both
3 fixed and random effect models (results not presented quantitatively). The larger risk
4 estimates at lag 0-4 can primarily be attributed to the strong associations observed in
5 Bangkok and Shanghai. However, it is worth noting that Bangkok differs from the three
6 Chinese cities included in this analysis in that it has a tropical climate and does not
7 exhibit seasonal patterns of mortality. As a result, [Wong et al. \(2010\)](#) examined the O₃-
8 mortality associations at lag 0-1 in only the three Chinese cities and found that risk
9 estimates were slightly reduced from 2.26% (95% CI: 1.36, 3.16) in the 4 city analysis to
10 1.84% (0.77, 2.86) in the 3 city analysis for a 30 ppb increase in 8-h max O₃
11 concentrations. Overall, the PAPA study further supports the observation of the
12 APHENA study that associations between O₃ and mortality occur over a relatively short-
13 time period, but also indicates that it may be difficult to interpret O₃-mortality
14 associations across cities with different climates and mortality patterns.

15 When comparing the studies that explicitly examined the potential for mortality
16 displacement in the O₃-mortality relationship, the results from [Samoli et al. \(2009\)](#), which
17 provide evidence that suggests mortality displacement, are not consistent with those
18 reported by [Zanobetti and Schwartz \(2008b\)](#). However, the shapes of the estimated
19 smooth distributed lag associations are similar ([Figure 6-33](#) and [Figure 6-34](#)). A closer
20 examination of these figures shows that in the European data beyond a lag of 5 days the
21 estimates remain negative whereas in the U.S. data the results remain near zero for the
22 corresponding lags. These observed difference could be due to the differences in the
23 model specification between the two studies, specifically the use of: an unconstrained
24 distributed lag model for apparent temperature up to 7 previous days ([Zanobetti and
25 Schwartz, 2008b](#)) versus a linear term for humidity and an unconstrained distributed lag
26 model of temperature up to 3 previous days ([Samoli et al., 2009](#)); and natural cubic
27 splines with 2 df per season ([Zanobetti and Schwartz, 2008b](#)) versus dummy variables per
28 month per year to adjust for season ([Samoli et al., 2009](#)). It is important to note that these
29 differences in model specification may have also influenced the city-to-city variation in
30 risk estimates observed in these two studies (i.e., homogenous estimates across cities in
31 [Zanobetti and Schwartz \(2008b\)](#) and heterogeneous estimates across cities in [Samoli et
32 al. \(2009\)](#)). Overall, the evidence of mortality displacement remains unclear, but [Samoli et
33 al. \(2009\)](#), [Zanobetti and Schwartz \(2008b\)](#), and [Katsouyanni et al. \(2009\)](#) all suggest that
34 the positive associations between O₃ and mortality are observed mainly in the first
35 few days after exposure.



Note: The triangles represent the percent increase in all-cause mortality for a 10 µg/m³ increase in 8-h max O₃ concentrations at each lag; the shaded area represents the 95% CIs.
 Source: Reprinted with permission of BMJ Group ([Samoli et al., 2009](#)).

Figure 6-34 Estimated combined smooth distributed lag in 21 European cities during the summer (June-August) months.

Adaptation

1 Controlled human exposure studies have demonstrated an adaptive response to O₃
 2 exposure for respiratory effects, such as lung function decrements, but this issue has not
 3 been examined in the epidemiologic investigation of mortality effects of O₃. [Zanobetti](#)
 4 [and Schwartz \(2008a\)](#) examined if there was evidence of an adaptive response in the
 5 O₃-mortality relationship in 48 U.S. cities from 1989 to 2000 (i.e., the same data analyzed
 6 in [Zanobetti and Schwartz \(2008b\)](#)). The authors examined all-cause mortality using a
 7 case-crossover design to estimate the same-day (i.e., lag 0) effect of O₃, matched on
 8 referent days from every-3rd-day in the same month and year as the case. [Zanobetti and](#)
 9 [Schwartz \(2008a\)](#) examined O₃-mortality associations by: season, month in the summer
 10 season (i.e., May through September), and age categories in the summer season
 11 ([Table 6-52](#)). The estimated O₃ mortality risk estimate at lag 0 was found to be highest in
 12 the summer (1.51% [95% CI: 1.14, 1.87%]; lag 0 for a 30 ppb increase in 8-h max O₃
 13 concentrations), and, within the warm months, the association was highest in July (1.96%

1 [95% CI: 1.42, 2.48%]; lag 0).¹ Upon further examination of the summer months, the
 2 authors also observed diminished effects in August (0.84% [95% CI: 0.33, 1.39%]; lag
 3 0). Based on these results, the authors concluded that the mortality effects of O₃ appear
 4 diminished later in the O₃ season.

Table 6-52 Percent excess all-cause mortality per 10 ppb increase in daily 8-h max ozone on the same day, by season, month, and age groups.

| | % | 95% CI |
|---------------------|-------|-------------|
| By Season | | |
| Winter | -0.13 | -0.56, 0.29 |
| Spring | 0.35 | 0.16, 0.54 |
| Summer | 0.50 | 0.38, 0.62 |
| Fall | 0.05 | -0.14, 0.24 |
| By Month | | |
| May | 0.48 | 0.28, 0.68 |
| June | 0.46 | 0.24, 0.68 |
| July | 0.65 | 0.47, 0.82 |
| August | 0.28 | 0.11, 0.46 |
| September | -0.09 | -0.35, 0.16 |
| By Age Group | | |
| 0-20 | 0.08 | -0.42, 0.57 |
| 21-30 | 0.10 | -0.67, 0.87 |
| 31-40 | 0.07 | -0.38, 0.52 |
| 41-50 | 0.08 | -0.27, 0.43 |
| 51-60 | 0.54 | 0.19, 0.89 |
| 61-70 | 0.38 | 0.16, 0.61 |
| 71-80 | 0.50 | 0.32, 0.67 |
| 80 | 0.29 | 0.13, 0.44 |

Source: [Zanobetti and Schwartz \(2008a\)](#).

5 To further evaluate the potential adaptive response observed in [Zanobetti and Schwartz](#)
 6 [\(2008a\)](#) the distribution of the O₃ concentrations across the 48 U.S. cities during July and
 7 August was examined. Both July and August were found to have comparable means of
 8 48.6 and 47.9 ppb with a reported maximum value of 97.9 and 96.0 ppb, respectively.
 9 Thus, the observed reduction in O₃-related mortality effect estimates in August (0.84%)

¹ These values have been standardized to the increment used throughout the ISA for max 8-h avg increase in O₃ concentrations of 30 ppb. These values differ from those presented in Table 6-52 from [Zanobetti and Schwartz \(2008a\)](#) because the authors presented values for a 10 ppb increase in max 8-h avg O₃ concentrations.

1 compared to July (1.96%) appears to support the existence of an adaptive response.
2 However, unlike an individual's adaptive response to decrements in lung function from
3 short-term O₃ exposure, an examination of mortality prevents a direct observation of
4 adaptation. Rather, for mortality the adaptation hypothesis is tested with a tacit
5 assumption that, whatever the mechanism for O₃-induced mortality, the risk of death
6 from short-term O₃ exposure is reduced over the course of the summer months through
7 repeated exposures. This idea would translate to a smaller population that would die from
8 O₃ exposure towards the end of summer. This may complicate the interpretation of the
9 distributed lag coefficients with long lag periods because the decreased coefficients may
10 reflect diminished effects of the late summer, rather than diminished effects that are
11 constant across the summer. These intertwined issues need to be investigated together in
12 future research.

Exposure Metric

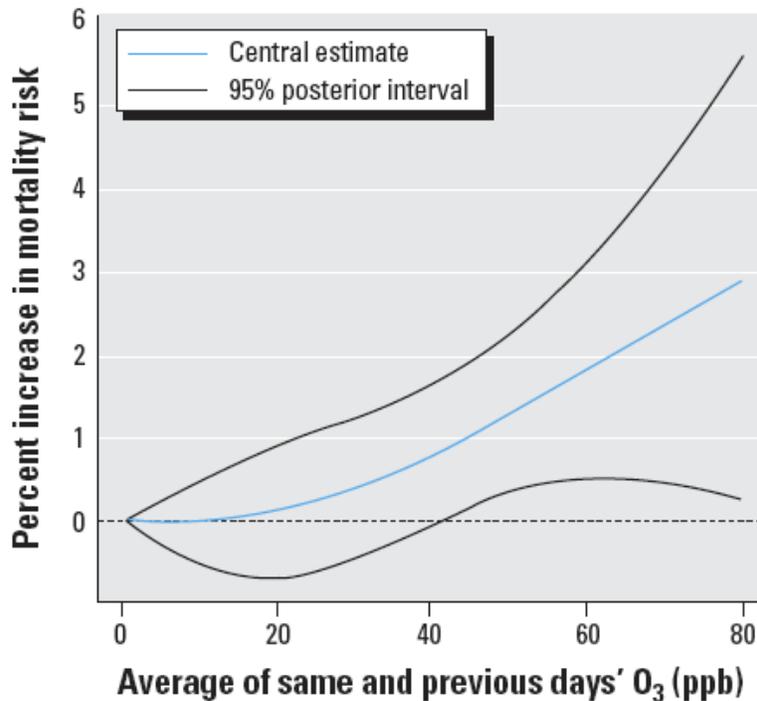
13 When examining the association between short-term O₃ exposure and mortality it is also
14 important to consider the exposure metric used (i.e., 24-h avg, 8-h max, and 1-h max). To
15 date, only a few studies have conducted analyses to examine the impact of different
16 exposure metrics on O₃ mortality risk estimates. In [Smith et al. \(2009b\)](#), the authors
17 examined the effect of different exposure metrics (i.e., 24-h avg, 8-h max, and 1-h max)
18 on O₃-mortality regression coefficients. When examining whether there are differences in
19 city-specific risk estimates when using different exposure metrics, [Smith et al. \(2009b\)](#)
20 found a rather high correlation (r = 0.7-0.8) between risk estimates calculated using
21 24-h avg versus 8-h max and 1-h max versus 8-h max averaging times. These results are
22 consistent with the correlations reported by [Darrow et al. \(2011a\)](#) (Section 6.2.7.3)
23 between the 8-h max and 24- avg exposure metrics.

24 In addition to these recent studies published since the 2006 O₃ AQCD, [Gryparis et al.](#)
25 [\(2004\)](#) also supports the high correlation between 1-h max and 8-h max O₃
26 concentrations reported in [Smith et al. \(2009b\)](#) and [Darrow et al. \(2011a\)](#) and the
27 subsequent high degree of similarity between mortality risk estimates calculated using
28 either metric. Although only a limited number of studies have examined the effect of
29 different exposure metrics on O₃-mortality risk estimates, these studies suggest relatively
30 comparable results across the exposure metrics used.

Ozone-Mortality C-R Relationship and Threshold Analyses

31 Several of the recent studies evaluated have applied a variety of statistical approaches to
32 examine the shape of the O₃-mortality C-R relationship and whether a threshold exists.
33 The approach used by [Bell et al. \(2006\)](#) consisted of applying four statistical models to

1 the NMMAPS data, which included 98 U.S. communities for the period 1987-2000.
2 These models included: a linear analysis (i.e., any change in O₃ concentration can be
3 associated with mortality) (Model 1); a subset analysis (i.e., examining O₃-mortality
4 relationship below a specific 24- avg concentration, ranging from 5 to 60 ppb) (Model 2);
5 a threshold analysis (i.e., assuming that an association between O₃ and mortality is
6 observed above a specific concentration and not below it, using the threshold values set at
7 an increment of 5 ppb between 0 to 60 ppb and evaluating a presence of a local minima in
8 AICs computed at each increment) (Model 3); and nonlinear models using natural cubic
9 splines with boundary knots placed at 0 and 80 ppb, and interior knots placed at 20 and
10 40 ppb (Model 4). A two-stage Bayesian hierarchical model was used to examine these
11 models and O₃-mortality risk estimates at the city-level in the first stage analysis and
12 aggregate estimates across cities in the 2nd stage analysis using the average of 0- and
13 1-day lagged 24-h avg O₃ concentrations. The results from all of these models suggest
14 that if a threshold exists it does so well below the current O₃ NAAQS. When restricting
15 the analysis to all days when the 1997 O₃ NAAQS 8-hour standard (i.e., 84 ppb daily
16 8-h max) is met in each community, [Bell et al. \(2006\)](#) found there was still a 0.60% (95%
17 PI: 0.30, 0.90%) increase in mortality per 20 ppb increase in 24-h avg O₃ concentrations
18 at lag 0-1. [Figure 6-35](#) shows the combined C-R curve obtained using the nonlinear
19 model (Model 4). Although these results suggest the lack of threshold in the O₃-mortality
20 relationship, it is difficult to interpret such a curve because: (1) there is uncertainty
21 around the shape of the C-R curve at 24-h avg O₃ concentrations generally below 20 ppb,
22 and (2) the C-R curve does not take into consideration the heterogeneity in O₃-mortality
23 risk estimates across cities.



Source: [Bell et al. \(2006\)](#)

Figure 6-35 Estimated combined C-R curve for nonaccidental mortality and 24-hour average ozone concentrations at lag 0-1 using the nonlinear (spline) model.

1 Using the same NMMAPS dataset as [Bell et al. \(2006\)](#), [Smith et al. \(2009b\)](#) further
 2 examined the O₃-mortality C-R relationship. Similar to [Bell et al. \(2006\)](#), [Smith et al.](#)
 3 [\(2009b\)](#) conduct a subset analysis, but instead of restricting the analysis to days with O₃
 4 concentrations below a cutoff the authors only include days above a defined cutoff in the
 5 analysis. The results of this “reversed subset” approach are in line with those reported by
 6 [Bell et al. \(2006\)](#); consistent positive associations at all cutoff points up to a defined
 7 concentration where the total number of days with 24-h avg O₃ concentrations above a
 8 value are so limited that the variability around the central estimate is increased. In the
 9 [Smith et al. \(2009b\)](#) analysis this observation was initially observed at 45 ppb, with the
 10 largest variability at 60 ppb; however, unlike [Bell et al. \(2006\)](#) where 73% of days are
 11 excluded when subsetting the data to less than 20 ppb, the authors do not detail the
 12 number of days of data included in the subset analyses at higher concentrations. In
 13 addition to the subset analysis, [Smith et al. \(2009b\)](#) examined the shape of the C-R curve
 14 using a piecewise linear approach with cutpoints at 8-h avg concentrations of 40 ppb,
 15 60 ppb, and 80 ppb. [Smith et al. \(2009b\)](#) found that the shape of the C-R curve is similar

1 to that reported by [Bell et al. \(2006\)](#) ([Figure 6-35](#)), but argue that slopes of the β for each
2 piece of the curve are highly variable with the largest variation in the 60-80 ppb range.
3 However, the larger variability around the β between 60-80 would be expected due to the
4 small number of days with O₃ concentrations within that range in an all-year analysis.
5 This result is consistent with that observed by [Bell et al. \(2006\)](#), which is presented in
6 [Figure 6-35](#).

7 The APHENA project ([Katsouyanni et al., 2009](#)) also analyzed the Canadian and
8 European datasets (the U.S. data were analyzed for PM₁₀ only) for evidence of a
9 threshold, using the threshold analysis method (Model 3) applied in [Bell et al. \(2006\)](#)
10 study described above. There was no evidence of a threshold in the Canadian data
11 (i.e., the pattern of AIC values for each increment of a potential threshold value varied
12 across cities, most of which showed no local minima). Likewise, the threshold analysis
13 conducted using the European data also showed no evidence of a threshold.

14 The PAPA study, did not examine whether a threshold exists in the O₃-mortality C-R
15 relationship, but instead the shape of the C-R curve individually for each city (Bangkok,
16 Hong Kong, Shanghai, and Wuhan) ([Wong et al., 2010](#)). Using a natural spline smoother
17 with 3df for the O₃ term, [Wong et al. \(2010\)](#) examined whether non-linearity was present
18 by testing the change in deviance between the smoothed, non-linear, model and an
19 unsmoothed, linear, model with 1 df. For each of the cities, both across the full range of
20 the O₃ distribution and specifically within the range of the 25th to 75th percentile of each
21 city's O₃ 24-h avg concentrations (i.e., a range of 9.7 ppb to 60.4 ppb across the cities)
22 there was no evidence of a non-linear relationship in the O₃-mortality C-R curve. It
23 should be noted that the range of the 25th to 75th percentiles in all of the cities, except
24 Wuhan, was lower than that observed in the U.S. using all-year data where the range
25 from the 25th to 75th percentiles is 30 ppb to 50 ppb ([Table 3-6](#)).

26 Additional threshold analyses were conducted using NMMAPS data, by [Xia and Tong](#)
27 ([2006](#)) and [Stylianou and Nicolich \(2009\)](#). Both studies used a new statistical approach
28 developed by [Xia and Tong \(2006\)](#) to examine thresholds in the O₃ mortality C-R
29 relationship. The approach consisted of an extended GAM model, which accounted for
30 the cumulative and nonlinear effects of air pollution using a weighted cumulative sum for
31 each pollutant, with the weights (non-increasing further into the past) derived by a
32 restricted minimization method. The authors did not use the term distributed lag model,
33 but their model has the form of distributed lag model, except that it allows for nonlinear
34 functional forms. Using NMMAPS data for 1987-1994 for 3 U.S. cities (Chicago,
35 Pittsburgh, and El Paso), [Xia and Tong \(2006\)](#) found that the extent of cumulative effects
36 of O₃ on mortality were relatively short. While the authors also note that there was
37 evidence of a threshold effect around 24-h avg concentrations of 25 ppb, the threshold

1 values estimated in the analysis were sometimes in the range where data density was low.
2 Thus, this threshold analysis needs to be replicated in a larger number of cities to confirm
3 this observation. It should be noted that the model used in this analysis did not include a
4 smooth function of days to adjust for unmeasured temporal confounders, and instead
5 adjusted for season using a temperature term. As a result, these results need to be viewed
6 with caution because some potential temporal confounders (e.g., influenza) do not always
7 follow seasonal patterns of temperature.

8 [Stylianou and Nicolich \(2009\)](#) examined the existence of thresholds following an
9 approach similar to [Xia and Tong \(2006\)](#) for all-cause, cardiovascular, and respiratory
10 mortality using data from NMMAPS for nine major U.S. cities (i.e., Baltimore, Chicago,
11 Dallas/Fort Worth, Los Angeles, Miami, New York, Philadelphia, Pittsburgh, and
12 Seattle) for the years 1987-2000. The authors found that PM₁₀ and O₃ were the two
13 important predictors of mortality. [Stylianou and Nicolich \(2009\)](#) found that the estimated
14 O₃-mortality risks varied across the nine cities with the models exhibiting apparent
15 thresholds, in the 10-45 ppb range for O₃ (3-day accumulation). However, given the city-
16 to-city variation in risk estimates, combining the city-specific estimates into an overall
17 estimate complicates the interpretation of a threshold. Unlike the [Xia and Tong \(2006\)](#)
18 analysis, [Stylianou and Nicolich \(2009\)](#) included a smooth function of time to adjust for
19 seasonal/temporal confounding, which could explain the difference in results between the
20 two studies.

21 In conclusion, the evaluation of the O₃-mortality C-R relationship did not find any
22 evidence that supports a threshold in the relationship between short-term exposure to O₃
23 and mortality within the range of O₃ concentrations observed in the U.S. Additionally,
24 recent evidence suggests that the shape of the O₃-mortality C-R curve remains linear
25 across the full range of O₃ concentrations. However, the studies evaluated demonstrated
26 that the heterogeneity in the O₃-mortality relationship across cities (or regions)
27 complicates the interpretation of a combined C-R curve and threshold analysis. Given the
28 effect modifiers identified in the mortality analyses that are also expected to vary
29 regionally (e.g., temperature, air conditioning prevalence), a national or combined
30 analysis may not be appropriate to identify whether a threshold exists in the O₃-mortality
31 C-R relationship. Overall, the studies evaluated support a linear O₃-mortality C-R
32 relationship and continue to support the conclusions from the 2006 O₃ AQCD, which
33 stated that “if a population threshold level exists in O₃ health effects, it is likely near the
34 lower limit of ambient O₃ concentrations in the United States” ([U.S. EPA, 2006b](#)).

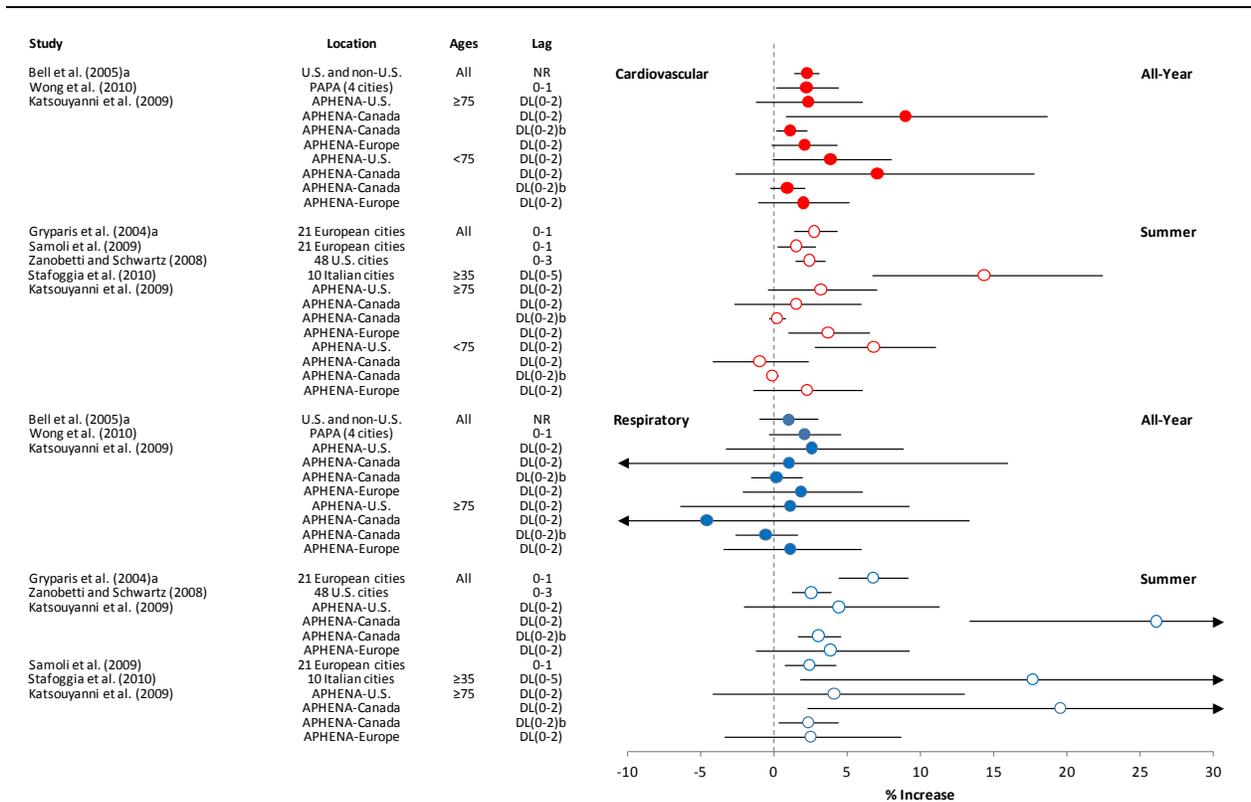
6.6.2.5 Associations of Cause-Specific Mortality and Short-term Ozone Exposure

1 In the 2006 O₃ AQCD, an evaluation of studies that examined cause-specific mortality
2 found consistent positive associations between short-term O₃ exposure and
3 cardiovascular mortality, with less consistent evidence for associations with respiratory
4 mortality. The majority of the evidence for associations between O₃ exposure and cause-
5 specific mortality were from single-city studies, which had small daily mortality counts
6 and subsequently limited statistical power to detect associations.

7 New multicity studies evaluated in this review build upon and confirm the associations
8 between short-term O₃ exposure and cause-specific mortality identified in the 2006 O₃
9 AQCD ([U.S. EPA, 2006b](#)) ([Figure 6-36](#); [Table 6-53](#)). In APHENA, a multicontinent
10 study that consisted of the NMMAPS, APHEA2 and Canadian multicity datasets,
11 consistent positive associations were reported for both cardiovascular and respiratory
12 mortality in all-year analyses when focusing on the natural spline model with 8 df/year
13 ([Figure 6-36](#); [Table 6-53](#)). The associations between O₃ exposure and cardiovascular and
14 respiratory mortality in all-year analyses were further supported by the multicity PAPA
15 study ([Wong et al., 2010](#)). The magnitude of cardiovascular mortality associations were
16 primarily larger in analyses restricted to the summer season compared to those observed
17 in all-year analyses ([Figure 6-36](#); [Table 6-53](#)). Additional multicity studies from the U.S.
18 ([Zanobetti and Schwartz, 2008b](#)) and Europe ([Stafoggia et al., 2010](#); [Samoli et al., 2009](#))
19 that conducted summer season analyses provide evidence supporting associations
20 between O₃ exposure and cardiovascular and respiratory mortality that are similar or
21 larger in magnitude compared to those observed in all-year analyses.

22 Of the studies evaluated, only the APHENA study ([Katsouyanni et al., 2009](#)) and an
23 Italian multicity study ([Stafoggia et al., 2010](#)) conducted an analysis of the potential for
24 copollutant confounding of the O₃ cause-specific mortality relationship. When focusing
25 on the natural spline model with 8 df/year and lag 1 results (as discussed in
26 Section [6.6.2.1](#)), the APHENA study found that O₃ cause-specific mortality risk estimates
27 were fairly robust to the inclusion of PM₁₀ in copollutant models in the European dataset
28 with more variability in the U.S. and Canadian datasets (i.e., copollutant risk estimates
29 increased and decreased for respiratory and cardiovascular mortality). In summer season
30 analyses cardiovascular O₃ mortality risk estimates were robust in the European dataset
31 and attenuated but remained positive in the U.S. datasets; whereas, respiratory O₃
32 mortality risk estimates were attenuated in the European dataset and robust in the U.S.
33 dataset. The authors did not examine copollutant models during the summer season in the
34 Canadian dataset ([Figure 6-29](#); [Table 6-45](#)). Interpretation of these results requires
35 caution; however, due to the different PM sampling schedules employed in each of these

1 study locations (i.e., primarily every-6th day in the U.S. and Canadian datasets and
 2 every-day in the European dataset). The results of the summer season analyses from the
 3 APHENA study ([Katsouyanni et al., 2009](#)) are consistent with those from a study of 10
 4 Italian cities during the summer months ([Stafoggia et al., 2010](#)). [Stafoggia et al. \(2010\)](#)
 5 found that cardiovascular (14.3% [95% CI: 6.7, 22.4%]) and cerebrovascular (8.5%
 6 [95% CI: 0.06, 16.3%]) mortality O₃ effect estimates were robust to the inclusion of PM₁₀
 7 in copollutant models (14.3% [95% CI: 6.7, 23.1%]) and 7.3% [95% CI: -1.2, 16.3],
 8 respectively), while respiratory mortality O₃ effects estimates (17.6% [95% CI: 1.8,
 9 35.5%]) were attenuated, but remained positive (9.2% [95% CI: -6.9, 28.8%]).



Effect estimates are for a 20 ppb increase in 24-h avg; 30 in 8-h max; and 40ppb increase in 1-h max O₃ concentrations. Red = cardiovascular; blue = respiratory; closed circles = all-year analysis; and open circles = summer-only analysis. An “a” represents studies from the 2006 O₃ AQCD. A “b” represents risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations (Section [6.2.7.2](#)).

Figure 6-36 Percent increase in cause-specific mortality.

Table 6-53 Corresponding effect estimates for Figure 6-36.

| Study* | Location | Ages | Lag | Avg Time | %Increase (95% CI) |
|--|--------------------|------|----------------------|----------|---------------------|
| Cardiovascular | | | | | |
| All-year - Cardiovascular | | | | | |
| Bell et al. (2005)^a | U.S. and non-U.S. | All | NR | 24-h avg | 2.23 (1.36,3.08) |
| Wong et al. (2010) | PAPA (4 cities) | | 0-1 | 8-h max | 2.20 (0.06, 4.37) |
| Katsouyanni et al. (2009) | APHENA-U.S. | ≥ 75 | DL(0-2) | 1-h max | 2.30 (-1.33, 6.04) |
| | APHENA-Canada | | DL(0-2) | | 8.96 (0.75,18.6) |
| | APHENA-Canada | | DL(0-2) ^b | | 1.1 (0.10,2.20) |
| | APHENA-europe | | DL(0-2) | | 2.06 (-0.24, 4.31) |
| | APHENA-U.S. | <75 | DL(0-2) | | 3.83 (-0.16, 7.95) |
| | APHENA-Canada | | DL(0-2) | | 7.03 (-2.71, 17.7) |
| | APHENA-Canada | | DL(0-2) ^b | | 0.87 (-0.35, 2.10) |
| | APHENA-europe | | DL(0-2) | | 1.98 (-1.09, 5.13) |
| Summer – Cardiovascular | | | | | |
| Gryparis et al. (2004)^a | 21 European cities | All | 0-1 | 8-h max | 2.7 (1.29,4.32) |
| Samoli et al. (2009) | 21 European cities | | 0-1 | 8-h max | 1.48 (0.18, 2.80) |
| Zanobetti and Schwartz (2008b) | 48 U.S. cities | | 0-3 | 8-h max | 2.42 (1.45, 3.43) |
| Stafoggia et al. (2010) | 10 Italian cities | ≥ 35 | DL(0-5) | 8-h max | 14.3 (6.65, 22.4) |
| Katsouyanni et al. (2009) | APHENA-U.S. | ≥ 75 | DL(0-2) | 1-h max | 3.18 (-0.47, 6.95) |
| | APHENA-Canada | | DL(0-2) | | 1.50 (-2.79, 5.95) |
| | APHENA-Canada | | DL(0-2) ^b | | 0.19 (-0.36, 0.74) |
| | APHENA-europe | | DL(0-2) | | 3.67 (0.95, 6.53) |
| | APHENA-U.S. | <75 | DL(0-2) | | 6.78 (2.70, 11.0) |
| | APHENA-Canada | | DL(0-2) | | -1.02 (-4.23, 2.30) |
| | APHENA-Canada | | DL(0-2) ^b | | -0.13 (-0.55, 0.29) |
| | APHENA-europe | | DL(0-2) | | 2.22 (-1.48, 6.04) |
| Respiratory | | | | | |
| All-years - Respiratory | | | | | |
| Bell et al. (2005)^a | U.S. and non-U.S. | All | NR | 24-h avg | 0.94 (-1.02, 2.96) |
| Wong et al. (2010) | PAPA (4 cities) | | 0-1 | 8-h max | 2.02 (-0.41, 4.49) |
| Katsouyanni et al. (2009) | APHENA-U.S. | | DL(0-2) | 1-h max | 2.54 (-3.32, 8.79) |
| | APHENA-Canada | | DL(0-2) | | 1.02 (-11.9, 15.9) |
| | APHENA-Canada | | DL(0-2) ^b | | 0.13 (-1.60, 1.90) |
| | APHENA-europe | | DL(0-2) | | 1.82 (-2.18, 6.04) |
| | APHENA-U.S. | ≥ 75 | DL(0-2) | | 1.10 (-6.48, 9.21) |
| | APHENA-Canada | | DL(0-2) | | -4.61 (-19.3, 13.3) |
| | APHENA-Canada | | DL(0-2) ^b | | -0.60 (-2.70, 1.60) |
| | APHENA-europe | | DL(0-2) | | 1.10 (-3.48, 5.95) |

| Study* | Location | Ages | Lag | Avg Time | %Increase (95% CI) |
|--|--------------------|------|----------------------|----------|--------------------|
| Summer - Respiratory | | | | | |
| Gryparis et al. (2004)^a | 21 European cities | All | 0-1 | 8-h max | 6.75 (4.38, 9.10) |
| Zanobetti and Schwartz (2008b) | 48 U.S. cities | | 0-3 | 8-h max | 2.51 (1.14, 3.89) |
| Katsouyanni et al. (2009) | APHENA-U.S. | | DL(0-2) | 1-h max | 4.40 (-2.10, 11.3) |
| | APHENA-Canada | | DL(0-2) | | 26.1 (13.3, 41.2) |
| | APHENA-Canada | | DL(0-2) ^b | | 3.00 (1.60, 4.50) |
| | APHENA-europe | | DL(0-2) | | 3.83 (-1.33, 9.21) |
| Samoli et al. (2009) | 21 European cities | | 0-1 | 8-h max | 2.38 (0.65, 4.19) |
| Stafoggia et al. (2010) | 10 Italian cities | ≥ 35 | DL(0-5) | 8-h max | 17.6 (1.78, 35.5) |
| Katsouyanni et al. (2009) | APHENA-U.S. | ≥ 75 | DL(0-2) | 1-h max | 4.07 (-4.23, 13.0) |
| | APHENA-Canada | | DL(0-2) | | 19.5 (2.22, 40.2) |
| | APHENA-Canada | | DL(0-2) ^b | | 2.30 (0.28, 4.40) |
| | APHENA-europe | | DL(0-2) | | 2.46 (-3.40, 8.62) |

*Studies from [Figure 6-36](#), plus others.

^aStudies from the 2006 O₃ AQCD.

^bRisk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O₃ concentrations (Section [6.2.7.2](#)).

1 Collectively, the results from the new multicity studies provide evidence of associations
2 between short-term O₃ exposure and cardiovascular and respiratory mortality with
3 additional evidence indicating these associations persist, and in some cases the magnitude
4 of associations are increased, in the summer season. Although copollutant analyses of
5 cause-specific mortality are limited, the APHENA study found that O₃ cause-specific
6 mortality risk estimates were fairly robust to the inclusion of PM₁₀ in copollutant models
7 when focusing on the dataset with daily PM₁₀ data (i.e., the European dataset), which is
8 supported by the results from [Stafoggia et al. \(2010\)](#). Additionally, APHENA found that
9 O₃ cause-specific mortality risk estimates were moderately to substantially sensitive
10 (e.g., increased or attenuated) to inclusion of PM₁₀ in the U.S. and Canadian
11 datasets. However, the mostly every-6th-day sampling schedule for PM₁₀ in the U.S. and Canadian
12 datasets greatly reduced their sample size and limits the interpretation of these results.

6.6.3 Summary and Causal Determination

13 The evaluation of new multicity studies that examined the association between short-term
14 O₃ exposure and mortality found evidence which supports the conclusions of the 2006 O₃
15 AQCD. These new studies reported consistent positive associations between short-term
16 O₃ exposure and all-cause (nonaccidental) mortality, with associations persisting or
17 increasing in magnitude during the warm season, and provide additional support for
18 associations between O₃ exposure and cardiovascular and respiratory mortality.

1 Recent studies further examined potential confounders (e.g., copollutants and seasonality)
2 of the O₃-mortality relationship. Because the PM-O₃ correlation varies across regions,
3 due to the difference in PM chemical constituents, interpretation of the combined effect
4 of PM on the relationship between O₃ and mortality is not straightforward. Unlike
5 previous studies that were limited to primarily examining the confounding effects of
6 PM₁₀, the new studies expanded their analyses to include multiple PM indices (e.g., PM₁₀,
7 PM_{2.5}, and PM components). An examination of copollutant models found evidence that
8 associations between O₃ and all-cause mortality were robust to the inclusion of PM₁₀ or
9 PM_{2.5} ([Stafoggia et al., 2010](#); [Katsouyanni et al., 2009](#); [Bell et al., 2007](#)), while other
10 studies found evidence for a modest reduction (~20-30%) when examining PM₁₀ ([Smith
11 et al., 2009b](#)). Additional evidence suggests potential sensitivity (e.g., increases and
12 attenuation) of O₃ mortality risk estimates to copollutants by age group or cause-specific
13 mortality (e.g., respiratory and cardiovascular) ([Stafoggia et al., 2010](#); [Katsouyanni et al.,
14 2009](#)). An examination of PM components, specifically sulfate, found evidence for
15 reductions in O₃-mortality risk estimates in copollutant models ([Franklin and Schwartz,
16 2008](#)). Overall, across studies, the potential impact of PM indices on O₃-mortality risk
17 estimates tended to be much smaller than the variation in O₃-mortality risk estimates
18 across cities suggesting that O₃ effects are independent of the relationship between PM
19 and mortality. However, interpretation of the potential confounding effects of PM on
20 O₃-mortality risk estimates requires caution. This is because the PM-O₃ correlation varies
21 across regions, due to the difference in PM components, complicating the interpretation
22 of the combined effect of PM on the relationship between O₃ and mortality. Additionally,
23 the limited PM or PM component datasets used as a result of the every-3rd- and 6th-day
24 PM sampling schedule instituted in most cities limits the overall sample size employed to
25 examine whether PM or one of its components confounds the O₃-mortality relationship.

26 An examination of potential seasonal confounding of the O₃-mortality relationship found
27 that the extent of smoothing or the methods used for adjustment can influence O₃ risk
28 estimates when not applying enough degrees of freedom to control for temporal/season
29 trends ([Katsouyanni et al., 2009](#)). This is because of the opposing seasonal trends
30 between O₃ and mortality.

31 The multicity studies evaluated within this section also examined the regional
32 heterogeneity observed in O₃-mortality risk estimates. These studies provide evidence
33 which suggests generally higher O₃-mortality risk estimates in northeastern U.S. cities
34 with some regions showing no associations between O₃ exposure and mortality
35 (e.g., Southwest, Urban Midwest) ([Smith et al., 2009b](#); [Bell and Dominici, 2008](#)).
36 Multicity studies that examined individual- and community-level characteristics
37 identified characteristics that may explain the observed regional heterogeneity in
38 O₃-mortality risk estimates as well as characteristics of populations potentially at greatest

1 risk for O₃-related health effects. An examination of community-level characteristics
2 found an increase in the O₃-mortality risk estimates in cities with higher unemployment,
3 percentage of the population Black/African-American, percentage of the working
4 population that uses public transportation, lower temperatures, and lower prevalence of
5 central air conditioning ([Medina-Ramón and Schwartz, 2008](#)). Additionally, a potential
6 interactive, or synergistic, effect on the O₃-mortality relationship was observed when
7 examining differences in the O₃-mortality association across temperature levels ([Ren et
8 al., 2008](#)). An examination of individual-level characteristics found evidence that older
9 age, female sex, Black race, having atrial fibrillation, SES indicators (i.e., educational
10 attainment, income level, and employment status), and out-of hospital deaths, specifically
11 in those individuals with diabetes, modify O₃-mortality associations ([Cakmak et al.,
12 2011](#); [Stafoggia et al., 2010](#); [Medina-Ramón and Schwartz, 2008](#)), and lead to increased
13 risk of O₃-related mortality. Overall, additional research is warranted to further confirm
14 whether these characteristics, individually or in combination, can explain the observed
15 regional heterogeneity.

16 Additional studies were evaluated that examined factors that may influence the shape of
17 the O₃-mortality C-R curve, such as multi-day effects, mortality displacement, adaptation,
18 the use of different exposure metrics (i.e., 24-h avg, 8-h max or 1-h max), and whether a
19 threshold exists in the O₃-mortality relationship. An examination of multiday effects in a
20 U.S. and European multicity study found conflicting evidence for mortality displacement,
21 but both studies suggest that the positive associations between O₃ and mortality are
22 observed mainly in the first few days after exposure ([Samoli et al., 2009](#); [Zanobetti and
23 Schwartz, 2008b](#)). A U.S. multicity study found evidence of an adaptive response to O₃
24 exposure, with the highest risk estimates earlier in the O₃ season (i.e., July) and
25 diminished effects later (i.e., August) ([Zanobetti and Schwartz, 2008a](#)). However, the
26 evidence of adaptive effects has an implication for the interpretation of multi-day effects,
27 and requires further analysis. The limited number of studies conducted that examined the
28 effect of using different exposure metrics (i.e., 1-h max, 8-h max, and 24-h avg) when
29 examining the O₃-mortality relationship found relatively comparable O₃-mortality risk
30 estimates across the exposure metrics used ([Smith et al., 2009b](#); [Gryparis et al., 2004](#)).
31 Analyses that specifically focused on the O₃-mortality C-R relationship supported a linear
32 O₃-mortality relationship and found no evidence of a threshold within the range of O₃
33 concentrations in the U.S., but did observe evidence for potential differences in the C-R
34 relationship across cities ([Katsouyanni et al., 2009](#); [Stylianou and Nicolich, 2009](#); [Bell et
35 al., 2006](#)). Collectively, these studies support the conclusions of the 2006 O₃ AQCD that
36 “if a population threshold level exists in O₃ health effects, it is likely near the lower limit
37 of ambient O₃ concentrations in the U.S.”

1 Studies that examined the association between short-term O₃ exposure and cause-specific
2 mortality confirm the associations with both cardiovascular and respiratory mortality
3 reported in the 2006 O₃ AQCD ([Stafoggia et al., 2010](#); [Wong et al., 2010](#); [Katsouyanni et](#)
4 [al., 2009](#); [Samoli et al., 2009](#); [Zanobetti and Schwartz, 2008b](#)). These associations were
5 primarily larger in magnitude during the summer season compared to all-year analyses.
6 Of the studies that examined the potential confounding effects of PM [i.e., [Stafoggia et al.](#)
7 [\(2010\)](#); [Katsouyanni et al. \(2009\)](#)], O₃ mortality associations remained relatively robust
8 in copollutant models, but interpretation of these studies was complicated by the different
9 PM sampling schedules (e.g., every-6th-day) employed in each study. Overall, the strong
10 evidence for respiratory effects due to short-term O₃ exposure (Section [6.2](#)) are consistent
11 across disciplines and provides coherence for the respiratory mortality associations
12 observed across studies. However, the strong evidence for O₃-induced cardiovascular
13 mortality is complicated by toxicological studies that provide initial evidence for a
14 biologically plausible mechanism for O₃-induced cardiovascular mortality, but a lack of
15 coherence with controlled human exposure and epidemiologic studies of cardiovascular
16 morbidity that do not demonstrate consistent evidence of O₃-induced cardiovascular
17 effects (Section [6.3](#)).

18 In conclusion, the recent epidemiologic studies build upon and confirm the associations
19 between short-term O₃ exposure and all-cause and cause-specific mortality reported in the
20 2006 O₃ AQCD. However, there is a lack of coherence across disciplines and consistency
21 across health outcomes for O₃-induced cardiovascular morbidity (Section [6.3](#)) which do
22 not support the relatively strong epidemiologic evidence for O₃-related cardiovascular
23 mortality. Overall, recent studies have provided additional information regarding key
24 uncertainties (previously identified - including the potential confounding effects of
25 copollutants and seasonal trend), individual- and community-level factors that may lead
26 to increased risk of O₃-induced mortality and the heterogeneity in O₃-mortality risk
27 estimates, and continued evidence of a linear no-threshold C-R relationship. Although
28 some uncertainties still remain, the collective body of evidence is sufficient to conclude
29 that there **is likely to be a causal relationship between short-term O₃ exposure and**
30 **total mortality.**

6.7 Overall Summary

31 The evidence reviewed in this chapter describes the recent findings regarding the health
32 effects of short-term exposure to ambient O₃ concentrations. [Table 6-54](#) provides an
33 overview of the causal determinations for each of the health categories evaluated.

Table 6-54 Summary of causal determinations for short-term exposures to ozone.

| Health Category | Causal Determination |
|--|---|
| Respiratory Effects | Causal relationship |
| Cardiovascular Effects | Suggestive of a causal relationship |
| Central Nervous System Effects | Suggestive of a causal relationship |
| Effects on Liver and Xenobiotic Metabolism | Inadequate to infer a causal relationship |
| Effects on Cutaneous and Ocular Tissues | Inadequate to infer a causal relationship |
| Total Mortality | Likely to be a causal relationship |

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7 INTEGRATED HEALTH EFFECTS OF LONG-TERM O₃ EXPOSURE

7.1 Introduction

1 This chapter reviews, summarizes, and integrates the evidence on relationships between
2 health effects and long-term exposures to O₃. Both epidemiologic and toxicological
3 studies provide a basis for examining long-term O₃ exposure health effects for respiratory
4 effects, cardiovascular effects, reproductive and developmental effects, central nervous
5 system effects, cancer outcomes, and mortality. Long-term exposure has been defined as
6 a duration of approximately 30 days (1 month) or longer¹. However, in order to
7 characterize the weight of evidence for the effects of O₃ on reproductive and
8 developmental effects in a consistent, cohesive and integrated manner, results from both
9 short-term and long-term exposure periods are included in that section, and are identified
10 accordingly in the text and tables.

11 Conclusions from the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) are summarized briefly at the
12 beginning of each section, and the evaluation of evidence from recent studies builds upon
13 what was available during the previous review. For each health outcome (e.g., respiratory
14 disease, lung function), results are summarized for studies from the specific scientific
15 discipline, i.e., epidemiologic and toxicological studies. The major sections
16 (i.e., respiratory, cardiovascular, mortality, reproductive/developmental, cancer) conclude
17 with summaries of the evidence for the various health outcomes within that category and
18 integration of the findings that lead to conclusions regarding causality based upon the
19 framework described in the Preamble to this ISA. Determination of causality is made for
20 the overall health effect category, such as respiratory effects, with coherence and
21 plausibility being based on evidence from across disciplines and also across the suite of
22 related health outcomes, including cause-specific mortality.

23 As mentioned in Chapter 2 (Section 2.3), epidemiologic studies generally present O₃-
24 related effect estimates for mortality and morbidity health outcomes based on an
25 incremental change in exposure. Studies traditionally present the relative risk per an
26 incremental change equal to the interquartile range in O₃ concentrations or some other
27 arbitrary value (e.g., 10 ppb). Additionally, various exposure metrics are used in O₃
28 epidemiologic studies, with the three most common being the maximum 1-h average
29 within a 24-h period (1-h max), the maximum 8-h average within a 24-h period
30 (8-h max), and 24-h average (24-h avg). For the purpose of presenting results from

¹ Unless otherwise specified, the term “chronic” generally refers to an annual exposure duration for epidemiology studies and a duration of greater than 10% of the lifespan of the animal in toxicological studies.

1 studies that use different exposure metrics, EPA consistently applies the same O₃
2 increments to facilitate comparisons between the results of various studies that may
3 present results for different incremental changes. Differences due to the use of varying
4 exposure metrics (e.g., 1-h max, 24-h avg) become less apparent when averaged across
5 longer exposure periods, because levels are typically lower and less variable. As such,
6 throughout this chapter an increment of 10 ppb was consistently applied across studies,
7 regardless of exposure metric, to facilitate comparisons between the results from these
8 studies.

7.2 Respiratory Effects

9 Studies reviewed in the 2006 O₃ AQCD examined evidence for relationships between
10 long-term O₃ exposure (several months to yearly) and effects on respiratory health
11 outcomes including declines in lung function, increases in inflammation, and
12 development of asthma in children and adults. Animal toxicology data provided a clearer
13 picture indicating that long-term O₃ exposure may have lasting effects. Chronic exposure
14 studies in animals have reported biochemical and morphological changes suggestive of
15 irreversible long-term O₃ impacts on the lung. In contrast to supportive evidence from
16 chronic animal studies, the epidemiologic studies on longer-term (annual) lung function
17 declines, inflammation, and new asthma development remained inconclusive.

18 Several studies reviewed in the 2006 O₃ AQCD ([Horak et al., 2002](#); [Frischer et al., 1999](#))
19 collectively indicated that O₃ exposure averaged over several summer months was
20 associated with smaller increases in lung function growth in children. For longer
21 averaging periods (annual), the definitive analysis in the Children's Health Study (CHS)
22 reported by [Gauderman et al. \(2004\)](#) provided little evidence that such long-term
23 exposure to ambient O₃ was associated with significant deficits in the growth rate of lung
24 function in children in contrast to the effects observed with other pollutants such as acid
25 vapor, NO₂, and PM_{2.5}. Limited epidemiologic research examined the relationship
26 between long-term O₃ exposures and inflammation. Consistent with evidence of
27 inflammation and allergic responses reported in experimental studies, an association
28 between 30-day average O₃ and increased eosinophil levels was observed in an Austrian
29 study ([Frischer et al., 2001](#)). The cross-sectional studies available for the 2006 O₃ AQCD
30 detected no associations between long-term O₃ exposures and asthma prevalence, asthma-
31 related symptoms or allergy to common aeroallergens in children after controlling for
32 covariates. However, longitudinal studies provided evidence that long-term O₃ exposure
33 influences the risk of asthma development in children ([McConnell et al., 2002](#)) and adults
34 ([McDonnell et al., 1999a](#); [Greer et al., 1993](#)).

1 New evidence presented below reports interactions between genetic variants and long-
2 term O₃ exposure in effects on new onset asthma in U.S. cohorts in multi-community
3 studies where protection by specific oxidant gene variants was restricted to children
4 living in low O₃ communities. Related studies report coherent relationships between
5 respiratory symptoms among asthmatics and long-term O₃ exposure. Short-term exposure
6 to O₃ is associated with increases in respiratory symptoms and asthma medication use in
7 children with asthma (Section [6.2.4.1](#)) and asthma hospitalizations in children
8 (Section [6.2.7.2](#)). A new line of evidence reports a positive concentration-response
9 relationship between first asthma hospitalization and long-term O₃ exposure. Results
10 from recent studies examining pulmonary function, inflammation, and allergic responses
11 are also presented.

7.2.1 Asthma

7.2.1.1 New Onset Asthma

12 Asthma is a heterogeneous disease with a high degree of temporal variability. Its
13 progression and symptoms can vary within an individual's experience over time. The
14 course of asthma may vary markedly between young children, older children and
15 adolescents, and adults. This variation is probably more dependent on age than on
16 symptoms ([NHLBI, 2007](#)). Longitudinal cohort studies have examined associations
17 between long-term O₃ exposures and the onset of asthma in adults and children
18 ([McConnell et al., 2002](#); [McDonnell et al., 1999a](#); [Greer et al., 1993](#)), with results
19 indicating a direct effect of long-term O₃ exposure on asthma risk in adults and effect
20 modification by O₃ in children.

21 Associations between long-term O₃ exposure and new cases of asthma were reported in a
22 cohort of nonsmoking adults in California ([McDonnell et al., 1999a](#); [Greer et al., 1993](#)).
23 The Adventist Health and Smog (AHSMOG) study cohort of 3,914 (age 27 to 87 years,
24 36% male) was drawn from nonsmoking, non-Hispanic white California Seventh Day
25 Adventists, who were surveyed in 1977, 1987, and 1992. To be eligible, subjects had to
26 have lived 10 or more years within 5 miles of their current residence in 1977. Residences
27 from 1977 onward were followed and linked in time and space to interpolate
28 concentrations of O₃, PM₁₀, SO₄²⁻, SO₂, and NO₂. New asthma cases were defined as self-
29 reported doctor-diagnosed asthma at either the 1987 or 1992 follow-up questionnaire
30 among those who had not reported having asthma upon enrollment in 1977. During the
31 10-year follow-up (1977 to 1987), the incidence of new asthma was 2.1% for males and
32 2.2% for females ([Greer et al., 1993](#)). Ozone concentration data were not provided. A

1 relative risk of 3.12 (95% CI: 1.16, 5.85) per 10-ppb increase in annual mean O₃
2 (exposure metric not stated) was observed in males, compared to a relative risk of 0.94
3 (95% CI: 0.65, 1.34) in females.

4 In the 15-year follow-up study (1977-1992), 3.2% of the eligible males and a slightly
5 greater 4.3% of the eligible females developed adult asthma ([McDonnell et al., 1999a](#)).
6 The mean 20-year average (1973-1992) for 8-h avg O₃ (9 a.m. to 5 p.m.) was 46.5 ppb
7 (SD 15.3). For males, the relative risk of developing asthma was 1.31 (95% CI: 1.01,
8 1.71) per 10-ppb increase in 8-h avg O₃. Once again, there was no evidence of a positive
9 association between O₃ and new-onset asthma in females (relative risk of 0.94 [95% CI:
10 0.87, 1.02]). The lack of an association does not necessarily indicate no effect of O₃ on
11 the development of asthma among females. For example, differences between females
12 and males in time-activity patterns may influence relative exposures to ambient O₃.
13 During summer 1992, the mean (SD) hours per week spent outdoors for male and female
14 asthma cases were 13.8 (10.6) and 11.4 (10.9), respectively, indicating potential greater
15 misclassification of exposure in females. None of the other pollutants (PM₁₀, SO₄²⁻, SO₂,
16 and NO₂) were associated with development of asthma in either males or females.
17 Adjusting for copollutants did not diminish the association between O₃ and asthma
18 incidence for males. In no case was the O₃ coefficient reduced by more than 10% in the
19 two-pollutant models compared to the model containing O₃ alone. The consistency of the
20 results in the two studies with different follow-up times, as well as the independent and
21 robust association between annual mean O₃ concentrations and asthma incidence, provide
22 supportive evidence that long-term O₃ exposure may be associated with the development
23 of asthma in adult males. However, because the AHSMOG cohort was drawn from a
24 narrow subject definition, the representativeness of this cohort to the general U.S.
25 population may be limited.

26 In children, the relationship between long-term O₃ exposure and new onset asthma has
27 been extensively investigated in the CHS. In this cohort, evidence provides stronger
28 support for long-term O₃ exposure modifying the risk of new onset asthma associated
29 with other potential risk factors than having a main effect on new onset asthma. Initiated
30 in the early 1990s, the CHS was originally designed to examine whether long-term
31 exposure to ambient pollutants was related to chronic respiratory outcomes in children in
32 12 communities in southern California ([Peters et al., 1999b](#); [Peters et al., 1999a](#)). New-
33 onset asthma was classified as having no prior history of asthma at study entry with
34 subsequent report of physician-diagnosed asthma at follow-up with the date of onset
35 assigned to be the midpoint of the interval between the interview date when asthma
36 diagnosis was first reported and the previous interview date. In a cohort recruited during
37 2002-2003 and followed for three years beginning in kindergarten or first grade,
38 [McConnell et al. \(2010\)](#) reported a hazard ratio for new onset asthma of 0.76 (95% CI:

1 0.38, 1.54) comparing the communities with the highest (59.8 ppb) and lowest (29.5 ppb)
2 annual average of 8-h avg (10 a.m.-6 p.m.) O₃. With adjustment for school and residential
3 modeled non-freeway traffic-related exposure, the estimated HR for O₃ was 1.01
4 (95% CI: 0.49, 2.11).

5 Similarly in a cohort recruited in 1993, asthma risk was not higher for residents of the six
6 high-O₃ communities versus residents of the six low-O₃ communities ([McConnell et al.,
7 2002](#)). In this study, 3,535 initially nonasthmatic children (ages 9 to 16 years at
8 enrollment) were followed for up to 5 years, during which 265 cases of new-onset asthma
9 were identified. Communities were stratified by 4-year average 1-h max O₃ levels, with
10 six high-O₃ communities (mean 75.4 ppb [SD 6.8]) and six low-O₃ communities (mean
11 50.1 ppb [SD 11.0]). Within the high-O₃ communities, asthma risk was 3.3 (95% CI: 1.9,
12 5.8) times greater for children who played three or more sports as compared with children
13 who played no sports. None of the children who lived in high-O₃ communities and played
14 three or more sports had a family history of asthma. In models with individual sports
15 entered as dummy variables, only tennis was significantly associated with asthma and
16 only in the high O₃ communities. This association was absent in the low-O₃ communities
17 (relative risk of 0.8 [95% CI: 0.4, 1.6]). The overall observed pattern of effects of sports
18 participation on asthma risk was robust to adjustment for SES, history of allergy, family
19 history of asthma, insurance, maternal smoking, and BMI.

20 Analyses aimed at distinguishing the effects of O₃ from effects of other pollutants
21 indicated that in communities with high O₃ and low levels of other pollutants there was a
22 4.2-fold (95% CI: 1.6, 10.7) increased risk of asthma in children playing three or more
23 sports, compared to children who played no sports. The relative risk in children playing
24 three or more sports was slightly lower (3.3 [95% CI: 1.6, 6.9]) in communities with a
25 combination of high levels of O₃ and other pollutants. Ozone concentrations were not
26 strongly correlated with PM₁₀, PM_{2.5}, NO₂, or inorganic acid vapors, and no associations
27 with asthma were found for these other pollutants. These results provide additional
28 support that the effects of physical activity on asthma are modified by long-term
29 O₃ exposure. Overall, the results from [McConnell et al. \(2002\)](#) suggest that playing sports
30 may indicate greater outdoor activity when O₃ levels are higher and an increased
31 ventilation rate, which may lead to increased O₃ exposure. It should be noted, however,
32 that these findings were based on a small number of new asthma cases (n = 29 among
33 children who played three or more sports) and were not based on a priori hypotheses.

34 Recent studies from the CHS provide evidence for gene-environment interactions in
35 effects on new-onset asthma by indicating that the lower risks associated with specific
36 genetic variants are found in children who live in lower O₃ communities ([Islam et al.,
37 2009](#); [Islam et al., 2008](#); [Oryszczyn et al., 2007](#); [Lee et al., 2004b](#); [Gilliland et al., 2002](#)).

1 Risk for new-onset asthma is related in part to genetic susceptibility, behavioral factors
2 and environmental exposure ([Gilliland et al., 1999](#)). Gene-environment interactions in
3 asthma have been well discussed in the literature ([von Mutius, 2009](#); [Holgate et al., 2007](#);
4 [Martinez, 2007a, b](#); [Rahman et al., 2006](#); [Hoffjan et al., 2005](#); [Kleeberger and Peden,](#)
5 [2005](#); [Ober, 2005](#)). Complex chronic diseases, such as asthma, are partially the result of a
6 sequence of biochemical reactions involving exposures to various environmental agents
7 metabolized by a number of different genes ([Conti et al., 2003](#)). Oxidative stress has been
8 proposed to underlie these mechanistic hypotheses ([Gilliland et al., 1999](#)). Genetic
9 variants may impact disease risk directly or modify disease risk by affecting internal dose
10 of pollutants and other environmental agents and/or their reaction products or by altering
11 cellular and molecular modes of action. Understanding the relation between genetic
12 polymorphisms and environmental exposure can help identify high-risk subgroups in the
13 population and provide better insight into pathway mechanisms for these complex
14 diseases.

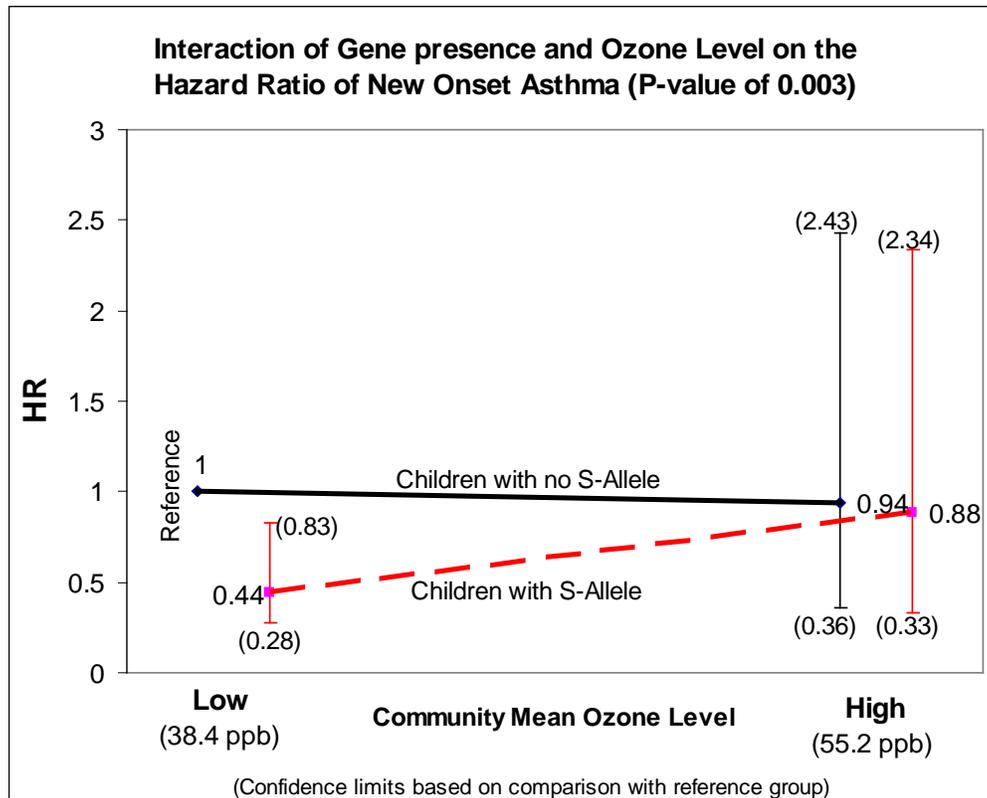
15 CHS analyses have found that asthma risk is related to interactions between O₃ and
16 variants in genes for enzymes such as heme-oxygenase (HO-1), arginases (ARG1 and 2),
17 and glutathione S transferase P1 (GSTP1) ([Himes et al., 2009](#); [Islam et al., 2008](#); [Li et al.,](#)
18 [2008](#); [Hanene et al., 2007](#); [Ercan et al., 2006](#); [Li et al., 2006a](#); [Tamer et al., 2004](#);
19 [Gilliland et al., 2002](#)). Biological plausibility for these findings is provided by evidence
20 that these enzymes have antioxidant and/or anti-inflammatory activity and participate in
21 well recognized modes of action in asthma pathogenesis. Further, several lines of
22 evidence demonstrate that secondary oxidation products of O₃ initiate the key modes of
23 action that mediate downstream health effects (Section [5.3.2](#)). For example, HO-1 has
24 been found to respond rapidly to oxidants, have anti-inflammatory and anti-oxidant
25 effects ([Exner et al., 2004](#)), relax airway smooth muscle, and be induced in airways
26 during asthma ([Carter et al., 2004](#)). The GSTP1 Val/Val genotype has been associated
27 with increased risk of having atopic asthma ([Tamer et al., 2004](#)). Gene-environment
28 interactions are discussed in greater detail in Section [5.4.2.1](#).

29 [Islam et al. \(2008\)](#) found that functional polymorphisms of the heme oxygenase-1 gene
30 (HMOX-1, [(GT)_n repeat]) influenced the risk of new-onset asthma, depending on
31 ethnicity and long-term community O₃ concentrations. Ozone-gene interactions were not
32 found for variants in other antioxidant genes: catalase (CAT [-262C >T -844C >T0]) or
33 and manganese superoxide dismutase (MNSOD, [Ala-9Val]). Analyses were restricted to
34 children of Hispanic (n = 576) or non-Hispanic white ethnicity (n = 1,125) and were
35 conducted with long-term pollutant levels averaged from 1994 to 2003. The effect of
36 ambient air pollution on the relationship between genetic polymorphism and new-onset
37 asthma was assessed using Cox proportional hazard regression models where the
38 community specific average air pollution levels were fitted as a continuous variable

1 together with the appropriate interaction terms for genes and air pollutants and a random
2 effect of community ([Berhane et al., 2004](#)).

3 Over the follow-up period, 160 new cases of asthma were diagnosed ([Islam et al., 2008](#)).
4 For HMOX-1, the interaction ($p = 0.003$) indicated a greater protective effect of the
5 S-allele (short, <23 (GT) $_n$ repeats) compared to the L-allele (long, >23 repeats) among
6 non-Hispanic white children who lived in the low O₃ community (nonparallelism
7 presented in [Figure 7-1](#)). Among children residing in low-O₃ communities, the hazard
8 ratio (HR) of new onset asthma associated with the S-allele was 0.44 (95% CI: 0.23,
9 0.83) compared to non-Hispanic white children who lived in low O₃ communities and had
10 no S-alleles. Biological plausibility for these results is provided by evidence that the
11 S-allele variant of HMOX-1 is more readily induced than those with more numerous
12 repeats. The S-allele was found to have a less protective effect in non-Hispanic white
13 children who resided in high O₃ communities (HR = 0.88; [95% CI: 0.33, 2.34] compared
14 to non-Hispanic white children in low O₃ communities with no S-allele). Because
15 HMOX-1 variants were not associated with asthma risk in Hispanic children, effect
16 modification by O₃ was not investigated. No significant interactions were observed
17 between PM₁₀ or other pollutants and the HMOX-1 gene; quantitative results were not
18 presented. Average O₃ levels showed low correlation with the other monitored pollutants.
19 The authors did not consider the lack of adjustment for multiple testing to be a concern in
20 this analysis because the selection of the genes was based on a priori hypotheses defined
21 by a well-studied biological pathway, in which oxidative stress serves as the link among
22 O₃ exposure, enzyme activity, and asthma.

23 Collectively, results from [Islam et al. \(2008\)](#) indicate that a variant in HMOX-1 that
24 produces a more readily inducible enzyme is associated with lower risk of new-onset
25 asthma in children who live in low O₃ communities. Results were not presented for the
26 main effects relating new-onset asthma to O₃ exposure. However, they do indicate that
27 that in environments of low ambient O₃, enzymes with greater antioxidative activity may
28 have the capacity to counter any temporary imbalance in an oxidant-antioxidant
29 relationship. However, in the presence of high background O₃, the protective effect may
30 be attenuated because with higher exposure to oxidants, the antioxidant genes may be at
31 their maximal level of inducibility, and variation in promoters no longer affects levels of
32 expression. Supporting evidence is provided by [Schroer et al. \(2009\)](#), who found that
33 infants with multiple environmental exposures were at increased risk of wheeze
34 regardless of variant in GSTP1, which encodes a gene with antioxidant activity.



Note: An interaction p-value of 0.003 was obtained from the hierarchical two stage Cox proportional hazard model fitting the community specific O₃ and controlling for random effect of the communities. The interaction indicates there is a greater protective effect of having a heme-oxygenase S-allele compared to having the L-allele among children living in communities with lower long-term ambient ozone concentrations. The HRs are off-set as opposed to overlapping in the figure to allow clearer presentation of the results.

Source: Developed by EPA with data from [Islam et al. \(2008\)](#) (data used with permission of American Thoracic Society).

Figure 7-1 Interaction of heme-oxygenase genetic variants and O₃ level on the Hazard Ratio (HR) of new-onset asthma in the 12 Children’s Health Study communities.

1 Expanding on the results of [McConnell et al. \(2002\)](#), [Islam et al. \(2009\)](#) provided
 2 evidence that variants in GSTM1 and GSTP1 may influence associations between
 3 outdoor exercise and new onset asthma. A primary conclusion that the authors ([Islam et
 4 al., 2009](#)) reported was that the GSTP1 Ile/Ile and GSTM1 null genotypes increased risk
 5 of new onset asthma during adolescence. The highest risk was found for participation in
 6 three or more team sports (compared to no sports) among children with GSTP1 Ile/Ile
 7 genotype living in high-O₃ communities (HR: 6.15, [95% CI: 2.2, 7.4]). No three-way
 8 interaction was found for GSTM1. These results demonstrate the potential importance of
 9 a combination of genetic variability, O₃ exposure, and outdoor activity on asthma risk. It
 10 is important to note that while some studies have found a modifying role of air pollution

1 on the association between GSTP1 Ile/Ile and asthma in children ([Lee et al., 2004b](#)),
2 others have found that the GSTP1 Val/Val variant to be associated with greater asthma
3 prevalence and increase the risk of O₃-associated respiratory morbidity (see discussion in
4 Section [6.2.4.1](#)).

5 The CHS also provided evidence of interactions between O₃ exposure and variants in
6 genes for arginase ([Salam et al., 2009](#)). Arginase catalyzes the conversion of L-arginine.
7 Because L-arginine is a precursor of NO, higher arginase activity can limit production of
8 NO and subsequent nitrosative stress. Epidemiologic evidence of associations of arginase
9 variants with asthma are limited ([Li et al., 2006a](#)); however, asthmatic subjects have been
10 found to have higher arginase activity than non-asthmatic subjects ([Morris et al., 2004](#)).
11 The modifying effect of O₃ and atopy on the association between ARG1 and ARG2
12 haplotypes and asthma were evaluated using likelihood ratio tests with appropriate
13 interaction terms. Having more copies of the ARG1h4 haplotype (compared to having
14 zero copies) was associated with lower odds of asthma, particularly among children with
15 atopic asthma living in high O₃ communities (OR: 0.12; [95% CI: 0.04, 0.43]). Having
16 more copies of the ARG2h3 haplotype (compared to having zero copies) was associated
17 with increased risk of childhood-onset asthma among children in both low and high O₃
18 communities. The implications of findings are somewhat limited because the functional
19 relevance of the ARG1 and ARG2 variants is not clear.

7.2.1.2 Prevalence of Asthma and Asthma Symptoms

20 Some cross-sectional studies reviewed in the 2006 O₃ AQCD observed positive
21 relationships between chronic exposure to O₃ and prevalence of asthma and asthmatic
22 symptoms in school children ([Ramadour et al., 2000](#); [Wang et al., 1999](#)) while others
23 ([Kuo et al., 2002](#); [Charpin et al., 1999](#)) did not. Recent studies provide additional
24 evidence.

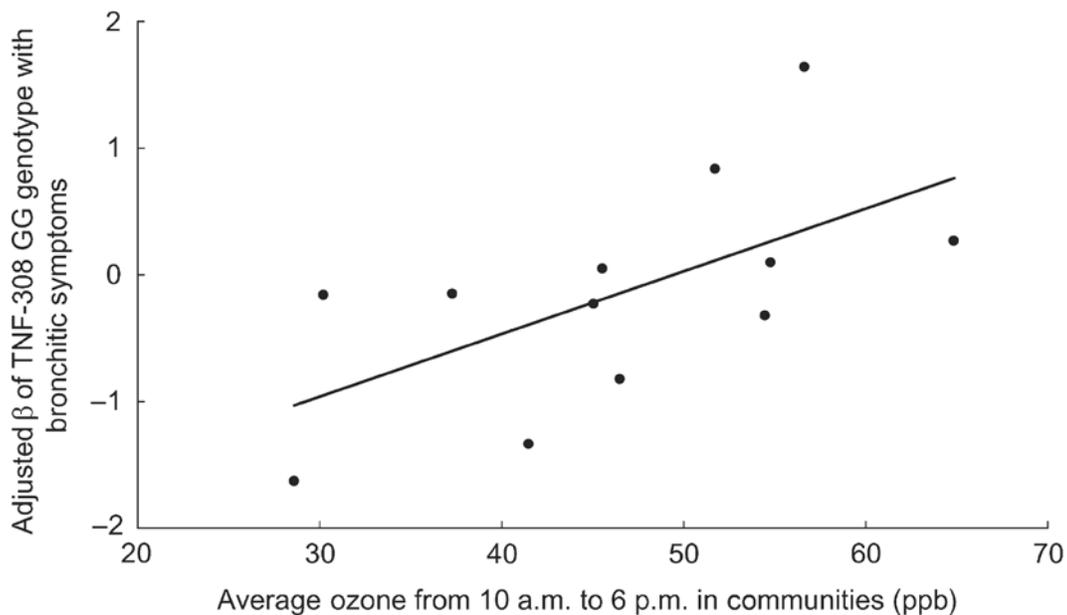
25 In a cross-sectional nationwide study of 32,672 Taiwanese school children, [Hwang et al.](#)
26 [\(2005\)](#) assessed the effects of air pollutants on the risk of asthma. The study population
27 was recruited from elementary and middle schools within 1 km of air monitoring stations.
28 The risk of asthma was related to O₃ in the one-pollutant model. The addition of other
29 pollutants (NO_x, CO₂, SO₂, and PM₁₀), in two-pollutant and three-pollutant models,
30 increased the O₃ risk estimates. The prevalence of childhood asthma was assessed in
31 Portugal by contrasting the risk of asthma between a high O₃ rural area and an area with
32 low O₃ levels ([Sousa et al., 2011](#); [Sousa et al., 2009](#); [Sousa et al., 2008](#)). The locations
33 were selected to provide a difference in O₃ levels without the confounding effects of
34 other pollutants. Both evaluation for asthma symptoms and FEV₁ suggested that O₃

1 increased asthma prevalence. [Clark et al. \(2010\)](#) investigated the effect of exposure to
2 ambient air pollution in utero and during the first year of life on risk of subsequent
3 incidence asthma diagnosis up to 3-4 years of age in a population-based nested case-
4 control study for all children born in southwestern British Columbia in 1999 and 2000
5 (n = 37,401; including 3,482 [9.3%] with asthma). Air pollution exposure for each
6 subject was estimated based on their residential address history using regulatory
7 monitoring data, land use regression modeling, and proximity to stationary pollutant
8 sources. Daily values from the three closest monitors within 50 km were used to calculate
9 exposures. Traffic-related pollutants were associated with the highest risk. Ozone was
10 inversely correlated with the primary traffic-related pollutants (r = -0.7 to -0.9). The low
11 reliability of asthma diagnosis in infants makes this study difficult to interpret ([Martinez
12 et al., 1995](#)). In a cross-sectional analysis, [Akinbami et al. \(2010\)](#) examined the
13 association between chronic exposure to outdoor pollutants (12-month avg levels by
14 county) and asthma outcomes in a national sample of children ages 3-17 years living in
15 U.S. metropolitan areas (National Health Interview Survey, N = 34,073). A 5-ppb
16 increase in estimated 8-h max O₃ concentration (annual average) yielded a positive
17 association for both currently having asthma and for having at least 1 asthma attack in the
18 previous year, while the adjusted odds ratios for other pollutants were not statistically
19 significant. Models in which pollutant value ranges were divided into quartiles produced
20 comparable results. Multi-pollutant models (SO₂ and PM) produced similar results. The
21 median value for 12-month avg O₃ levels was 39.5 ppb and the IQR was 35.9-43.7 ppb.
22 The adjusted odds for current asthma for the highest quartile (49.9-59.5 ppb) of estimated
23 O₃ exposure was 1.56 (95% CI: 1.15, 2.10) with a positive concentration-response
24 relationship apparent from the lowest quartile to the highest. Thus, this cross-sectional
25 analysis and [Hwang et al. \(2005\)](#) provides further evidence relating O₃ exposure and the
26 risk of asthma.

27 Relationships between long-term exposure and respiratory symptoms in asthmatic
28 children also were examined in the CHS. [McConnell et al. \(1999\)](#) examined the
29 association between O₃ levels and the prevalence of chronic lower respiratory tract
30 symptoms in 3,676 cohort children with asthma. In this cross-sectional study, bronchitis,
31 phlegm, and cough were not associated with annual mean 1-h max O₃ concentrations in
32 children with asthma or wheeze. All other pollutants examined (PM₁₀, PM_{2.5}, NO₂, and
33 gaseous acid) were associated with an increase in phlegm but not cough. The mean
34 annual average 1-h max O₃ concentration was 65.6 ppb (range 35.5 to 97.5) across the
35 12 communities. In another CHS analysis, [McConnell et al. \(2003\)](#) evaluated
36 relationships between air pollutants and bronchitic symptoms among 475 children with
37 asthma. The mean 4-year average 8-h avg O₃ (10 a.m.-6 p.m.) concentration was
38 47.2 ppb (range 28.3 to 65.8) across the 12 communities. For a 10-ppb increase in
39 8-h avg O₃ averaged over 4 years, the between-community odds ratio was 0.90 (95% CI:

1 0.82, 1.00) whereas the within-community (i.e., difference between one- and four-year
2 average) odds ratio was larger, i.e., 1.79 (95% CI: 1.00, 3.21). The authors commented
3 that if the larger within-community effect estimates were correct, then other cross-
4 sectional (between-community) studies might have underestimated the true effect of air
5 pollution on bronchitic symptoms in children. These differences might be attributable to
6 confounding by poorly measured or unmeasured risk factors that vary between
7 communities. Within community effects may more accurately represent risk associated
8 with pollutant exposure because the analyses characterize health effects associated with
9 changing pollutant concentrations within a community, thereby minimizing potential
10 confounding by factors that are constant over time within a community. PM_{2.5}, NO₂, and
11 organic carbon also were associated with bronchitic symptoms. In two-pollutant models,
12 the within-community effect estimates for O₃ were markedly reduced and no longer
13 statistically significant in some cases.

14 CHS also examined interactions between TNF- α 308 genotype and long-term O₃
15 exposure in the occurrence of bronchitic symptoms among children with asthma ([Lee et](#)
16 [al., 2009b](#)). Increased airway levels of the cytokine TNF- α has been related to
17 inflammation, and the GG genotype has been linked to lower expression of TNF- α .
18 Asthmatic children with the GG genotype had a lower prevalence of bronchitic symptoms
19 compared with children carrying at least one A-allele (e.g., GA or AA genotype). Low-
20 versus high-O₃ strata were defined as less than or greater than 50- ppb O₃ avg. Asthmatic
21 children with TNF-308 GG genotype had a significantly reduced risk of bronchitic
22 symptoms with low-O₃ exposure (OR: 0.53 [95% CI: 0.31, 0.91]). The risk was not
23 reduced in children living in high-O₃ communities (OR: 1.42 [95% CI: 0.75, 2.70]). The
24 difference in genotypic effects between low- and high-O₃ environments was statistically
25 significant among asthmatics (P for interaction = 0.01), but not significant among non-
26 asthmatic children. [Figure 7-2](#) presents adjusted O₃ community-specific regression
27 coefficients plotted against ambient O₃ concentration, using weights proportional to the
28 inverse variance. Investigators further reported no substantial differences in the effect of
29 the GG genotype on bronchitic symptoms by long-term exposure to PM₁₀, PM_{2.5}, NO₂,
30 acid vapor, or second-hand smoke.



Note: Using indicator variables for each category of genotype and O₃ exposure, investigators calculated effect estimates for TNF- α GG genotype on the occurrence of bronchitic symptoms among children with asthma.
 Source: Reprinted with permission of John Wiley & Sons, ([Lee et al., 2009b](#)).

Figure 7-2 Ozone modifies the effect of TNF GG genotype on bronchitic symptoms among children with asthma in the CHS.

1 Another CHS analyses reported interrelationships between variants in CAT and
 2 myeloperoxidase (MPO) genes, ambient pollutants, and respiratory-related school
 3 absences for 1,136 Hispanic and non-Hispanic white cohort children ([Wenten et al.,](#)
 4 [2009](#)). A related study ([Gilliland et al., 2001](#)), found increased O₃ exposure to be related
 5 greater school absenteeism due to respiratory illness but did not consider genetic variants.
 6 [Wenten et al. \(2009\)](#) hypothesized that variation in the level or function of antioxidant
 7 enzymes would modulate respiratory illness risk, especially under high levels of
 8 oxidative stress expected from high ambient O₃ exposure. The joint effect of variants in
 9 these two genes (genetic epistasis) on respiratory illness was examined because the
 10 enzyme products operate on the same substrate within the same biological pathway. Risk
 11 of respiratory-related school absences was elevated for children with CAT GG plus MPO
 12 GA or AA genotypes (RR: 1.35 [95% CI: 1.03, 1.77] compared to GG for both genes)
 13 and reduced for children with CAT GA or AA plus MPO GA or AA (RR: 0.81 [95% CI:
 14 0.55, 1.19] compared to GG for both genes). Both CAT GG and MPO GA or AA
 15 genotypes produce a lower activity enzyme. In analyses that stratified communities into
 16 high and low O₃ exposure groups by median levels (46.9 ppb), the protective effect of
 17 CAT GA or AA plus MPO GA or AA genotype was largely limited to children living in

1 communities with high ambient O₃ levels (RR: 0.42 [95% CI: 0.20, 0.89]). The
2 association of respiratory-illness absences with functional variants in CAT and MPO that
3 differ by air pollution levels illustrates the need to consider genetic epistasis in assessing
4 gene-environment interactions.

5 Collective evidence from CHS provides an important demonstration of gene-environment
6 interactions. In the complex gene-environment setting a modifying effect might not be
7 reflected in an exposure main effect. The simultaneous occurrence of main effect and
8 interaction effect can occur. The study of gene-environment interactions helps to dissect
9 disease mechanisms in humans by using information on susceptibility genes to focus on
10 the biological pathways that are most relevant to that disease ([Hunter, 2005](#)).

11 The French Epidemiology study on Genetics and Environment of Asthma (EGEA)
12 investigated the relationship between ambient air pollution and asthma severity in a
13 cohort in five French cities (Paris, Lyon, Marseille, Montpellier, and Grenoble) ([Rage et
14 al., 2009b](#)). In this cross-sectional study, asthma severity over the past 12 months was
15 assessed among 328 adult asthmatics using two methods: (1) a four-class severity score
16 that integrated clinical events and type of treatment; and (2) a five-level asthma score
17 based only on symptoms. Two measures of exposure were also assessed: (1) [first
18 method]) closest monitor data from 1991 to 1995 where a total of 93% of the subjects
19 lived within 10 km of a monitor, but where 70% of the O₃ concentrations were
20 back-extrapolated values; and (2) [second method]) a validated spatial model that used
21 geostatistical interpolations and then assigned air pollutants to the geocoded residential
22 addresses of all participants and individually assigned exposure to ambient air pollution
23 estimates. Higher asthma severity scores were significantly related to both the 8-h avg O₃
24 during April-September and the number of days with 8-h O₃ averages above 55 ppb. Both
25 exposure assessment methods and severity score methods resulted in very similar
26 findings. Effect estimates of O₃ were similar in three-pollutant models. No PM data were
27 available. Since these estimates were not sensitive to the inclusion of ambient NO₂ in the
28 three-pollutant models, the authors viewed the findings not to be explained by particles
29 which usually have substantial correlations between PM and NO₂. Effect estimates for O₃
30 in three-pollutant models including O₃, SO₂, and NO₂ yielded OR for O₃-days of 2.74
31 (95% CI: 1.68, 4.48) per IQR days of 10-28 (+18) ppb. The effect estimates for SO₂ and
32 NO₂ in the three-pollutant model were 1.33 (95% CI: 0.85, 2.11) and 0.94 (95% CI: 0.68,
33 1.29) respectively. Taking into account duration of residence did not change the result.
34 This study suggests that a higher asthma severity score is related to long-term O₃
35 exposure.

36 An EGEA follow-up study ([Jacquemin et al., In Press](#)), examines the relationship
37 between asthma and O₃, NO₂, and PM₁₀. New aspects considered include: (1)

1 examination of three domains of asthma control (symptoms, exacerbations, and lung
2 function); (2) levels of asthma control (controlled, partially controlled, and uncontrolled
3 asthma); and (3) PM₁₀ and multi-pollutant analysis. In this cross-sectional analysis,
4 EGEA2 studied 481 adult subjects with current asthma from 2003 to 2007. The IQRs
5 were 11 (41-52) µg/m³ for annual O₃ and 13 (25-38) µg/m³ for summer (April-
6 September) O₃. The association between asthma control and air pollutants was expressed
7 by ORs (reported for one IQR of the pollutant), derived from multinomial logistic
8 regression. For each factor, the simultaneous assessment of the risk for uncontrolled
9 asthma and for partly controlled asthma was compared with controlled asthma using a
10 composite of the three domains. In crude and adjusted models, O₃-sum and PM₁₀ were
11 positively associated with partly controlled and uncontrolled asthma, with a clear gradient
12 from controlled, partly controlled (OR = 1.53, 95% CI: 1.01, 2.33) and uncontrolled
13 (OR = 2.14, 95% CI: 1.34, 3.43) (from the multinomial logistic regression).

14 Separately, they used a composite asthma control classification that used the ordinal
15 logistic regression for risk comparing controlled to partly controlled asthma and
16 comparing partly controlled to uncontrolled asthma. For these two pollutants, the ORs
17 assessed using the ordinal logistic regression were significant (ORs were 1.69 (95% CI:
18 1.22, 2.34) and 1.35 (95% CI: 1.13, 1.64) for O₃-sum and PM₁₀, respectively). For two
19 pollutant models using the ordinal logistic regression, the adjusted ORs for O₃-sum and
20 PM₁₀ included simultaneously in a unique model were 1.50 (95% CI: 1.07, 2.11) for O₃-
21 sum and 1.28 (95% CI: 1.06, 1.55) for PM₁₀, respectively. This result suggests that the
22 effects of both pollutants are independent.

23 The analysis of the associations between air pollution for all asthma subjects and each
24 one of the three asthma control domains showed the following: (1) for lung function
25 defined dichotomously as percent predicted FEV₁ value <or >=80 (OR = 1.35, 95% CI:
26 0.80, 2.28 for adjusted O₃-sum); (2) for symptoms defined as asthma attacks or dyspnea
27 or woken by asthma attack or shortness of breath in the past three months (OR = 1.59,
28 95% CI: 1.10, 2.30 for adjusted O₃-sum); and for exacerbations defined at least one
29 hospitalizations or ER visits in the last year or oral corticosteroids in the past three
30 months (OR = 1.58, 95% CI: 0.97, 2.59 for adjusted O₃-sum). Since the estimates for
31 both pollutants were more stable and significant when using the integrated measure of
32 asthma control, this indicates that the results are not driven by one domain. These results
33 support an effect of long-term exposure to O₃ on asthma control in adulthood in subjects
34 with pre-existing asthma.

35 [Goss et al. \(2004\)](#) investigated the effect of O₃ on pulmonary exacerbations and lung
36 function in individuals over the age of 6 years with cystic fibrosis (n = 11,484). The study
37 included patients enrolled in the Cystic Fibrosis Foundation National Patient Registry,

1 which contains demographic and clinical data collected annually at accredited centers for
2 cystic fibrosis. For 1999 through 2000, the annual mean O₃ concentration, calculated
3 from 1-h averages from 616 monitors in the U.S. EPA Aerometric Information Retrieval
4 System (AIRS), was 51.0 ppb (SD 7.3). Exposure was assessed by linking air pollution
5 values from AIRS with the patient's home ZIP code. No clear association was found
6 between annual mean O₃ and lung function parameters. However, a 10 ppb increase in
7 annual mean O₃ was associated with a 10% (95% CI: 3, 17) increase in the odds of two or
8 more pulmonary exacerbations. Significant excess odds of pulmonary exacerbations also
9 were observed with increased annual mean PM₁₀ and PM_{2.5} concentrations. The O₃ effect
10 was robust to adjustment for PM₁₀ and PM_{2.5}, 8% (95% CI: 1, 15) increase in odds of two
11 or more pulmonary exacerbations per 10 ppb increase in annual mean O₃.

7.2.2 Asthma Hospital Admissions and ED Visits

12 The studies on O₃-related hospital discharges and emergency department (ED) visits for
13 asthma and respiratory disease that were available in the 2006 O₃ AQCD mainly looked
14 at the daily time metric. Collectively the short-term O₃ studies presented earlier in
15 Section [6.2.7.5](#) indicate that there is evidence for increases in both hospital admissions
16 and ED visits related to both all respiratory outcomes and asthma with stronger
17 associations in the warm months. New studies evaluated long-term O₃ exposure metrics,
18 providing a new line of evidence that suggests a positive exposure-response relationship
19 between first asthma hospital admission and long-term O₃ exposure.

20 An ecologic study ([Moore et al., 2008](#)) evaluated time trends in associations between
21 declining warm-season O₃ concentrations and hospitalization for asthma in children in
22 California's South Coast Air Basin who ranged in age from birth to 19 years. Quarterly
23 average concentrations from 195 spatial grids, 10×10 km, were used. Ozone was the only
24 pollutant associated with increased hospital admissions over the study period. A linear
25 relation was observed for asthma hospital discharges ([Moore et al., 2008](#)). A matched
26 case-control study ([Karr et al., 2007](#)) was conducted of infant bronchiolitis (ICD 9, code
27 466.1) hospitalization and two measures of long-term pollutant exposure (the month prior
28 to hospitalization and the lifetime average) for O₃ in the South Coast Air Basin of
29 southern California among 18,595 infants born between 1995 and 2000. Ozone was
30 associated with reduced risk in the single-pollutant model, but this relation did not persist
31 in multi-pollutant models (CO, NO₂, and PM_{2.5}).

32 In a cross-sectional study, [Meng et al. \(2010\)](#) examined associations between air
33 pollution and asthma morbidity in the San Joaquin Valley in California by using the 2001
34 California Health Interview Survey data from subjects ages 1 to 65+ who reported

1 physician-diagnosed asthma (n = 1,502). Subjects were assigned annual average
2 concentrations for O₃ based on residential ZIP code and the closet air monitoring station
3 within 8 km but did not have data on duration of residence. Multi-pollutant models for O₃
4 and PM did not differ substantially from single-pollutant estimates, indicating that
5 pollutant multi-collinearity is not a problem in these analyses. The authors reported
6 increased asthma-related ED visits or hospitalizations for O₃ (OR = 1.49; [95% CI: 1.05,
7 2.11] per 10 ppb) for all ages. Positive associations were obtained for symptoms, but
8 95% confidence intervals included null values. Associations for symptoms for adults
9 (ages 18 +) were observed (OR = 1.40; [95% CI: 1.02, 1.91] per 10 ppb).

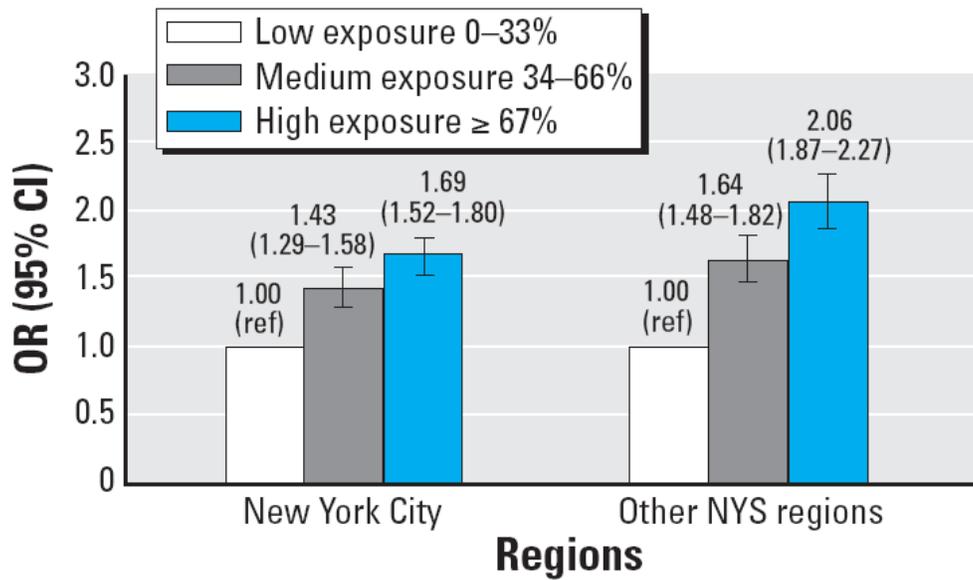
10 Associations between air pollution and poorly controlled asthma among adults in
11 Los Angeles and San Diego Counties were investigated using the California Health
12 Interview Survey data collected between November 2000 and September 2001 ([Meng et](#)
13 [al., 2007](#)). Each respondent was assigned an annual average concentration measured at
14 the nearest station within 5 miles of the residential cross-street intersection. Poorly
15 controlled asthma was defined as having daily or weekly asthma symptoms or at least one
16 ED visit or hospitalization because of asthma during the past 12 months. This cross-
17 sectional study reports an OR of 3.34 (95% CI: 1.01, 11.09) for poorly controlled asthma
18 when comparing those 65 years of age and older above the 90th percentile (28.7 ppb)
19 level to those below that level. Co-pollutant (PM) analysis produced similar results.

20 Evidence associating long-term O₃ exposure to first asthma hospital admission in a
21 concentration-response relationship is provided in a retrospective cohort study ([Lin et al.,](#)
22 [2008b](#)). This study investigated the association between chronic exposure to O₃ and
23 childhood asthma admissions (defined as a principal diagnosis of ICD9, code 493) by
24 following a birth cohort of 1,204,396 eligible births born in New York State during
25 1995-1999 to first asthma admission or until 31 December 2000. There were 10,429
26 (0.87%) children admitted to the hospital for asthma between 1 and 6 years of age. The
27 asthma hospitalization rate in New York State in 1993 was 2.87 per 1,000 ([Lin et al.,](#)
28 [1999](#)). Three annual indicators (all 8-h max from 10:00 a.m. to 6:00 p.m.) were used to
29 define chronic O₃ exposure: (1) mean concentration during the follow-up period
30 (41.06 ppb); (2) mean concentration during the O₃ season (50.62 ppb); and (3) proportion
31 of follow-up days with O₃ levels >70 ppb. In this study the authors aimed to predict the
32 risk of having asthma admissions in a birth cohort, but the time to the first admission in
33 children that is usually analyzed in survival models was not their primary interest. The
34 effects of co-pollutants were assessed and controlled for using the Air Quality Index
35 (AQI). Interaction terms were used to assess potential effect modifications. A positive
36 association between chronic exposure to O₃ and childhood asthma hospital admissions
37 was observed indicating that children exposed to high O₃ levels over time are more likely
38 to develop asthma severe enough to be admitted to the hospital. The various factors were

1 examined and differences were found for younger children (1-2 years), poor
2 neighborhoods, Medicaid/self-paid births, geographic region and others. As shown in
3 [Figure 7-3](#), positive concentration-response relationships were observed. Asthma
4 admissions were significantly associated with increased O₃ levels for all chronic exposure
5 indicators (ORs, 1.16-1.68). When estimating the O₃ effect using the exceedance
6 proportion, an increase was observed (OR = 1.68; [95% CI: 1.64, 1.73]) in hospital
7 admissions with an IQR (2.51%) increase in O₃. A proportional hazards model for the
8 New York City data was run as a sensitivity analysis and it yielded similar results
9 between asthma admissions and chronic exposure to O₃ (Cox model: HR = 1.14,
10 [95% CI: 1.124, 1.155] is similar to logistic model results: OR = 1.16 [95% CI: 1.15,
11 1.17]) ([Lin, 2010](#)). Thus, this study provides evidence associating long-term O₃ exposure
12 to first asthma hospital admission in a concentration-response relationship.

13 In considering relationships between long-term pollutant exposure and chronic disease
14 health endpoints, [Künzli \(2012\)](#) offers two hypotheses relevant to research on air
15 pollution and chronic disease where chronic pathologies are found with acute expressions
16 of the chronic disease: “H1: Exposure provides a basis for the development of the
17 underlying chronic pathology, which increases the pool of people with chronic conditions
18 prone to exacerbations; H2: Exposure triggers an acute event (or a state of frailty that
19 results in an event with a delay of a few days or weeks) among those with the disease.”
20 [Künzli \(2012\)](#) states if associations of pollution with events are much larger in the long-
21 term studies, it provides some indirect evidence in support of H1. If air pollution
22 increases the pool of subjects with the chronic pathology (H1), more acute events are
23 expected to be seen for higher exposures since events due to various causes are part of the
24 chronic disease pathway.

25 [Künzli \(2012\)](#) makes such a comparison noting larger associations with long-term NO₂
26 exposures for adult asthma hospital admissions ([Andersen et al., 2012](#)) as compared to
27 short-term NO₂ exposures for asthma hospital admissions ([Peel et al., 2005](#)). In a further
28 example, [Pope \(2007\)](#) makes similar conclusions comparing long-term PM mortality
29 study results to short-term PM mortality studies. The results of [Lin et al. \(2008b\)](#) for first
30 asthma hospital admission, presented below, show effect estimates that are larger than
31 those reported in a study of asthma hospital admissions in New York State by [Silverman
32 and Ito \(2010\)](#), discussed in Chapter 6 (both studies are for young children). This
33 provides some support for the hypothesis that O₃ exposure may not only have triggered
34 the events but also increased the pool of asthmatics.



Note: Adjusted for child’s sex, age, birth weight, and gestational age; maternal race, ethnicity, age, education, insurance, and smoking status during pregnancy; and regional poverty level and temperature. ORs by low, medium, and high exposure are shown for New York City (NYC: low [37.3 ppb], medium [37.3–38.11 ppb], high [38.11+ ppb]) and other New York State regions (Other NYS regions: low [42.58 ppb], medium [42.58–45.06 ppb], high [45.06+ ppb]) for first asthma hospital admission.

Source: [Lin \(2010\)](#); [Lin et al. \(2008b\)](#)

Figure 7-3 Ozone-asthma concentration-response relationship using the mean concentration during the entire follow-up period for first asthma hospital admission.

7.2.3 Pulmonary Structure and Function

7.2.3.1 Pulmonary Structure and Function: Evidence from Epidemiology Studies

1 The definitive 8-year follow-up analysis of the first cohort of the CHS, which is
 2 discussed in Section 7.2 ([Gauderman et al., 2004](#)), provided little evidence that long-term
 3 exposure to ambient O₃ was associated with significant deficits in the growth rate of lung
 4 function in children. A later CHS study ([Islam et al., 2007](#)) examined relationships
 5 between air pollution, lung function, and new onset asthma and reported no substantial
 6 differences in the effect of O₃ on lung function. Ozone concentrations from the least to
 7 most polluted communities (mean annual average of 8-h avg O₃) ranged from 30 to
 8 65 ppb, as compared to the ranges observed for the other pollutants, which had 4-fold- to
 9 8-fold differences in concentrations. In a more recent CHS study, [Breton et al. \(2011\)](#)
 10 hypothesized that genetic variation in genes on the glutathione metabolic pathway may

1 influence the association between ambient air pollutant exposures and lung function
2 growth in children. They investigated whether genetic variation in glutathione genes
3 GSS, GSR, GCLC, and GCLM was associated with lung function growth in healthy
4 children using data collected on 2,106 children over an 8-year time-period as part of the
5 Children's Health Study. [Breton et al. \(2011\)](#) found that variation in the GSS locus was
6 associated with differences in risk of children for lung function growth deficits associated
7 with NO₂, PM₁₀, PM_{2.5}, elemental carbon, organic carbon, and O₃. The negative effects of
8 air pollutants were largely observed within participants who had a particular GSS
9 haplotype. The effects ranged from -124.2 to -149.1 mL for FEV₁, -92.9 to -126.7 mL for
10 FVC and -193.9 to -277.9 mL/sec for MMEF for all pollutants except O₃, for which some
11 positive associations were reported: 25.9 mL for FEV₁; 0.1 mL for FVC, and
12 166.5 mL/sec for MMEF. Ozone was associated with larger decreases in lung function in
13 children without this haplotype, when compared to the other pollutants with values of
14 -76.6 mL for FEV₁, -17.2 mL for FVC, and -200.3 mL/sec for MMEF, but only the
15 association with MMEF was statistically significant.

16 As discussed in the 2006 O₃ AQCD, a study of freshman students at the University of
17 California, Berkeley reported that lifetime exposure to O₃ was associated with decreased
18 measures of small airways (<2 mm) function (FEF₇₅ and FEF₂₅₋₇₅) ([Tager et al., 2005](#)).
19 There was an interaction with the FEF₂₅₋₇₅/FVC ratio, a measure of intrinsic airway size.
20 Subjects with a large ratio (indicating an increased airway size relative to their lung
21 volume) were less likely to have decreases in FEF₇₅ and FEF₂₅₋₇₅ for a given estimated
22 lifetime exposure to O₃. [Kinney and Lippmann \(2000\)](#) examined 72 nonsmoking adults
23 (mean age 20 years) from the second-year class of students at the U.S. Military Academy
24 in West Point, NY, and reported results that appear to be consistent with a decline in lung
25 function that may in part be due to O₃ exposures over a period of several summer months.
26 [Ihorst et al. \(2004\)](#) examined 2,153 children with a median age of 7.6 years and reported
27 pulmonary function results which indicated that significantly lower FVC and FEV₁
28 increases were associated with higher O₃ exposures over the medium-term of several
29 summer months, but not over several months in the winter. Semi-annual mean O₃
30 concentrations ranged from 22 to 54 ppb during the summer months and 4 to 36 ppb
31 during the winter months. Further, over the longer-term 3.5-year period [Ihorst et al.](#)
32 [\(2004\)](#) found that higher mean summer months O₃ levels were not associated with growth
33 rates in lung function and for FVC and FEV₁, in contrast to the significant medium-term
34 effects. [Frischer et al. \(1999\)](#) found that higher O₃ over one summer season, one winter
35 season, and greater increases from one summer to the next over a three-year period were
36 associated with smaller increases in lung function growth, indicating both medium and
37 longer-term effects.

1 [\(Mortimer et al., 2008a, b\)](#) examined the association of prenatal and lifetime exposures to
2 air pollutants with pulmonary function and allergen sensitization in a subset of asthmatic
3 children (ages 6-11) included in the Fresno Asthmatic Children's Environment Study
4 (FACES). Monthly means of pollutant levels for the years 1989-2000 were created and
5 averaged separately across several important developmental time-periods, including: the
6 entire pregnancy, each trimester, the first 3 years of life, the first 6 years of life, and the
7 entire lifetime. In the first analysis [\(Mortimer et al., 2008a\)](#), negative effects on
8 pulmonary function were found for exposure to PM₁₀, NO₂, and CO during key neonatal
9 and early life developmental periods. The authors did not find a negative effect of
10 exposure to O₃ within this cohort. In the second analysis [\(Mortimer et al., 2008b\)](#),
11 sensitization to at least one allergen was associated, in general, with higher levels of CO
12 and PM₁₀ during the entire pregnancy and second trimester, and higher PM₁₀ during the
13 first 2 years of life. Lower exposure to O₃ during the entire pregnancy or second trimester
14 was associated with an increased risk of allergen sensitization. Although the pollutant
15 metrics across time periods were correlated, the strongest associations with the outcomes
16 were observed for prenatal exposures. Though it may be difficult to disentangle the effect
17 of prenatal and postnatal exposures, the models from this group of studies suggest that
18 each time period of exposure may contribute independently to different dimensions of
19 school-aged children's pulmonary function. For 4 of the 8 pulmonary-function measures
20 (FVC, FEV₁, PEF, FEF₂₅₋₇₅), prenatal exposures were more influential on pulmonary
21 function than early-lifetime metrics, while, in contrast, the ratio of measures (FEV₁/FVC
22 and FEF₂₅₋₇₅/FVC) were most influenced by postnatal exposures. When lifetime metrics
23 were considered alone, or in combination with the prenatal metrics, the lifetime measures
24 were not associated with any of the outcomes. This suggests that the timing of the O₃
25 exposure may be more important than the overall dose, and prenatal exposures are not
26 just markers for lifetime or current exposures.

27 [Latzin et al. \(2009\)](#) examined whether prenatal exposure to air pollution was associated
28 with lung function changes in the newborn. Tidal breathing, lung volume, ventilation
29 inhomogeneity and eNO were measured in 241 unsedated, sleeping neonates
30 (age = 5 weeks). Consistent with the previous studies, no association was found for
31 prenatal exposure to O₃ and lung function.

32 In a cross-sectional study of adults, [Qian et al. \(2005\)](#) examined the association of long-
33 term exposure to O₃ and PM₁₀ with pulmonary function from data of 10,240 middle-aged
34 subjects who participated in the Atherosclerosis Risk in Communities (ARIC) study in
35 four U.S. communities. A surrogate for long-term O₃ exposure from daily data was
36 determined at the individual level. Ozone was significantly and negatively associated
37 with measures of pulmonary function.

1 To determine the extent to which long-term exposure to outdoor air pollution accelerates
2 adult decline in lung function, [Forbes et al. \(2009b\)](#) studied the association between
3 chronic exposure to outdoor air pollution and lung function in approximately 42,000
4 adults aged 16 and older who were representatively sampled cross-sectionally from
5 participants in the Health Survey for England (1995, 1996, 1997, and 2001). FEV₁ was
6 not associated with O₃ concentrations. In contrast to the results for PM₁₀, NO₂, and SO₂,
7 combining the results of all the survey years showed that a 5-ppb difference in O₃ was
8 counter-intuitively associated with a higher FEV₁ by 22 mL.

9 In a prospective cohort study consisting of school-age, non-asthmatic children in
10 Mexico City (n = 3,170) who were 8 years of age at the beginning of the study, [Rojas-
11 Martinez et al. \(2007\)](#) evaluated the association between long-term exposure to O₃, PM₁₀
12 and NO₂ and lung function growth every 6 months from April 1996 through May 1999.
13 Exposure data were provided by 10 air quality monitor stations located within 2 km of
14 each child's school. Over the study period, 8-h O₃ concentrations ranged from 60 ppb
15 (SD, ± 25) in the northeast area of Mexico City to 90 ppb (SD, ± 34) in the southwest,
16 with an overall mean of 69.8 ppb. In multi-pollutant models, an IQR increase in mean O₃
17 concentration of 11.3 ppb was associated with an annual deficit in FEV₁ of 12 mL in girls
18 and 4 mL in boys. Single-pollutant models showed an association between ambient
19 pollutants (O₃, PM₁₀, and NO₂) and deficits in lung function growth. While the estimates
20 from co-pollutant models were not substantially different than single pollutant models,
21 independent effects for pollutants could not be estimated accurately because the traffic-
22 related pollutants were correlated. To reduce exposure misclassification,
23 microenvironmental and personal exposure assessments were conducted in a randomly
24 selected subsample of 60 children using passive O₃ samplers. Personal O₃ concentrations
25 were correlated (p <0.05) with the measurements obtained from the fixed-site air
26 monitoring stations.

27 In the 2006 O₃ AQCD, few studies had investigated the effect of chronic O₃ exposure on
28 pulmonary function. The strongest evidence was for medium-term effects of extended O₃
29 exposures over several summer months on lung function (FEV₁) in children, i.e., reduced
30 lung function growth being associated with higher ambient O₃ levels. Longer-term
31 studies (annual), investigating the association of chronic O₃ exposure on lung function
32 (FEV₁) such as the definitive 8-year follow-up analysis of the first cohort ([Gauderman et
33 al., 2004](#)) provides little evidence that long-term exposure to ambient O₃ at current levels
34 is associated with significant deficits in the growth rate of lung function in children.
35 Analyses indicated that there was no evidence that either 8-h avg O₃ (10 a.m. to 6 p.m.)
36 or 24-h avg O₃ was associated with any measure of lung function growth over a 4-year
37 (age 10 to 14 years; ([Gauderman et al., 2000](#))) or 8-year (age 10 to 18 years; ([Gauderman
38 et al., 2004](#))) period. However, most of the other pollutants examined (including PM_{2.5},

1 NO₂, acid vapor, and elemental carbon) were found to be significantly associated with
2 reduced growth in lung function. In addition, there was only about a 2- to 2.5-fold
3 difference in O₃ concentrations from the least to most polluted communities (mean
4 annual average of 8-h avg O₃ ranged from 30 to 65 ppb), versus the ranges observed for
5 the other pollutants (which had 4- to 8-fold differences in concentrations).

6 Short-term O₃ exposure studies presented in Section [6.2.1.2](#) provide a cumulative body of
7 epidemiologic evidence that strongly supports associations between ambient O₃ exposure
8 and decrements in lung function among children. For new studies of long-term O₃
9 exposure relationship to pulmonary function, one study, where O₃ and other pollutant
10 levels were higher (90 ppb at high end of the range) than those in the CHS, observes a
11 relationship between O₃ concentration and pulmonary function declines in school-aged
12 children. Two studies of adult cohorts provide mixed results where long- term exposures
13 were at the high end of the range with levels of 49.5 ppb in one study and 27 ppb IQR in
14 the other. Toxicological studies examining monkeys have provided data for airway
15 resistance in an asthma model but this is difficult to compare to FEV₁ results. Thus there
16 is little new evidence to build upon the very limited studies of pulmonary function
17 (FEV₁) from the 2006 O₃ AQCD.

7.2.3.2 Pulmonary Structure and Function: Evidence from Toxicological Studies and Nonhuman Primate Asthma Models

18 Long-term studies in animals allow for greater insight into the potential effects of
19 prolonged exposure to O₃, that may not be easily measured in humans, such as structural
20 changes in the respiratory tract. As reviewed in the 1996 and 2006 O₃ AQCDs and
21 Chapter [5](#) of this ISA, there are both qualitative and quantitative uncertainties in the
22 extrapolation of data generated by rodent toxicology studies to the understanding of
23 health effects in humans. Despite these uncertainties, epidemiologic studies observing
24 functional changes in humans can attain biological plausibility, in conjunction with long-
25 term toxicological studies, particularly O₃-inhalation studies performed in non-human
26 primates whose respiratory system most closely resembles that of the human. An
27 important series of studies have used nonhuman primates to examine the effect of O₃
28 alone or in combination with an inhaled allergen, house dust mite antigen, on
29 morphology and lung function. These animals exhibit the hallmarks of allergic asthma
30 defined for humans, including: a positive skin test for HDMA with elevated levels of IgE
31 in serum and IgE-positive cells within the tracheobronchial airway walls; impaired
32 airflow which is reversible by treatment with aerosolized albuterol; increased abundance
33 of immune cells, especially eosinophils, in airway exudates and bronchial lavage; and

1 development of nonspecific airway responsiveness ([NHLBI, 2007](#)). [Hyde et al. \(2006\)](#)
2 compared asthma models of rodents (mice) and the nonhuman primate model to
3 responses in humans and concluded that the unique responses to inhaled allergen shown
4 in the rhesus monkeys make it the most appropriate animal model of human asthma.
5 These studies and others have demonstrated changes in pulmonary function and airway
6 morphology in adult and infant nonhuman primates repeatedly exposed to
7 environmentally relevant concentrations of O₃ ([Joad et al., 2008](#); [Carey et al., 2007](#);
8 [Plopper et al., 2007](#); [Fanucchi et al., 2006](#); [Joad et al., 2006](#); [Evans et al., 2004](#); [Larson et](#)
9 [al., 2004](#); [Tran et al., 2004](#); [Evans et al., 2003](#); [Schelegle et al., 2003](#); [Fanucchi et al.,](#)
10 [2000](#); [Hyde et al., 1989](#); [Harkema et al., 1987a](#); [Harkema et al., 1987b](#); [Fujinaka et al.,](#)
11 [1985](#)). Many of the observations found in adult monkeys have also been noted in infant
12 rhesus monkeys, although a direct comparison of the degree of effects between adult and
13 infant monkeys has not been reported. The findings of these nonhuman primate studies
14 have also been observed in rodent studies discussed at the end of this section and
15 included in [Table 7-1](#).

16 The initial observations in adult nonhuman primates have been expanded in a series of
17 experiments using infant rhesus monkeys repeatedly exposed to 0.5 ppm O₃ starting at
18 1 month of age¹ ([Plopper et al., 2007](#)). The purpose of these studies, designed by Plopper
19 and colleagues, was to determine if a cyclic regimen of O₃ inhalation would amplify the
20 allergic responses and structural remodeling associated with allergic sensitization and
21 inhalation in the infant rhesus monkey. In terms of pulmonary function changes, after
22 several episodic exposures of infant monkeys to O₃, they observed a significant increase
23 in the baseline airway resistance, which was accompanied by a small increase in airway
24 responsiveness to inhaled histamine ([Schelegle et al., 2003](#)), although neither
25 measurement was statistically different from filtered air control values. Exposure of
26 animals to inhaled house dust mite antigen alone also produced small but not statistically
27 significant changes in baseline airway resistance and airway responsiveness, whereas the
28 combined exposure to both (O₃ + antigen) produced statistically significant and greater
29 than additive changes in both functional measurements. This nonhuman primate evidence
30 of an O₃-induced change in airway resistance and responsiveness supports the biologic
31 plausibility of long-term exposure to O₃ contributing to the effects of asthma in children.
32 To understand which conducting airways and inflammatory mechanisms are involved in
33 O₃-induced airway hyperresponsiveness in the infant rhesus monkey, a follow-up study
34 examined airway responsiveness ex vivo in lung slices ([Joad et al., 2006](#)). Using video
35 microscopy to morphometrically evaluate the response of bronchi and respiratory

¹ [Schelegle et al. \(2003\)](#) used a two-by-two block design. Twenty-four infant rhesus monkeys (30 days old) were exposed to 11 episodes (total of 6-months exposure period) of filtered air (FA), house dust mite allergen (HDMA), O₃ (5 days each followed by 9 days of FA). Ozone was delivered for 8h/day at 0.5 ppm. Twelve of the monkeys (HDMA, and HDMA + O₃ groups) were sensitized to house dust mite allergen (HDMA, confirmed by skin testing). To evaluate the potential for recovery, the 5 months of exposure were followed by another 6 months in FA until the monkeys were reevaluated at 12 months of age.

1 bronchioles to methacholine, (a bronchoconstricting agent commonly used to evaluate
2 airway responsiveness in asthmatics), the investigators observed differential effects for
3 the two airway sizes. While episodic exposure to O₃ alone (0.5 ppm) had little effect on
4 ex vivo airway responsiveness in bronchi and respiratory bronchioles, exposure to dust
5 mite antigen alone produced airway hyperresponsiveness in the large bronchi, whereas
6 O₃ + antigen produced significant increases in airway hyperresponsiveness only in the
7 respiratory bronchioles. These results suggest that ozone's effect on airway
8 responsiveness occurs predominantly in the smaller bronchioles, where dosimetric
9 models indicate the dose would be higher.

10 The functional changes in the conducting airways of infant rhesus monkeys exposed to
11 either O₃ alone or O₃ + antigen were accompanied by a number of cellular and
12 morphological changes, including a significant 4-fold increase in eosinophils, (a cell type
13 important in allergic asthma), in the bronchoalveolar lavage of infant monkeys exposed
14 to O₃ alone. Thus, these studies demonstrate both functional and cellular changes in the
15 lung of infant monkeys after cyclic exposure to 0.5 ppm O₃. This concentration, provides
16 relevant information to understanding the potentially damaging effects of ambient O₃
17 exposure on the respiratory tract of humans. No concentration-response data, however,
18 are available from these nonhuman primate studies.

19 In addition to these functional and cellular changes, significant structural changes in the
20 respiratory tract have been observed in infant rhesus monkeys exposed to O₃. During
21 normal respiratory tract development, conducting airways increase in diameter and length
22 in the infant rhesus monkey. Exposure to O₃ alone (5 days of 0.5 ppm O₃ at 8 h/day,
23 followed by 9 days of filtered air exposures for 11 cycles), however, markedly affected
24 the growth pattern of distal conducting airways ([Fanucchi et al., 2006](#)). Whereas the first
25 alveolar outpocketing occurred at airway generation 13 or 14 in filtered air-control infant
26 monkeys, the most proximal alveolarized airways occurred at an average of 10 airway
27 generations in O₃-exposed monkeys. Similarly, the diameter and length of the terminal
28 and respiratory bronchioles were significantly decreased in O₃-exposed monkeys.
29 Importantly, the O₃-induced structural pathway changes persisted after recovery in
30 filtered air for 6 months after cessation of the O₃ exposures. These structural effects were
31 accompanied by significant increases in mucus goblet cell mass, alterations in smooth
32 muscle orientation in the respiratory bronchioles, epithelial nerve fiber distribution, and
33 basement membrane zone morphometry. These latter effects are noteworthy because of
34 their potential contribution to airway obstruction and airway hyperresponsiveness which
35 are central features of asthma.

36 Because many cellular and biochemical factors are known to contribute to allergic
37 asthma, the effect of exposure to O₃ alone or O₃ + antigen on immune system parameters

1 was also examined in infant rhesus monkeys. Mast cells, which contribute to asthma via
2 the release of potent proteases, were elevated in animals exposed to antigen alone but O₃
3 alone had little effect on mast cell numbers and the response of animals exposed to O₃ +
4 antigen was not different from that of animals exposed to antigen alone; thus suggesting
5 that mast cells played little role in the interaction between O₃ and antigen in this model of
6 allergic asthma ([VanWinkle et al., 2010](#)). Increases in CD4+ and CD8+ lymphocytes
7 were observed at 6 months of age in the blood and bronchoalveolar lavage fluid of infant
8 rhesus monkeys exposed to O₃ + antigen but not in monkeys exposed to either agent
9 alone ([Miller et al., 2009](#)). Activated lymphocytes (i.e., CD25+ cells) were
10 morphometrically evaluated in the airway mucosa and significantly increased in infant
11 monkeys exposed to antigen alone or O₃ + antigen. Although O₃ alone had no effect on
12 CD25+ cells, it did alter the anatomic distribution of CD25+ cells within the airways.
13 Ozone had only a small effect on these sets of immune cells and did not produce a strong
14 interaction with an inhaled allergen in this nonhuman primate model.

15 In addition to alterations in the immune system, nervous system interactions with
16 epithelial cells are thought to play a contributing role to airway hyperresponsiveness. A
17 critical aspect of postnatal lung development is the laying of nerve axons with specific
18 connections serving to maintain lung homeostasis. Aberrant innervation patterns may
19 underlie allergic airways disease pathology and long-term decrements in airway function.
20 As noted in the 2006 O₃ AQCD, exposure of infant rhesus monkeys altered the normal
21 development of neural innervation in the epithelium of the conducting airways ([Larson et
22 al., 2004](#)). Significant mean reductions in nerve fiber density were observed in the
23 midlevel airways of animals exposed to O₃ alone (49% reduction), and O₃ + antigen (55%
24 reduction). Moreover, the morphology of nerve bundles was altered. The persistence of
25 these effects was examined after a 6-month recovery period, and although nerve
26 distribution remained atypical, there was a dramatic increase in airway nerve density
27 (hyperinnervation) ([Kajekar et al., 2007](#)). Thus, in addition to structural, immune, and
28 inflammatory effects, exposure to O₃ produces alterations in airway innervation which
29 may contribute to O₃-induced exacerbation of asthma. Evaluation of the pathobiology of
30 airway remodeling in growing lungs of neonates using an animal model where exposure
31 to allergen generates reactive airway disease with all the hallmarks of asthma in humans
32 illustrates that exposure to O₃ and allergen early in life produces a large number of
33 disruptions of fundamental growth and differentiation processes.

34 A number of studies in both nonhuman primates and rodents demonstrate that O₃
35 exposure can increase collagen synthesis and deposition, inducing fibrotic-like changes in
36 the lung ([Last et al., 1994](#); [Chang et al., 1992](#); [Moffatt et al., 1987](#); [Reiser et al., 1987](#);
37 [Last et al., 1984](#)). Increased collagen content is often associated with elevated abnormal
38 cross links that appear to be irreversible ([Reiser et al., 1987](#)). Generally changes in

1 collagen content have been observed in rats exposed to 0.5 ppm O₃ or higher, although
2 extracellular matrix thickening has been observed in the lungs of rats exposed to an urban
3 pattern of O₃ with daily peaks of 0.25 ppm for 38 weeks ([Chang et al., 1992](#); [Chang et al.,
4 1991](#)). A more recent study using an urban pattern of exposure to 0.5 ppm O₃
5 demonstrated that O₃-induced collagen deposition in mice is dependent on the activity of
6 TGF-β ([Katre et al., 2011](#)). Sex differences have been observed with respect to increased
7 centriacinar collagen deposition and crosslinking, which was observed in female but not
8 male rats exposed to 0.5 and 1.0 ppm O₃ for 20 months ([Last et al., 1994](#)). Few other
9 long-term exposure morphological studies have presented sex differences and most only
10 evaluated males.

11 As described in the 1996 and 2006 O₃ AQCDs, perhaps the largest chronic O₃ study was
12 an NIEHS-NTP/HEI funded rodent study conducted by multiple investigators studying a
13 number of different respiratory tract endpoints ([Catalano et al., 1995b](#)). Rats were
14 exposed to 0.12, 0.5, or 1.0 ppm O₃ for 6 h/day and 5 d/week for 20 months. The most
15 prominent changes were observed in the nasal cavity where a large fraction of O₃ is
16 absorbed. Alterations in nasal function (increased mucous flow) and structure (goblet cell
17 metaplasia) were observed at 0.5 and 1.0 ppm but not 0.12 ppm O₃. In the lung, the
18 centriacinar region (CAR) was the anatomical site most affected by O₃. The epithelial cell
19 lining was changed to resemble that seen in respiratory bronchioles and the interstitial
20 volume was increased. Biochemical analyses demonstrated increased collagen and
21 glycoaminoglycans, an observation that supported the structural changes. As in the nose,
22 these changes were observed only at the two highest exposure concentrations.
23 Importantly, despite these morphologic and biochemical changes after 20 months of
24 exposure, detailed pulmonary function testing revealed little to no measurable change in
25 function. Thus, minor respiratory tract changes were observed after chronic exposure to
26 O₃ up to 1.0 ppm in the F344 rat model.

27 It is unclear what the long-term impact of O₃-induced structural changes may be.
28 Simulated seasonal (episodic) exposure studies suggest that such exposures might have
29 cumulative impacts, and a number of studies indicate that structural changes in the
30 respiratory system are persistent or irreversible. For example, O₃-induced hyperplasia
31 was still evident in the nasal epithelia of rats 13 weeks after recovery from 0.5 ppm O₃
32 exposure ([Harkema et al., 1999](#)). In a study of episodic exposure to 0.25 ppm O₃, [Chang
33 et al. \(1992\)](#) observed no reversal of basement membrane thickening in rat lungs up to 17
34 weeks post-exposure. Thickening of the sub-basement membrane is one of the persistent
35 structural features observed in human asthmatics ([NHLBI, 2007](#)). Episodic exposure
36 (0.25 ppm O₃, every other month) of young monkeys induced equivalent morphological
37 changes compared to continuously exposed animals, even though they were exposed for
38 half the time and evaluation occurred a month after exposure ceased as opposed to

1 immediately ([Tyler et al., 1988](#)). Notably, episodic O₃ exposure increased total lung
2 collagen content, chest wall compliance, and inspiratory capacity, suggesting a delay in
3 lung maturation in episodically-exposed animals. These changes were in contrast to the
4 continuously exposed group, which did not differ from the air exposed group in these
5 particular parameters but did exhibit greater bronchiolitis than the episodically exposed
6 animals. In a study by Harkema and colleagues ([Harkema et al., 1993, 1987b](#)), monkeys
7 (both males and females) were acutely exposed for 8 h/day to 0.15 ppm O₃ (6 days) or
8 chronically to 0.15 ppm or 0.3 ppm O₃ (90 days). For most endpoints in the nasal cavity,
9 the observed morphologic changes and inflammation were greater in the monkeys
10 exposed for 6 days compared to 90 days, whereas in the respiratory bronchioles of the
11 same animals, there were no significant time or concentration dependent differences
12 (increased epithelial thickness and proportion of cuboidal cells) between the 6 and 90 day
13 exposure groups.

14 [Stokinger \(1962\)](#) reported that chronic bronchitis, bronchiolitis, and emphysematous and
15 fibrotic changes develop in the lung tissues of mice, rats, hamsters, and guinea pigs
16 exposed 6 h/day, 5 days/week for 14.5 months to a concentration slightly above 1 ppm
17 O₃. Rats continuously exposed for 3 to 5 months to 0.8 ppm O₃ develop a disease that
18 resembles emphysema, and they finally die of respiratory failure ([Stephens et al., 1976](#)).
19 Ozone results in a greater response of fibroblasts in the lesion, thickening of the alveolar
20 septae, and an increase in number of alveolar macrophages in the proximal alveoli.

Table 7-1 Respiratory effects in nonhuman primates and rodents resulting from long-term ozone exposure

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|--|---|--|---|---|
| Pinkerton et al. (1998) ; Harkema et al. (1997a) ; Harkema et al. (1997b) ; Catalano et al. (1995b) ; Catalano et al. (1995a) ; (Chang et al., 1995) ; Pinkerton et al. (1995) ; Stockstill et al. (1995) ; Harkema et al. (1994) ; Last et al. (1994) ; Plopper et al. (1994) | Rat, male and female, Fischer F344, 6-8 weeks old | 0.12 0.5 1.0 | 6 h/day, 5 days/week for 20 months | Effects similar to (or a model of) early fibrotic human disease were greater in the periacinar region than in terminal bronchioles. Thickened alveolar septa observed at 0.12 ppm O ₃ . Other effects (e.g., mucous cell metaplasia in the nose, mild fibrotic response in the parenchyma, and increased collagen in CAR of females) observed at 0.5 to 1.0 ppm. Some morphometric changes (epithelial thickening and bronchiolarization) occurred after 2 or 3 months of exposure to 1.0 ppm. |
| Herbert et al. (1996) | Mice, male and female, B6C3F1, 6-7 weeks old, | 0.12 0.50 1.0 | 6 h/day, 5 days/week for 24 and 30 months | Similar to the response of rats in the same study (see rat above). Effects were seen in the nose and centriacinar region of the lung at 0.5 and 1.0 ppm. |
| Chang et al. (1991) | Rat, male, F344, 6 weeks old | Continuous: 0.12 or 0.25 Episodic/urban: baseline 0.06; peak 0.25 | Continuous: 12 h/day for 6 weeks Simulated urban pattern; slow rise to peak 9 h/day, 5 days/week, 13 weeks | Increased Type 1 and 2 epithelial volume assessed by TEM. Linear relationship observed between increases in Type 1 epithelial cell volume and concentration x time product. Degree of injury not related to pattern of exposure (continuous or episodic). |
| Chang et al. (1992) | Rat, male, F344, 6 weeks old | baseline 0.06; peak 0.25 | Slow rise to peak 9 h/day, 5 days/week, 13 and 78 weeks Recovery in filtered air for 6 or 17 weeks | Progressive epithelial hyperplasia, fibroblast proliferation, and interstitial matrix accumulation observed using TEM. Interstitial matrix thickening due to deposition of basement membrane and collagen fibers. Partial recovery of interstitial matrix during follow-up periods in air; but no resolution of basement membrane thickening. |
| Barry et al. (1985) ; (1983) | Rat, male, 1 day old or 6 weeks old | 0.12 (adults only) 0.25 | 12 h/day for 6 weeks | Lung and alveolar development not significantly affected. Increased Type 1 and 2 epithelial cells and AM in CAR alveoli, thickened Type 1 cells with smaller volume and less surface coverage as assessed by TEM (adults and juveniles). In adults, smaller but statistically significant similar changes at 0.12 ppm, suggesting linear concentration-response relationship. No statistically significant age-related effects observed. |
| Tyler et al. (1988) | Monkey; male, <i>Macaca fascicularis</i> , 7 mo old | 0.25 | 8 h/day, 7 days/week, Daily for 18 mo or episodically every other month for 18 mo Episodic group evaluated 1 mo postexposure | Increased collagen content, chest wall compliance, and inspiratory capacity in episodic group only. Respiratory bronchiolitis in both groups. Episodically exposed group incurred greater alterations in physiology and biochemistry and equivalent changes in morphometry even though exposed for half the time as the daily exposure group. |
| Harkema et al. (1999) | Rat, male, Fischer F344/N HSD, 10-14 weeks old | 0.25 0.5 | 8 h/day, 7 days/week for 13 weeks | Mucous cell hyperplasia in nasal epithelium after exposure to 0.25 and 0.5 ppm O ₃ ; still evident after 13 weeks recovery from 0.5 ppm O ₃ exposure. |
| Van Bree et al. (2002) | Rat, male, Wistar, 7 weeks old, n = 5/group | 0.4 | 23.5 h/day for 1, 3, 7, 28, or 56 days | Acute inflammatory response in BALF reached a maximum at day 1 and resolved within 6 days during exposure. Centriacinar region inflammatory responses throughout O ₃ exposure with increased collagen and bronchiolarization still present after a recovery period. |
| Katre et al. (2011) | Mice; male, C57BL/6, 6-8 weeks old | 0.5 | 8 h/day, [5 days/week O ₃ , and 2 days filtered air] for 5 or 10 cycles | Sustained elevation in TGF-β and PAI-1 in lung (5 or 10 cycles); elevated α-SMA and increased collagen deposition in airway walls (after 10 cycles). Collagen increase shown to depend on TGF-β. |

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|--|--|----------------------|--|--|
| Schelegle et al. (2003) ; | Monkey; Rhesus, 30 days old ^a | 0.5 | 8 h/day for 5 days, every 5 days for a total of 11 episodes | Goblet cell metaplasia, increased AHR, and increased markers of allergic asthma (e.g., eosinophilia) were observed, suggesting that episodic exposure to O ₃ alters postnatal morphogenesis and epithelial differentiation and enhances the allergic effects of house dust mite allergen in the lungs of infant primates. |
| Harkema et al. (1993, 1987b) | Monkey; <i>Macaca radiata</i> , M, F 2-6 years old | 0.15 0.3 | 8 h/day for 90 days | Significant increase in epithelial thickness in respiratory bronchioles which was accompanied by increase in cuboidal cells; nasal lesions consisted of ciliated cell necrosis and secretory cell hyperplasia; no concentration response effects |
| Larson et al. (2004) | Monkey; <i>Macaca mulatta</i> , 30 days old ^a | 0.5 | 11 episodes of 5 days each, 8 h/day followed by 9 days of recovery | O ₃ or O ₃ + house dust mite antigen caused changes in density and number of airway epithelial nerves in small conducting airways. Suggests episodic O ₃ alters pattern of neural innervation in epithelial compartment of developing lungs. |
| Plopper et al. (2007) | Monkey; Rhesus, 30 days old ^a | 0.5 | 5 months of episodic exposure; 5 days O ₃ followed by 9 days of filtered air, 8h/day. | Non-significant increases airway resistance and airway responsiveness with O ₃ or inhaled allergen alone. Allergen + O ₃ produced additive changes in both measures. |
| Fanucchi et al. (2006) | Monkey; male Rhesus, 30 days old | 0.5 | 5 months of episodic exposure; 5 days O ₃ followed by 9 days of filtered air, 8h/day. | Cellular changes and significant structural changes in the distal respiratory tract in infant rhesus monkeys exposed to O ₃ postnatally. |
| Reiser et al. (1987) | Monkey; male and female <i>Cynomolgus</i> 6-7 mo old | 0.61 | 8 h/day for 1 year | Increased lung collagen content associated with elevated abnormal cross links that were irreversibly deposited. |

^asex not reported

1 Collectively, evidence from animal studies strongly suggests that chronic O₃ exposure is
2 capable of damaging the distal airways and proximal alveoli, resulting in lung tissue
3 remodeling and leading to apparent irreversible changes. Potentially, persistent
4 inflammation and interstitial remodeling play an important role in the progression and
5 development of chronic lung disease. Further discussion of the modes of action that lead
6 to O₃-induced morphological changes can be found in Section [5.3.7](#). The findings
7 reported in chronic animal studies offer insight into potential biological mechanisms for
8 the suggested association between seasonal O₃ exposure and reduced lung function
9 development in children as observed in epidemiologic studies (see Section [7.2.3](#)).
10 Discussion of mechanisms involved in lifestage susceptibility and developmental effects
11 can be found in Section [5.4.2.4](#).

7.2.4 Pulmonary Inflammation, Injury, and Oxidative Stress

12 The 2006 O₃ AQCD stated that the extensive human clinical and animal toxicological
13 evidence, together with the limited epidemiologic evidence available, suggests a causal
14 role for O₃ in inflammatory responses in the airways. Short-term exposure epidemiologic

1 studies discussed earlier in Section [6.2.3.2](#) show consistent associations of O₃ exposure
2 and increased airway inflammation and oxidative stress. Further discussion of the
3 mechanisms underlying inflammation and oxidative stress responses can be found in
4 Section [5.3.3](#). Though the majority of recent studies focus on short-term exposures,
5 several epidemiologic and toxicology studies of long-term exposure add to observations
6 of O₃-induced inflammation and injury.

7 Inflammatory markers and peak expiratory pulmonary function were examined in 37
8 allergic children with physician-diagnosed mild persistent asthma in a highly polluted
9 urban area in Italy and then again 7 days after relocation to a rural location with
10 significantly lower pollutant levels ([Renzetti et al., 2009](#)). The authors observed a 4-fold
11 decrease in nasal eosinophils and a statistically significant decrease in fractional exhaled
12 nitric oxide along with an improvement in lower airway function. Several pollutants were
13 examined, including PM₁₀, NO₂, and O₃, though pollutant-specific results were not
14 presented. These results are consistent with studies showing that traffic-related exposures
15 are associated with increased airway inflammation and reduced lung function in children
16 with asthma and contribute to the notion that this negative influence may be rapidly
17 reversible. Exhaled NO (eNO) has been shown to be a useful biomarker for airway
18 inflammation in large population-based studies ([Linn et al., 2009](#)). Thus, while the time
19 scale of 7 days between examinations for eNO needs to be evaluated for appropriateness,
20 the results suggest that inflammatory responses are reduced when O₃ levels are decreased.

21 Chest radiographs (CXR) of 249 children in Mexico City who were chronically exposed
22 to O₃ and PM_{2.5} were analyzed by [Calderón-Garcidueñas et al. \(2006\)](#). They reported an
23 association between chronic exposures to O₃ and other pollutants and a significant
24 increase in abnormal CXR's and lung CTs suggestive of a bronchiolar, peribronchiolar,
25 and/or alveolar duct inflammatory process, in clinically healthy children with no risk
26 factors for lung disease. These CXR and CT results should be viewed with caution
27 because it is difficult to attribute effects to O₃ exposure.

28 In a cross-sectional study, [Wood et al. \(2009\)](#) examined the association of outdoor air
29 pollution with respiratory phenotype (PiZZ type) in alpha 1-antitrypsin deficiency
30 (α -ATD) from the U.K. α -ATD registry. This deficiency leads to exacerbated responses
31 to inflammatory stimuli. In total, 304 PiZZ subjects underwent full lung function testing
32 and quantitative high-resolution computed tomography to identify the presence and
33 severity of COPD – emphysema. Mean annual air pollution data for 2006 was matched to
34 the location of patients' houses and used in regression models to identify phenotypic
35 associations with pollution controlling for covariates. Relative trends in O₃ levels were
36 assessed to validate use of a single year's data to indicate long-term exposure and
37 validation; data showed good correlations between modeled and measured data ([Stedman](#)

1 [and Kent, 2008](#)). Regression models showed that estimated higher exposure to O₃
2 exposure was associated with worse gas transfer and more severe emphysema, albeit
3 accounting for only a small proportion of the lung function variability. This suggests that
4 a gene-specific group demonstrates a long-term O₃ exposure effect.

5 The similarities of nonhuman primates to humans make them attractive models in which
6 to study the effects of O₃ on the respiratory tract. The nasal mucous membranes, which
7 protect the more distal regions of the respiratory tract, are susceptible to injury from O₃.
8 [Carey et al. \(2007\)](#) conducted a study of O₃ exposure in infant rhesus macaques, whose
9 nasal airways closely resemble that of humans. Monkeys were exposed either acutely for
10 5 days (8 h/day) to 0.5 ppm O₃, or episodically for several biweekly cycles alternating
11 5 days of 0.5 ppm O₃ with 9 days of filtered air (0 ppm O₃), designed to mimic human
12 exposure (70 days total). All monkeys acutely exposed to O₃ had moderate to marked
13 necrotizing rhinitis, with focal regions of epithelial exfoliation, numerous infiltrating
14 neutrophils, and some eosinophils. The distribution, character, and severity of lesions in
15 episodically exposed monkeys were similar to that of acutely exposed animals. Neither
16 group exhibited the mucous cell metaplasia proximal to the lesions, observed in adult
17 monkeys exposed continuously to 0.3 ppm O₃ in another study ([Harkema et al., 1987a](#)).
18 Adult monkeys also exhibit attenuation of inflammatory responses with continued daily
19 exposure ([Harkema et al., 1987a](#)), but inflammation did not resolve over time in young
20 episodically exposed monkeys ([Carey et al., 2011](#)). Inflammation in conducting airways
21 has also been observed in rats chronically exposed to O₃. Using an agar-based technique
22 to fill the alveoli so that only the rat bronchi are lavaged, a 90-day exposure of rats to
23 0.8 ppm O₃ (8 h/day) elicited significantly elevated pro-inflammatory eicosanoids PGE₂
24 and 12-HETE in the conducting airway compared to filtered air-exposed rats ([Schmelzer
25 et al., 2006](#)).

26 Persistent inflammation and injury leading to interstitial remodeling may play an
27 important role in the progression and development of chronic lung disease. Chronic
28 airway inflammation is an important component of both asthma and COPD. The
29 epidemiological evidence supporting an association between long-term exposure to O₃
30 and inflammation or injury is limited. However, animal studies clearly demonstrate O₃-
31 induced inflammation and injury, which may or may not attenuate with chronic exposure
32 depending on the model. Further discussion of how O₃ initiates inflammation can be
33 found in Section [5.3.3](#).

7.2.5 Allergic Responses

1 The association of air pollutants with childhood respiratory allergies was examined in the
2 U.S. using the 1999-2005 National Health Interview Survey of approximately 70,000
3 children, and ambient air pollution data from the U.S. EPA, with monitors within 20
4 miles of each child's residential block ([Parker et al., 2009](#)). The authors examined the
5 associations between the reporting of respiratory allergy or hay fever and medium-term
6 exposure to O₃ over several summer months, controlling for demographic and geographic
7 factors. Increased respiratory allergy/hay fever was associated with increased O₃ levels
8 (adjusted OR per 10 ppb = 1.20; [95% CI: 1.15, 1.26]). These associations persisted after
9 stratification by urban-rural status, inclusion of multiple pollutants (O₃, SO₂, NO₂, PM),
10 and definition of exposure by differing exposure radii; smaller samples within 5 miles of
11 monitors were remarkably similar to the primary results. No associations between the
12 other pollutants and the reporting of respiratory allergy/hay fever were apparent.
13 [Ramadour et al. \(2000\)](#) reported no relationship between O₃ levels and rhinitis symptoms
14 and hay fever. [Hwang et al. \(2006\)](#) report the prevalence of allergic rhinitis (adjusted OR
15 per 10 ppb = 1.05; [95% CI: 0.98, 1.12]) in a large cross-sectional study in Taiwan. In a
16 large cross-sectional study in France, [Penard-Morand et al. \(2005\)](#) reported a positive
17 relationship between lifetime allergic rhinitis and O₃ exposure in a two-pollutant model
18 with NO₂. These studies related positive outcomes of allergic response and O₃ exposure
19 but with variable strength for the effect estimates. A toxicological study reported that
20 five weeks of continuous exposure to 0.4 ppm O₃ (but not 0.1 or 0.2 ppm O₃) augmented
21 sneezing and nasal secretions in a guinea pig model of nasal allergy ([Iijima and](#)
22 [Kobayashi, 2004](#)). Nasal eosinophils, which participate in allergic disease and
23 inflammation, and allergic antibody levels in serum were also elevated by exposure to
24 concentrations as low as 0.2 ppm ([Iijima and Kobayashi, 2004](#)).

25 Nasal eosinophils were observed to decrease by 4-fold in 37 atopic, mildly asthmatic
26 children 7 days after relocation from a highly polluted urban area in Italy to a rural
27 location with significantly lower pollutant levels ([Renzetti et al., 2009](#)). Inflammatory
28 and allergic effects of O₃ exposure (30 day mean) such as increased eosinophil levels
29 were observed in children in an Austrian study ([Frischer et al., 2001](#)). Episodic exposure
30 of infant rhesus monkeys to 0.5 ppm O₃ for 5 months appears to significantly increase the
31 number and proportion of eosinophils in the blood and airways (lavage) [protocol
32 described above in Section 7.2.3.1 for [Fanucchi et al. \(2006\)](#)] ([Maniar-Hew et al., 2011](#)).
33 These changes were not evident at 1 year of age (6 months after O₃ exposure ceased).
34 Increased eosinophils levels have also been observed after acute or prolonged exposures
35 to O₃ in adult bonnet and rhesus monkeys ([Hyde et al., 1992](#); [Eustis et al., 1981](#)).

1 Total IgE levels were related to air pollution levels in 369 adult asthmatics in five French
2 centers using generalized estimated equations (GEE) as part of the EGEA study described
3 earlier ([Rage et al., 2009a](#)). Geostatistical models were performed on 4×4 km grids to
4 assess individual outdoor air pollution exposure that was assigned to subject's home
5 address. Ozone concentrations were positively related to total IgE levels and an increase
6 of 5 ppb of O₃ resulted in an increase of 20.4% (95% CI: 3.0, 40.7) in total IgE levels.
7 Nearly 75% of the subjects were atopic. In two-pollutant models including O₃ and NO₂, the
8 O₃ effect estimate was decreased by 25% while the NO₂ effect estimate was decreased by
9 57%. Associations were not sensitive to adjustment for covariates or the season of IgE
10 measurements. These cross-sectional results suggest that exposure to O₃ may increase
11 total IgE in adult asthmatics.

12 Although very few toxicological studies of long-term exposure examining allergy are
13 available, short-term exposure studies in rodents and nonhuman primates demonstrate
14 allergic skewing of immune responses and enhanced IgE production. Due to the
15 persistent nature of these responses, the short-term toxicological evidence lends
16 biological plausibility to the limited epidemiologic findings of an association between
17 long-term O₃ exposure and allergic outcomes.

7.2.6 Host Defense

18 Short-term exposures to O₃ have been shown to cause decreases in host defenses against
19 infectious lung disease in animal models. Acute O₃-induced suppression of alveolar
20 phagocytosis and immune functions observed in animals appears to be transient and
21 attenuated with continuous or repeated exposures, although chronic exposure (weeks,
22 months) has been shown to slow alveolar clearance. In an important study investigating
23 the effects of longer term O₃ exposure on alveolobronchiolar clearance, rats were exposed
24 to an urban pattern of O₃ (continuous 0.06 ppm, 7 days/week with a slow rise to a peak of
25 0.25 ppm and subsequent decrease to 0.06 ppm over a 9 h period for 5 days/week) for
26 6 weeks and were exposed 3 days later to chrysotile asbestos, which can cause pulmonary
27 fibrosis and neoplasia ([Pinkerton et al., 1989](#)). After 30 days, the lungs of the O₃-exposed
28 animals had twice the number and mass of asbestos fibers as the air-exposed rats.
29 However, chronic exposures of 0.1 ppm do not cause greater effects on infectivity than
30 short exposures, due to defense parameters becoming reestablished with prolonged
31 exposures. No detrimental effects were seen with a 120-day exposure to 0.5 ppm O₃ on
32 acute lung injury from influenza virus administered immediately before O₃ exposure
33 started. However, O₃ was shown to increase the severity of postinfluenzal alveolitis and
34 lung parenchymal changes ([Jakab and Bassett, 1990](#)). A recent study by [Maniar-Hew et](#)
35 [al. \(2011\)](#) demonstrated that the immune system of infant rhesus monkeys episodically

1 exposed to 0.5 ppm O₃ for 5 months¹ appeared to be altered in ways that could diminish
2 host defenses. Reduced numbers of circulating leukocytes were observed, particularly
3 polymorphonuclear leukocytes (PMNs) and lymphocytes, which were decreased in the
4 blood and airways (bronchoalveolar lavage). These changes did not persist at 1 year of
5 age (6 months postexposure); rather, increased numbers of monocytes were observed at
6 that time point. Challenge with LPS, a bacterial ligand that activates monocytes and other
7 innate immune cells, elicited lower responses in O₃-exposed animals even though the
8 relevant reactive cell population was increased. This was observed in both an in vivo
9 inhalation challenge and an ex vivo challenge of peripheral blood mononuclear cells.
10 Thus a decreased ability to respond to pathogenic signals was observed six months after
11 O₃ exposure ceased, in both the lungs and periphery.

7.2.7 Respiratory Mortality

12 A limited number of epidemiologic studies have assessed the relationship between long-
13 term exposure to O₃ and mortality. The 2006 O₃ AQCD concluded that an insufficient
14 amount of evidence existed “to suggest a causal relationship between chronic O₃
15 exposure and increased risk for mortality in humans” ([U.S. EPA, 2006b](#)). Though total
16 and cardio-pulmonary mortality were considered in these studies, respiratory mortality
17 was not specifically considered. In the most recent follow-up analysis of the ACS cohort
18 ([Jerrett et al., 2009](#)), cardiopulmonary deaths were subdivided into respiratory and
19 cardiovascular, separately, as opposed to combined in the [Pope et al. \(2002\)](#) work. A
20 10-ppb increment in exposure to O₃ elevated the risk of death from respiratory causes and
21 this effect was robust to the inclusion of PM_{2.5}. The association between increased O₃
22 concentrations and increased risk of death from respiratory causes was insensitive to the
23 use of a random-effects survival model allowing for spatial clustering within the
24 metropolitan area and state of residence, and to adjustment for several ecologic variables
25 considered individually. Additionally, a recent study ([Zanobetti and Schwartz, 2011](#))
26 observed an association between long-term exposure to O₃ and elevated risk of mortality
27 among Medicare enrollees that had previously experienced an emergency hospital
28 admission due to COPD.

7.2.8 Summary and Causal Determination

29 The epidemiologic studies reviewed in the 2006 O₃ AQCD detected no associations
30 between long-term (annual) O₃ exposures and asthma-related symptoms, asthma

¹ Exposure protocol is described above in Section [7.2.3.2](#) for [Fanucchi et al. \(2006\)](#).

1 prevalence, or allergy to common aeroallergens among children after controlling for
2 covariates. Little evidence was available to relate long-term exposure to ambient O₃
3 concentrations with deficits in the growth rate of lung function in children. Additionally,
4 limited evidence was available evaluating the relationship between long-term O₃
5 concentrations and pulmonary inflammation and other endpoints. From toxicological
6 studies, it appeared that O₃-induced inflammation tapered off during long-term
7 exposures, but that hyperplastic and fibrotic changes remained elevated and in some
8 cases even worsened after a postexposure period in clean air. Episodic exposures were
9 also known to cause more severe pulmonary morphologic changes than continuous
10 exposure ([U.S. EPA, 2006b](#)).

11 The recent epidemiologic evidence base consists of studies using a variety of designs and
12 analysis methods evaluating the relationship between long-term exposure to ambient O₃
13 concentrations and measures of respiratory health effects and mortality conducted by
14 different research groups in different locations. See [Table 7-2](#) for O₃ concentrations
15 associated with selected studies. [Table 7-2](#) is organized by longitudinal and cross-
16 sectional studies both presented alphabetically. The positive results from various designs
17 and locations support a relationship between long-term exposure to ambient O₃
18 concentrations and respiratory health effects and mortality.

19 Earlier studies reported associations of new-onset asthma and O₃ in an adult cohort in
20 California ([McDonnell et al., 1999a](#); [Greer et al., 1993](#)) but only in males. In the CHS
21 cohort of children in 12 Southern California communities, long-term exposure to O₃
22 concentrations was not associated with increased risk of developing asthma ([McConnell
23 et al., 2010](#)); however, greater outdoor exercise was associated with development of
24 asthma in children living in communities with higher ambient O₃ concentrations
25 ([McConnell et al., 2002](#)). Recent CHS studies examined interactions among genetic
26 variants, long-term O₃ exposure, and new onset asthma in children. These prospective
27 cohort studies are methodologically rigorous epidemiology studies, and evidence
28 indicates gene-O₃ interactions. These studies have provided data supporting decreased
29 risk of certain different genetic variants on new onset asthma (e.g., HMOX-1, ARG) that
30 is limited to children either in low ([Islam et al., 2008](#)) or high ([Salam et al., 2009](#)) O₃
31 communities. Gene-environment interaction also was demonstrated with findings that
32 greater outdoor exercise increased risk of asthma in GSTP1 Ile/Ile children living in high
33 O₃ communities ([Islam et al., 2009](#)). Biological plausibility for these these gene-O₃
34 environment interactions is provided by evidence that these enzymes have antioxidant
35 and/or anti-inflammatory activity and participate in well recognized modes of action in
36 asthma pathogenesis. As O₃ is a source of oxidants in the airways, oxidative stress serves
37 as the link among O₃ exposure, enzyme activity, and asthma.

Table 7-2 Summary of selected key new studies examining annual ozone exposure and respiratory health effects

| Study; Health Effect; Location | Annual Mean O₃ Concentration (ppb) | O₃ Range (ppb) Percentiles |
|---|---|--|
| Longitudinal | | |
| Islam et al. (2008) ; New-onset asthma; CHS | 55.2 high vs. 38.4 low communities 10:00 a.m. to 6:00 p.m. average | See left |
| Islam et al. (2009) ; New-onset asthma; CHS | 55.2 high vs. 38.4 low communities 10:00 a.m. to 6:00 p.m. | See left |
| Lin et al. (2008b) ; First asthma hospital admission; New York State - 10 regions | Range of mean O ₃ concentrations over the 10 New York Regions 37.51 to 47.78 8-h max 10:00 a.m. to 6:00 p.m. | See left |
| Salam et al. (2009) ; Childhood onset asthma; CHS | O ₃ greater than or less than 50 ppb | See left |
| Cross-sectional | | |
| Akinbami et al. (2010) ; Current asthma United States | 12 month median 39.8 8hr max | IQR 35.9 to 43.7 |
| Hwang et al. (2005) ; Prevalence of asthma; Taiwan | Mean 23.14 | Range 18.65 to 31.17 |
| Jacquemin et al. (In Press) ; Asthma control in adults; Five French cities | Median 46.9 ppb; 8-h average | 25th-75th 41-52 |
| Lee et al. (2009b) ; Bronchitic symptoms in asthmatic children; CHS | Above and below 50 ppb | See left |
| Meng et al. (2010) ; Asthma ED visits or hospitalizations; San Joaquin Valley, CA | Median 30.3 ppb Yearly based on hourly | 25-75% range 27.1 to 34.0 |
| Moore et al. (2008) ; Asthma hospital admissions; South Coast Basin | Median 87.8 ppb Quarterly 1hr daily max | Range 28.6 to 199.9 |
| Rage et al. (2009a) ; Asthma severity; Five French cities | Mean 30 ppb 8-h average | 25th-75th 21-36 |
| Wenten et al. (2009) ; Respiratory school absence, U.S. | Median 46.9 ppb; 10a.m. – 6 p.m. average | Min-Max 27.6-65.3 |

1 Studies using a cross-sectional design provide support for a relationship between long-
2 term O₃ exposure and health effects in asthmatics. A long-term O₃ exposure study relates
3 bronchitic symptoms to TNF-308 genotype asthmatic children with ambient O₃ exposure
4 in the CHS ([Lee et al., 2009b](#)). A study in five French cities reports effects on asthma
5 severity related to long-term O₃ exposure ([Rage et al., 2009b](#)). A follow-up study of this

1 cohort ([Jacquemin et al., In Press](#)) supports an effect of cumulative long-term O₃
2 exposure on asthma control in adulthood in subjects with pre-existing asthma. [Akinbami](#)
3 [et al. \(2010\)](#) and [Hwang et al. \(2005\)](#) provide further evidence relating O₃ exposures and
4 the risk of asthma. For the respiratory health of a cohort based on the general U.S.
5 population, risk of respiratory-related school absences was elevated for children with the
6 CAT and MPO variant genes related to communities with high ambient O₃ levels
7 ([Wenten et al., 2009](#)).

8 Long-term O₃ exposure was related to first childhood asthma hospital admissions in a
9 positive concentration-response relationship in a New York State birth cohort ([Lin et al.,](#)
10 [2008b](#)). A separate hospitalization cross-sectional study in San Joaquin Valley, California
11 reports similar findings ([Meng et al., 2010](#)). Another study relates asthma hospital
12 admissions to quarterly average O₃ in the South Coast Air Basin of California ([Moore et](#)
13 [al., 2008](#)).

14 Information from toxicological studies indicates that long term exposure to O₃ during
15 gestation or development can result in irreversible morphological changes in the lung,
16 which in turn can influence the function of the respiratory tract. Studies by Plopper and
17 colleagues using an allergic asthma model have demonstrated changes in pulmonary
18 function and airway morphology in adult and infant nonhuman primates repeatedly
19 exposed to environmentally relevant concentrations of O₃ ([Fanucchi et al., 2006](#); [Joad et](#)
20 [al., 2006](#); [Schelegle et al., 2003](#); [Harkema et al., 1987b](#)). This nonhuman primate
21 evidence of an O₃-induced change in airway responsiveness supports the biologic
22 plausibility of long term exposure to O₃ contributing to effects of asthma in children.
23 Results from epidemiologic studies examining long-term O₃ exposure and pulmonary
24 function effects are inconclusive with some new studies relating effects at higher
25 exposure levels. The definitive 8-year follow-up analysis of the first cohort of the CHS,
26 which is discussed in Section 7.2 ([Gauderman et al., 2004](#)), provided little evidence that
27 long-term exposure to ambient O₃ was associated with significant deficits in the growth
28 rate of lung function in children. Other cross-sectional studies provide mixed results.

29 Several studies (see [Table 7-3](#)) provide results adjusted for potential confounders,
30 presenting results for both O₃ and PM (single and multipollutant models) as well as other
31 pollutants where PM effects were not provided. As shown in the table, O₃ associations
32 are generally robust to adjustment for potential confounding by PM.

Table 7-3 Studies providing evidence concerning potential confounding by PM for available endpoints.

| Study Endpoint | Exposure | Single Pollutant O ₃ | Single Pollutant PM | O ₃ with PM | PM with O ₃ |
|---|-------------------------------------|---------------------------------|---|--|---|
| Asthma Related Health Effect Endpoint | | | | | |
| Akinbami et al. (2010) Asthma prevalence in children | IQR 35.9-43.7 ppb | 1.56 (1.15, 2.10) | PM _{2.5} 1.43 (0.98, 2.10) | Adjusted for SO ₂ , PM _{2.5} , PM ₁₀ 1.86 (1.02-3.40) Adjusted for PM _{2.5} , PM ₁₀ 1.36 (0.91-2.02) | PM _{2.5} 1.24 (0.70-2.21) PM _{2.5} 1.26 0.80-1.98) |
| Hwang et al. (2005) Asthma risk in children | 10 ppb O ₃ | 1.138 (1.001, 1.293) | 0.934 (0.909, 0.960) | PM ₁₀ 1.253 (1.089, 1.442) | 0.925 (0.899, 0.952) |
| Jacquemin et al. (In Press) Asthma control in adults | IQR 25-38 ppb O ₃ summer | 1.69 (1.22, 2.34) | 1.33 (1.06, 1.67) | PM ₁₀ 1.50 (1.07, 2.11) | 1.28 (1.06, 1.55) |
| Lee et al. (2009b) Bronchitic symptoms asthmatics | High O ₃ >50 ppb | 1.42 (0.75, 2.70) | NA | No substantial differences PM ₁₀ , PM _{2.5} | NA |
| Lin et al. (2008b) Asthma admissions in children | IQR 2.5% | 1.16 (1.15, 1.17) | NA | Air Quality Index 1.24 (1.23, 1.25) | NA |
| Meng et al. (2007) Asthma control | 1 ppm | 1.70 (0.91, 3.18) | PM ₁₀ 2.06 (1.17, 3.61) women | Did not differ | NA |
| Meng et al. (2010) Asthma ED visits, Hospitalization | 10 ppb | 1.49 (1.05, 2.11) | PM ₁₀ 1.29 (0.99, 1.69) | Did not differ | NA |
| Rage et al. (2009b) Asthma severity in adults | IQR 28.5-33.9 ppb | 2.53 (1.69, 3.79) | NA | No PM data Three pollutant (O ₃ , NO ₂ , SO ₂) 2.74 (1.68, 4.48) | NA |
| Other Respiratory Health Effect Endpoints | | | | | |
| Karr et al. (2007) Bronchiolitis Hospitalization | 10 ppb | 0.92 (0.88, 0.96) | 1.09 (1.04, 1.14) | PM _{2.5} 1.02 (0.94, 1.10) | 1.09 (1.03, 1.15) |
| Parker et al. (2009) Respiratory allergy | 10 ppb | 1.24 (1.15, 1.34) | 1.23 (1.04, 1.46) | Multi-pollutant 1.18 (1.09, 1.27) | 1.29 (1.07, 1.56) |
| Rojas-Martinez et al. (2007) FEV ₁ (mL) Deficit Girls | 11.3 ppb IQR | -24 (-30, -19) | PM ₁₀ IQR 36.4 ug/m ³ -29(-36, -21) | -17 (-23, -12) | -24 (-31, -16) |

The highest quartile is shown for all results
NA = not available

1 There is limited evidence for an association between long-term exposure to ambient O₃
2 concentrations and respiratory mortality ([Jerrett et al., 2009](#)) and this effect was robust to
3 the inclusion of PM_{2.5}. The association between increased O₃ concentrations and
4 increased risk of death from respiratory causes was insensitive to a number of different
5 model specifications. Additionally, there is evidence that long-term exposure to O₃ is
6 associated with mortality among individuals that had previously experienced an
7 emergency hospital admission due to COPD ([Zanobetti and Schwartz, 2011](#)).

8 Taken together, the recent epidemiologic studies of respiratory health effects (including
9 respiratory symptoms, new-onset asthma and respiratory mortality) combined with
10 toxicological studies in rodents and nonhuman primates, provide biologically plausible
11 evidence that there **is likely to be a causal relationship between long-term exposure**
12 **to O₃ and respiratory effects**. The strongest epidemiologic evidence for a relationship
13 between long-term O₃ exposure and respiratory effects is provided by studies that
14 demonstrate interactions between exercise or different genetic variants and long-term
15 measures of O₃ exposure on new-onset asthma in children; and increased respiratory
16 symptom effects in asthmatics. Additional studies of respiratory health effects and a
17 study of respiratory mortality provide a collective body of evidence supporting these
18 relationships. Studies considering other pollutants provide data suggesting that the effects
19 related to O₃ are independent from potential effects of the other pollutants. Some studies
20 provide evidence for a positive concentration-response relationship. Short-term studies
21 provide supportive evidence with increases in respiratory symptoms and asthma
22 medication use, hospital admissions and ED visits for all respiratory outcomes and
23 asthma, and decrements in lung function in children. The recent epidemiologic and
24 toxicological data base provides a compelling case to support the hypothesis that a
25 relationship exists between long-term exposure to ambient O₃ and measures of
26 respiratory health effects.

7.3 Cardiovascular Effects

7.3.1 Cardiovascular Disease

7.3.1.1 Cardiovascular Epidemiology

27 Long-term exposure to O₃ and its effects on cardiovascular morbidity were not
28 considered in the 2006 O₃ AQCD. However, recent studies have assessed the chronic
29 effects of O₃ concentration on cardiovascular morbidity ([Chuang et al., 2011](#); [Forbes et](#)

1 [al., 2009a; Chen et al., 2007a](#)). The association between O₃ concentration and markers of
2 lipid peroxidation and antioxidant capacity was examined among 120 nonsmoking
3 healthy college students, aged 18-22 years, from the University of California, Berkeley
4 (February—June 2002) ([Chen et al., 2007a](#)). By design, students were chosen from
5 geographic areas so they had experienced different concentrations of O₃ over their
6 lifetimes and during recent summer vacation in either greater Los Angeles (LA) or the
7 San Francisco Bay Area (SF). A marker of lipid peroxidation, 8-isoprostane (8-iso-PGF)
8 in plasma, was assessed. This marker is formed continuously under normal physiological
9 conditions but has been found at elevated concentrations in response to environmental
10 exposures. A marker of overall antioxidant capacity, ferric reducing ability of plasma
11 (FRAP), was also measured. The lifetime average O₃ concentration estimates (from
12 estimated monthly averages) did not show much overlap between the two geographic
13 areas [median (range): LA, 42.9 ppb (28.5-65.3); SF, 26.9 ppb (17.6-33.5)]. Estimated
14 lifetime average O₃ concentration was related to 8-iso-PGF [$\beta = 0.025$ (pg/mL)/8-h ppb
15 O₃, $p = 0.0007$]. For the 17-ppb lifetime O₃ concentration difference between LA and SF
16 participants, there was a 17.41-pg/mL (95% CI: 15.43, 19.39) increase in 8-iso-PGF. No
17 evidence of association was observed between lifetime O₃ concentration and FRAP
18 [$\beta = -2.21$ (pg/mL)/8-h ppb O₃, $p = 0.45$]. The authors note that O₃ was highly correlated
19 with PM_{10-2.5} and NO₂ in this study population; however, their inclusion in the O₃ models
20 did not substantially modify the magnitude of the associations with O₃. Because the
21 average lifetime concentration results were supported by shorter-term exposure period
22 results from analyses considering O₃ concentrations up to 30 days prior to sampling, the
23 authors conclude that persistent exposure to O₃ can lead to sustained oxidative stress and
24 increased lipid peroxidation. However, because there was not much overlap in average
25 lifetime O₃ concentration estimates between LA and SF, it is possible that the risk
26 estimates involving the lifetime O₃ exposures could be confounded by unmeasured
27 factors related to other differences between the two cities.

28 [Forbes et al. \(2009a\)](#) used the annual average exposures to assess the relationship
29 between chronic ambient air pollution and levels of fibrinogen and C-reactive protein
30 (CRP) in a cross-sectional study conducted in England. Data were collected from the
31 Health Survey of England for 1994, 1998, and 2003. The sampling strategy was designed
32 to obtain a representative sample of the English population; however, due to small group
33 sizes, only data from white ethnic groups were analyzed. For analyses, the annual
34 concentrations of O₃ were averaged for the year of data collection and the previous year
35 with the exception of 1994 (because pollutant data were not available for 1993). Median
36 O₃ concentrations were 26.7 ppb, 25.4 ppb, and 28 ppb for 1994, 1998, and 2003,
37 respectively. Year specific adjusted effect estimates were created and combined in a
38 meta-analysis. No evidence of association was observed for O₃ and levels of fibrinogen
39 or CRP (e.g., the combined estimates for the percent change in fibrinogen and CRP for a

1 10 ppb increase in O₃ were -0.28 [95% CI: -2.43, 1.92] and -3.05 [95% CI: -16.10,
2 12.02], respectively).

3 A study was performed in Taiwan to examine the association between long-term O₃
4 concentrations and blood pressure and blood markers using the Social Environment and
5 Biomarkers of Aging Study (SEBAS) ([Chuang et al., 2011](#)). Individuals included in the
6 study were 54 years of age and older. The mean annual O₃ concentration during the study
7 period was 22.95 ppb (SD 6.76 ppb). Positive associations were observed between O₃
8 concentrations and both systolic and diastolic blood pressure [changes in systolic and
9 diastolic blood pressure were 21.51mmHg (95% CI: 16.90, 26.13) and 20.56 mmHg
10 (95% CI: 18.14, 22.97) per 8.95 ppb increase in O₃, respectively). Increased O₃
11 concentrations were also associated with increased levels of total cholesterol, fasting
12 glucose, hemoglobin A1c, and neutrophils. No associations were observed between O₃
13 concentrations and triglyceride and IL-6 levels. The observed associations were reduced
14 when other pollutants were added to the models. Further research will be important for
15 understanding the effects, if any, of chronic O₃ exposure on cardiovascular morbidity
16 risk.

7.3.1.2 Cardiovascular Toxicology

17 Three new studies have investigated the cardiovascular effects of long-term exposure to
18 O₃ in animal models (See [Table 7-3](#) for study details). In addition to the short-term
19 exposure effects described in Section [6.3.3](#), a recent study found that O₃ exposure in
20 genetically hyperlipidemic mice enhanced aortic atherosclerotic lesion area compared to
21 air exposed controls ([Chuang et al., 2009](#)). [Chuang et al. \(2009\)](#) not only provided
22 evidence for increased atherogenesis in susceptible mice, but also reported an elevated
23 vascular inflammatory and redox state in wild-type mice and infant primates
24 (Section [6.3.3](#)). This study is compelling in that it identifies biochemical and cellular
25 events responsible for transducing the airway epithelial reactions of O₃ into
26 proinflammatory responses that are apparent in the extrapulmonary vasculature ([Cole and
27 Freeman, 2009](#)).

28 Another recent study provides further evidence for increased vascular inflammation and
29 oxidation and long term effects in the extrapulmonary space. Rats episodically exposed to
30 O₃ for 16 weeks presented marked increases in gene expression of biomarkers of
31 oxidative stress, thrombosis, vasoconstriction, and proteolysis ([Kodavanti et al., 2011](#)).
32 Ozone exposure upregulated aortic mRNA expression of heme oxygenase-1 (HO-1),
33 tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), von
34 Willebrand factor (vWf), thrombomodulin, endothelial nitric oxide synthase (eNOS),

1 endothelin-1 (ET-1), matrix metalloprotease-2 (MMP-2), matrix metalloprotease-3
2 (MMP-3), and tissue inhibitor of matrix metalloprotease-2 (TIMP-2). In addition, O₃
3 exposure depleted some cardiac mitochondrial phospholipid fatty acids (C16:0 and
4 C18:1), which may be the result of oxidative modifications. The authors speculate that
5 oxidatively modified lipids and proteins produced in the lung and heart promote vascular
6 pathology through activation of lectin-like oxidized-low density lipoprotein receptor-1
7 (LOX-1). Activated LOX-1 induces expression of a number of the biomarkers induced by
8 O₃ exposure and is considered pro-atherogenic. Both LOX-1 mRNA and protein were
9 increased in mouse aorta after O₃ exposure. This study provides a possible pathway and
10 further support to the observed O₃ induced atherosclerosis.

11 Vascular occlusion resulting from atherosclerosis can block blood flow through vessels
12 causing ischemia. The restoration of blood flow or reperfusion can cause injury to the
13 tissue from subsequent inflammation and oxidative damage. Ozone exposure enhanced
14 the sensitivity to myocardial ischemia-reperfusion (I/R) injury in rats while increasing
15 oxidative stress levels and pro-inflammatory mediators and decreasing production of
16 anti-inflammatory proteins ([Perepu et al., 2010](#)). Both long- and short-term O₃ exposure
17 decreased the left ventricular developed pressure, rate of change of pressure
18 development, and rate of change of pressure decay and increased left ventricular end
19 diastolic pressure in isolated perfused hearts (Section [6.3.3](#) for short-term exposure
20 discussion). In this ex vivo heart model, O₃ induced oxidative stress by decreasing SOD
21 enzyme activity and increasing malondialdehyde levels. Ozone also elicited a
22 proinflammatory state evident by an increase in TNF- α and a decrease in the
23 anti-inflammatory cytokine IL-10. The authors conclude that O₃ exposure will result in a
24 greater I/R injury.

25 Overall, the few animal studies that have been conducted suggest that long-term O₃
26 exposure may result in cardiovascular effects. These studies demonstrate O₃-induced
27 atherosclerosis and injury. In addition, evidence is presented for a potential mechanism
28 for the development of vascular pathology that involves increased oxidative stress and
29 proinflammatory mediators, activation of LOX-1 by O₃ oxidized lipids and proteins, and
30 upregulation of genes responsible for proteolysis, thrombosis, and vasoconstriction.
31 Further discussion of the mechanisms that may lead to cardiovascular effects from O₃
32 exposure can be found in Section [5.3.8](#).

Table 7-3 Characterization of Study Details for Section 7.3.1.2.

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|---|---|----------------------|--------------------------------|---|
| Chuang et al. (2009) | Mice; ApoE ^{-/-} ; M; 6 weeks | 0.5 | 8 wks, 5 days/week, 8 h/day | Enhanced aortic atherosclerotic lesion area compared to air controls. |
| Kodavanti et al. (2011) | Rat; Wistar; M; 10-12 weeks | 0.4 | 16 wks, 1 day/week, 5 h/day | Increased vascular inflammation and oxidative stress, possibly through activation of LOX-1 signaling. |
| Perepu et al. (2010) | Rat; Sprague-Dawley; Weight: 50-75 g | 0.8 | 56 days, 8 h/day | Enhanced the sensitivity to myocardial I/R injury while increasing oxidative stress and pro-inflammatory mediators and decreasing production of anti-inflammatory proteins. |

No previous studies investigated cardiovascular effects from long-term exposure to O₃.

For details, see Section [7.3.1.2](#)

7.3.2 Cardiovascular Mortality

1 A limited number of epidemiologic studies have assessed the relationship between long-
2 term exposure to O₃ and mortality. The 2006 O₃ AQCD concluded that an insufficient
3 amount of evidence existed “to suggest a causal relationship between chronic O₃
4 exposure and increased risk for mortality in humans” ([U.S. EPA, 2006b](#)). Though total
5 and cardio-pulmonary mortality were considered in these studies, cardiovascular
6 mortality was not specifically considered. In the most recent follow-up analysis of the
7 ACS cohort ([Jerrett et al., 2009](#)), cardiopulmonary deaths were subdivided into
8 respiratory and cardiovascular, separately, as opposed to combined in the [Pope et al.](#)
9 ([2002](#)) work. A 10-ppb increment in exposure to O₃ elevated the risk of death from the
10 cardiopulmonary, cardiovascular, and ischemic heart disease. Inclusion of PM_{2.5} as a
11 copollutant attenuated the association with exposure to O₃ for all of the cardiovascular
12 endpoints to become null. Additionally, a recent study ([Zanobetti and Schwartz, 2011](#))
13 observed an association between long-term exposure to O₃ and elevated risk of mortality
14 among Medicare enrollees that had previously experienced an emergency hospital
15 admission due to congestive heart failure (CHF) or myocardial infarction (MI).

7.3.3 Summary and Causal Determination

16 Previous AQCDs did not address the cardiovascular effects of long-term O₃ exposure due
17 to limited data availability. The evidence remains limited; however the emerging data is
18 supportive of a role for O₃ in chronic cardiovascular diseases. Few epidemiologic studies
19 have investigated cardiovascular morbidity after long-term O₃ exposure, and the majority
20 only assessed cardiovascular disease related biomarkers. The studies used annual or

1 multi-year averages of air monitoring data for exposure assessment. As described in
2 Section [4.6](#), this exposure assignment method is typical of long-term epidemiologic
3 studies, and analyses suggest that annual average concentrations are representative of
4 exposure metrics accounting for residential mobility. A study on O₃ and cardiovascular
5 mortality reported no association after adjustment for PM_{2.5} levels. Further epidemiologic
6 studies on cardiovascular morbidity and mortality after long-term exposure have not been
7 published.

8 Toxicological evidence on long-term O₃ exposure is also limited but three strong
9 toxicological studies have been published since the previous AQCD. These studies
10 provide evidence for O₃ enhanced atherosclerosis and I/R injury, corresponding with
11 development of a systemic oxidative, proinflammatory environment. Further discussion
12 of the mechanisms that may lead to cardiovascular effects can be found in Section [5.3.8](#).
13 Although questions exist for how O₃ inhalation causes systemic effects, a recent study
14 proposes a mechanism for development of vascular pathology that involves activation of
15 LOX-1 by O₃ oxidized lipids and proteins. This activation may also be responsible for O₃
16 induced changes in genes involved in proteolysis, thrombosis, and vasoconstriction.
17 Taking into consideration the findings of toxicological studies, and the emerging
18 evidence from epidemiologic studies, the generally limited body of evidence **is**
19 **suggestive of a causal relationship between long-term exposures to O₃ and**
20 **cardiovascular effects.**

7.4 Reproductive and Developmental Effects

21 Although the body of literature characterizing the health effects associated with exposure
22 to O₃ is large and continues to grow, the research focusing on adverse birth outcomes is
23 relatively small. Among these studies, various measures of birth weight and fetal growth,
24 such as low birth weight (LBW), small for gestational age (SGA), and intrauterine
25 growth restriction (IUGR), and preterm birth (<37-week gestation; [PTB]) have received
26 more attention in air pollution research, while congenital malformations are less studied.
27 There are also recent studies on reproductive and developmental effects and infant
28 mortality.

29 A major issue in studying environmental exposures and reproductive and developmental
30 effects (including infant mortality) is selecting the relevant exposure period, since the
31 biological mechanisms leading to these outcomes and the critical periods of exposure are
32 poorly understood. To account for this, many epidemiologic studies evaluate multiple
33 exposure periods, including long-term (months to years) exposure periods, such as entire
34 pregnancy, individual trimesters or months of pregnancy, and short-term (days to weeks)

1 exposure periods such as the days and weeks immediately preceding birth. Due to the
2 length of gestation in rodents (18-24 days, on average), animal toxicological studies
3 investigating the effects of O₃ generally utilize short-term exposure periods. Thus, an
4 epidemiologic study that uses the entire pregnancy as the exposure period is considered
5 to have a long-term exposure period (about 40 weeks, on average), while a toxicological
6 study conducted with rats that also uses the entire pregnancy as the exposure period is
7 considered to have a short-term exposure period (about 18-24 days, on average). In order
8 to characterize the weight of evidence for the effects of O₃ on reproductive and
9 developmental effects in a consistent, cohesive and integrated manner, results from both
10 short-term and long-term exposure periods are included in this section and are identified
11 accordingly in the text and tables throughout this section.

12 Due to the poorly understood biological mechanisms and uncertainty regarding relevant
13 exposure studies, all of the studies of reproductive and developmental outcomes,
14 including infant mortality, are evaluated in this section. Infant development processes,
15 much like fetal development processes, may be particularly sensitive to O₃-induced
16 health effects. Exposures proximate to the death may be most relevant if exposure causes
17 an acute effect. However, exposure occurring in early life might affect critical growth and
18 development, with results observable later in the first year of life, or cumulative exposure
19 during the first year of life may be the most important determinant. In dealing with the
20 uncertainties surrounding these issues, studies have considered several exposure metrics
21 based on different periods of exposure, including both short- and long-term exposure
22 periods. In the toxicological literature, a challenge in interpreting data from studies that
23 use very young murine pups, is that pups can have differential exposure to O₃ doses,
24 versus their respective dams, because of the physiology and behavior associated with the
25 early postnatal period. Namely, young pups tend to nuzzle close to their mothers and are
26 often housed in cages with litter used in nest formation. Both the dam's fur and the
27 bedding can absorb and react with O₃, decreasing the dose that a young animal might
28 receive. The reproductive and developmental studies are characterized in this chapter, as
29 they contribute to the weight of evidence for an effect of O₃ on reproductive and
30 developmental effects.

31 Infants and fetal development processes may be particularly at-risk for O₃-induced health
32 effects, and although the physical mechanisms are not fully understood, several
33 hypotheses have been proposed; these include: oxidative stress, systemic inflammation,
34 vascular dysfunction and impaired immune function (Section 5.3). Study of these
35 outcomes can be difficult given the need for detailed exposure data and potential
36 residential movement of mothers during pregnancy. Air pollution epidemiologic studies
37 reviewed in the 2006 O₃ AQCD examined impacts on birth-related endpoints, including
38 intrauterine, perinatal, postneonatal, and infant deaths; premature births; intrauterine

1 growth retardation; very low birth weight (weight <1,500 grams) and low birth weight
2 (weight <2,500 grams); and birth defects. However, in the limited number of studies that
3 investigated O₃, no associations were found between O₃ and birth outcomes, with the
4 possible exception of birth defects.

5 Several recent articles have reviewed methodological issues relating to the study of
6 outdoor air pollution and adverse birth outcomes ([Chen et al., 2010a](#); [Woodruff et al.,
7 2009](#); [Ritz and Wilhelm, 2008](#); [Slama et al., 2008](#)). Some of the key challenges to
8 interpretation of these study results include the difficulty in assessing exposure as most
9 studies use existing monitoring networks to estimate individual exposure to ambient air
10 pollution; the inability to control for potential confounders such as other risk factors that
11 affect birth outcomes (e.g., smoking); evaluating the exposure window (e.g., trimester) of
12 importance; and limited evidence on the physiological mechanism of these effects ([Ritz
13 and Wilhelm, 2008](#); [Slama et al., 2008](#)).

14 Overall, the evidence for an association between exposure to ambient O₃ and
15 reproductive and developmental outcomes is growing, yet remains relatively small.
16 Recently, an international collaboration was formed to better understand the relationships
17 between air pollution and adverse birth outcomes and to examine some of these
18 methodological issues through standardized parallel analyses in datasets from different
19 countries ([Woodruff et al., 2010](#)). Initial results from this collaboration have examined
20 PM and birth weight ([Parker et al., 2011](#)); work on O₃ has not yet been performed.
21 Although early animal studies ([Kavlock et al., 1980](#)) found that exposure to O₃ in the late
22 gestation of pregnancy in rats led to some abnormal reproductive performances for
23 neonates, to date human studies have reported inconsistent results for the association of
24 ambient O₃ concentrations and birth outcomes.

7.4.1 Effects on Sperm

25 A limited amount of research has been conducted to examine the association between air
26 pollution and male reproductive outcomes, specifically semen quality. To date, the
27 epidemiologic studies have considered various exposure durations before semen
28 collection that encompass either the entire period of spermatogenesis (i.e., 90 days) or
29 key periods of sperm development that correspond to epididymal storage, development of
30 sperm motility, and spermatogenesis. In an analysis conducted as part of the Teplice
31 Program, 18-year-old men residing in the heavily polluted district of Teplice in the Czech
32 Republic were found to be at greater risk of having abnormalities in sperm morphology
33 and chromatin integrity than men of similar age residing in Prachatice, a less polluted
34 district ([Selevan et al., 2000](#); [Sram et al., 1999](#)). A follow-up longitudinal study

1 conducted on a subset of the same men from Teplice revealed associations between total
2 episodic air pollution and abnormalities in sperm chromatin ([Rubes et al., 2005](#)). A
3 limitation of these studies is that they did not identify specific pollutants or their
4 concentrations.

5 More recent epidemiologic studies conducted in the U.S. have also reported associations
6 between ambient air pollution and sperm quality for individual air pollutants, including
7 O₃ and PM_{2.5}. In a repeated measures study in Los Angeles, CA, [Sokol et al. \(2006\)](#)
8 reported a reduction in average sperm concentration during three exposure windows
9 (short-term exposures of 0-9, 10-14, and 70-90 days before semen collection, as well as
10 long-term exposures of 0-90 days before semen collection) associated with high ambient
11 levels of O₃ in healthy sperm donors. This effect persisted under a joint additive model
12 for O₃, CO, NO₂ and PM₁₀. The authors did not detect a reduction in sperm count. [Hansen
13 et al. \(2010\)](#) investigated the effect of exposure to O₃ and PM_{2.5} (using the same exposure
14 windows used by [Sokol et al. \(2006\)](#) on sperm quality in three southeastern counties
15 (Wake County, NC; Shelby County, TN; Galveston County, TX). Outcomes included
16 sperm concentration and count, morphology, DNA integrity and chromatin maturity.
17 Overall, the authors found both protective and adverse effects, although some results
18 suggested adverse effects on sperm concentration, count and morphology.

19 The biological mechanisms linking ambient air pollution to decreased sperm quality have
20 yet to be determined, though O₃-induced oxidative stress, inflammatory reactions, and the
21 induction of the formation of circulating toxic species have been suggested as possible
22 mechanisms (see Section [5.3.8](#)). Decremental effects on testicular morphology have been
23 demonstrated in a toxicological study with histological evidence of O₃-induced depletion
24 of germ cells in testicular tissue and decreased seminiferous tubule epithelial layer.
25 [Jedlinska-Krakowska et al. \(2006\)](#) demonstrated histopathological evidence of impaired
26 spermatogenesis (round spermatids/ spermatocytes, giant spermatid cells, and focal
27 epithelial desquamation with denudation to the basement membrane). The exposure
28 protocol used five-month-old adult rats exposed to O₃ as adults (long-term exposure,
29 0.5 ppm, 5 h/day for 50 days). This degeneration could be rescued by vitamin E
30 administration, indicating an antioxidant effect. Vitamin C administration had no effect at
31 low doses of ascorbic acid and exacerbated the O₃-dependent damage at high doses, as
32 would be expected as vitamin C can be a radical generator instead of an antioxidant at
33 higher doses. In summary, this study provided toxicological evidence of impaired
34 spermatogenesis with O₃ exposure that was rescued with certain antioxidant
35 supplementation.

36 Overall, there is limited epidemiologic evidence for an association with O₃ concentration
37 and decreased sperm concentration. A recent toxicological study provides limited

1 evidence for a possible biological mechanism (histopathology showing impaired
2 spermatogenesis) for such an association.

7.4.2 Effects on Reproduction

3 Evidence suggests that exposure to air pollutants during pregnancy may be associated
4 with adverse birth outcomes, which has been attributed to the increased sensitivity of the
5 fetus due to physiologic immaturity. Gametes (i.e., ova and sperm) may be even more at-
6 risk, especially outside of the human body, as occurs with assisted reproduction. Smokers
7 require twice the number of in vitro fertilization (IVF) attempts to conceive as non-
8 smokers ([Feichtinger et al., 1997](#)), suggesting that a preconception exposure can be
9 harmful to pregnancy. A recent study used an established national-scale, log-normal
10 kriging method to spatially estimate daily mean concentrations of criteria pollutants at
11 addresses of women undergoing their first IVF cycle and at their IVF labs from 2000 to
12 2007 in the northeastern U.S. ([Legro et al., 2010](#)). Increasing O₃ concentration at the
13 patient's address during ovulation induction (short-term exposure, ~12 days) was
14 significantly associated with an increased chance of live birth (OR = 1.13, [95% CI: 1.05,
15 1.22] per 10 ppb increase), but with decreased odds of live birth when exposed from
16 embryo transfer to live birth (long-term exposure, ~200 days) (OR = 0.79, [95% CI: 0.69,
17 0.90] per 10 ppb increase). After controlling for NO₂ in a copollutant model, however, O₃
18 was no longer significantly associated with IVF failure. The results of this study suggest
19 that short-term exposure to O₃ during ovulation was beneficial (perhaps due to early
20 conditioning to O₃), whereas long-term exposure to O₃ (e.g., during gestation) was
21 detrimental, and reduced the likelihood of a live birth.

22 In most toxicological studies, reproductive success appears to be unaffected by O₃
23 exposure. Nonetheless, one study has reported that 25% of the BALB/c mouse dams in
24 the highest O₃ exposure group (1.2 ppm, short-term exposure GD9-18) did not complete
25 a successful pregnancy, a significant reduction ([Sharkhuu et al., 2011](#)). Ozone
26 administration (continuous 0.4, 0.8 or 1.2 ppm O₃) to CD-1 mouse dams during the
27 majority of pregnancy (short-term exposure, PD7-17, which excludes the
28 pre-implantation period), led to no adverse effects on reproductive success (proportion of
29 successful pregnancies, litter size, sex ratio, frequency of still birth, or neonatal mortality)
30 ([Bignami et al., 1994](#)). There was a nearly statistically significant increase in pregnancy
31 duration (0.8 and 1.2 ppm O₃). Initially, dam body weight (0.8 and 1.2 ppm O₃), water
32 consumption (0.4, 0.8 and 1.2 ppm O₃) and food consumption (0.4, 0.8 and 1.2 ppm O₃)
33 during pregnancy were decreased with O₃ exposure but these deficits dissipated a week or
34 two after the initial exposure ([Bignami et al., 1994](#)). The anorexigenic effect of O₃
35 exposure on the pregnant dam appears to dissipate with time; the dams seem to adapt to

1 the O₃ exposure. In males, data exist showing morphological evidence of altered
2 spermatogenesis in O₃ exposed animals ([Jedlińska-Krakowska et al., 2006](#)). Some
3 evidence suggests that O₃ may affect reproductive success when combined with other
4 chemicals. [Kavlock et al. \(1979\)](#) showed that O₃ acted synergistically with sodium
5 salicylate to increase the rate of pup resorptions after midgestational exposure (1.0 ppm
6 O₃, short-term exposure, GD9-GD12). At low concentrations of O₃ exposure,
7 toxicological studies show reproductive effects to include a transient anorexigenic effect
8 of O₃ on gestational weight gain, and a synergistic effect of O₃ on salicylate-induced pup
9 resorptions; other fecundity, pregnancy- and gestation-related outcomes appear
10 unaffected by O₃ exposure.

11 Collectively, there is very little epidemiologic evidence for the effect of short- or long-
12 term exposure to O₃ on reproductive success, and the reproductive success in rats appears
13 to be unaffected in toxicological studies of short-term exposure to O₃.

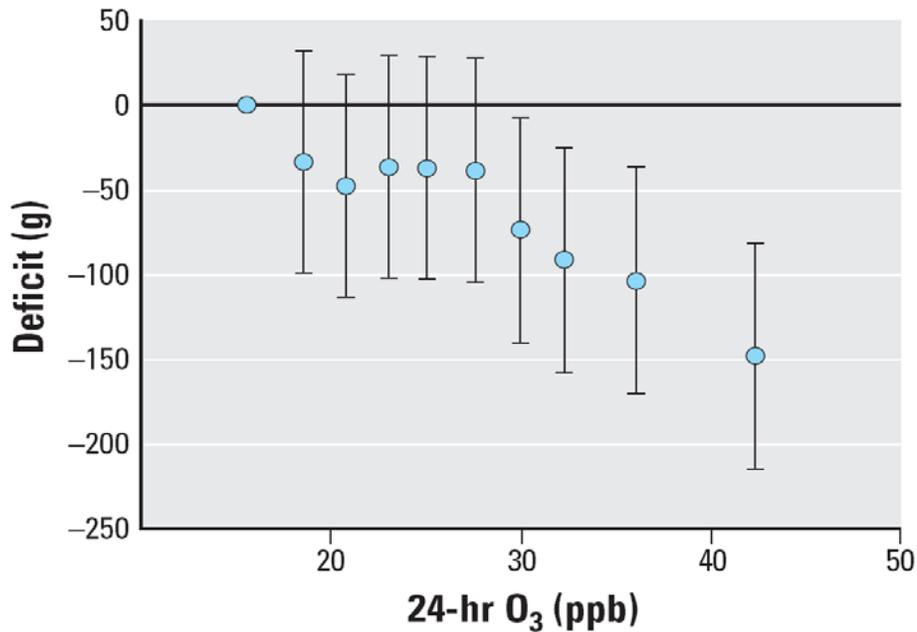
7.4.3 Birth Weight

14 With birth weight routinely collected in vital statistics and being a powerful predictor of
15 infant mortality, it is the most studied outcome within air pollution-birth outcome
16 research. Air pollution researchers have analyzed birth weight as a continuous variable
17 and/or as a dichotomized variable in the form of LBW (<2,500 g [5 lbs, 8 oz]).

18 Birth weight is primarily determined by gestational age and intrauterine growth, but also
19 depends on maternal, placental and fetal factors as well as on environmental influences.
20 In both developed and developing countries, LBW is the most important predictor for
21 neonatal mortality and is a significant determinant of postneonatal mortality and
22 morbidity. Studies report that infants who are smallest at birth have a higher incidence of
23 diseases and disabilities, which continue into adulthood ([Hack and Fanaroff, 1999](#)).

24 The strongest evidence for an effect of O₃ on birth weight comes from the Children's
25 Health Study conducted in southern California. In this study, [Salam et al. \(2005\)](#) report
26 that maternal exposure to 24-h avg O₃ concentrations averaged over the entire pregnancy
27 was associated with reduced birth weight (39.3 g decrease [95% CI: -55.8, -22.8] in birth
28 weight per 10 ppb and 8-h avg (19.2-g decrease [95% CI: -27.7, -10.7] in birth weight per
29 10 ppb). This effect was stronger for concentrations averaged over the second and third
30 trimesters. PM₁₀, NO₂ and CO concentrations averaged over the entire pregnancy were
31 not statistically significantly associated with birth weight, although CO concentrations in
32 the first trimester and PM₁₀ concentrations in the third trimester were associated with a
33 decrease in birth weight. Additionally, the authors observed a concentration-response
34 relationship of birth weight with 24-h avg O₃ concentrations averaged over the entire

1 pregnancy that was clearest above the 30-ppb level (see [Figure 7-4](#)). Relative to the
2 lowest decile of 24-h avg O₃, estimates for the next 5 lowest deciles were approximately
3 -40 g to -50 g, with no clear trend and with 95% confidence bounds that included zero.
4 The highest four deciles of O₃ exposure showed an approximately linear decrease in birth
5 weight, and all four 95% CIs excluded zero, and ranged from mean decreases of
6 74 grams to decreases of 148 grams.



Note: Deficits are plotted against the decile-group-specific median O₃ exposure. Error bars represent 95% CIs. Indicator variables for each decile of O₃ exposure (except the least-exposed group) were included in a mixed model.
Source: [Salam et al. \(2005\)](#).

Figure 7-4 Birthweight deficit by decile of 24-h avg ozone concentration averaged over the entire pregnancy compared with the decile group with the lowest ozone exposure.

7 Several additional studies conducted in the U.S. and Canada also investigated the
8 association between ambient O₃ concentrations and birth weight and report some weak
9 evidence for an association. [Morello-Frosch et al. \(2010\)](#) estimated ambient O₃
10 concentrations throughout pregnancy and for each trimester in the neighborhoods of
11 women who delivered term singleton births between 1996 and 2006 in California. A
12 10-ppb increase in the O₃ concentration averaged across the entire pregnancy was
13 associated with a 5.7-g decrease (95% CI: -6.6, -4.9) in birth weight when exposures
14 were calculated using monitors within 10 km of the maternal address at date of birth.

1 When the distance from the monitor was restricted to 3 km, the decrease in birth weight
2 associated with a 10-ppb increase in O₃ concentration was 8.9 g (95% CI: -10.6, -7.1).
3 These results persisted in copollutant models and in models that stratified by trimester of
4 exposure, SES, and race. [Darrow et al. \(2011b\)](#) did not observe an association with birth
5 weight and O₃ concentrations during two exposure periods of interest (i.e., the first month
6 and last trimester), but did find an association with reduced birth weight when examining
7 the cumulative air pollution concentration during the entire pregnancy period.
8 Additionally, they observed effect modification by race and ethnicity, such that
9 associations between birth weight and third-trimester O₃ concentrations were
10 significantly stronger in Hispanics and non-Hispanic African Americans than in non-
11 Hispanic whites. [Chen et al. \(2002\)](#) used 8-h avg O₃ concentrations to create exposure
12 variables based on average maternal exposure for each trimester. Ozone was not found to
13 be related to birth weight in single-pollutant models, though the O₃ effect during the third
14 trimester was borderline statistically significant in a copollutant model with PM₁₀.

15 Several studies found no association between ambient O₃ concentrations and birth
16 weight. [Wilhelm and Ritz \(2005\)](#) extended previous analyses of term LBW ([Ritz et al.,
2000](#); [Ritz and Yu, 1999](#)) to include the period 1994-2000. The authors examined varying
17 residential distances from monitoring stations to see if the distance affected risk
18 estimation, exploring the possibility that effect attenuation may result from local pollutant
19 heterogeneity inadequately captured by ambient monitors. As in their previous studies,
20 the authors observed associations between elevated concentrations of CO and PM₁₀ both
21 early and late in pregnancy and risk of term LBW. After adjusting for CO and/or PM₁₀
22 the authors did not observe associations between O₃ and term LBW in any of their
23 models. [Brauer et al. \(2008\)](#) evaluated the impacts of air pollution (CO, NO₂, NO, O₃,
24 SO₂, PM_{2.5}, PM₁₀) on birth weight for the period 1999-2002 using spatiotemporal
25 residential exposure metrics by month of pregnancy in Vancouver, BC. Quantitative
26 results were not presented for the association between O₃ and LBW, though the authors
27 observed associations that were largely protective. [Dugandzic et al. \(2006\)](#) examined the
28 association between LBW and ambient levels of air pollutants by trimester of exposure
29 among a cohort of term singleton births from 1988-2000. Though there was some
30 indication of an association with SO₂ and PM₁₀, there were no effects for O₃.

31
32 Similarly, studies conducted in Australia, Latin America, and Asia report limited
33 evidence for an association between ambient O₃ and measures of birth weight. In Sydney,
34 Australia, [Mannes et al. \(2005\)](#) found that O₃ concentrations in the second trimester of
35 pregnancy had small adverse effects on birth weight (7.5-g decrease; [95% CI: -13.8, 1.2]
36 per 10 ppb), although this effect disappeared when the analysis was limited to births with
37 a maternal address within 5 km of a monitoring station (87.7-g increase; [95% CI: 10.5,
38 164.9] per 10 ppb). [Hansen et al. \(2007\)](#) reported that trimester and monthly specific

1 exposures to all pollutants were not statistically significantly associated with a reduction
 2 in birth weight in Brisbane, Australia. In Sao Paulo, Brazil, [Gouveia et al. \(2004\)](#) found
 3 that O₃ exhibited a small inverse relation with birth weight over the third trimester (6.0-g
 4 decrease; [95% CI: -30.8, 18.8] per 10 ppb). [Lin et al. \(2004b\)](#) reported a positive, though
 5 not statistically significant, exposure-response relationship for O₃ during the entire
 6 pregnancy in a Taiwanese study. In a study performed in Korea, [Ha et al. \(2001\)](#) reported
 7 no O₃ effect during the first trimester of pregnancy, but they found that during the third
 8 trimester of pregnancy O₃ was associated with LBW (RR = 1.05 [95% CI: 1.02, 1.08] per
 9 10 ppb).

Table 7-4 Brief Summary of Epidemiologic Studies of Birth Weight.

| Study | Location Sample Size | Mean O ₃ (ppb) | Exposure assessment | Effect Estimate ^a (95% CI) |
|--|--|-----------------------------------|--|--|
| Salam et al. (2005) | California, U.S. (n = 3,901) | 24-h avg: 27.3 8 h: 50.6 | ZIP code level | Entire pregnancy: -39.3 g (-55.8, -22.8) T1: -6.1 g (-16.8, 4.8) T2: -20.0 g (-31.7, -8.4) T3: -20.7 g (-32.1, -9.3) |
| Morello-Frosch et al. (2010) | California, U.S. (n = 3,545,177) | 24-h avg: 23.5 | Nearest Monitor (within 10, 5, 3 km) | Entire pregnancy: -5.7 g (-6.6, -4.9) T1: -2.1 g (-2.9, -1.4) T2: -2.3 g (-3.1, -1.5) T3: -1.3 g (-2.1, -0.6) |
| Darrow et al. (2011b) | Atlanta, GA (N=406,627) | 8-h max: 44.8 | Population-weighted spatial average | Entire pregnancy: -12.3 g (-17.8, -6.8) First 28 days -0.5 g (-3.0, 2.1) T3: -0.9g (-4.5, 2.8) |
| Chen et al. (2002) | Northern Nevada, U.S. (n = 36,305) | 8-h: 27.2 | County level | Entire pregnancy: 20.9 g (6.3, 35.5) T1: 23.4 g (-35.6, 82.4) T2: -19.4 g (-77.0, 38.2) T3: 7.7 g (-50.9, 66.3) |
| Wilhelm and Ritz (2005) | Los Angeles County, CA (n = 136,134) | 1-h: 21.1-22.2 | Varying distances from monitor | T1: NR T3: NR 6 weeks before birth: NR |
| Brauer et al. (2008) | Vancouver, BC, Canada (n = 70,249) | 24-h avg: 14 | Nearest Monitor (within 10 km) Inverse Distance Weighting (IDW) | Entire pregnancy: NR First 30 days of pregnancy: NR Last 30 days of pregnancy: NR T1: NR T3: NR |
| Dugandzic et al. (2006) | Nova Scotia, Canada (n = 74,284) | 24-h avg: 21 | Nearest Monitor (within 25 km) | T1: 0.97 (0.81, 1.18) ^d T2: 1.06 (0.87, 1.27) ^d T3: 1.01 (0.83-1.24) ^d |

| Study | Location Sample Size | Mean O ₃ (ppb) | Exposure assessment | Effect Estimate ^a (95% CI) |
|---------------------------------------|---|------------------------------------|--|---|
| Mannes et al. (2005) | Sydney, Australia (n = 138,056) | 1-h max: 31.6 | Citywide avg and <5 km from monitor | T1: -0.9 g (-6.6, 4.8) T2: -7.5 g (-13.8, 1.2) T3: -4.5 g (-10.8, 1.8) Last 30 days: -1.1 g (-5.6, 3.4) |
| Hansen et al. (2007) | Brisbane, Australia (n = 26,617) | 8 h max: 26.7 | Citywide avg | T1: 2.8 g (-10.5, 16.0) T2: 4.4 g (-11.4, 20.1) T3: 11.3 g (-4.4, 27.1) |
| Gouveia et al. (2004) | Sao Paulo, Brazil (n = 179,460) | 1-h max: 31.5 | Citywide avg | T1: -3.2 g (-25.6, 19) T2: -0.2 g (-23.8, 23.4) T3: -6.0 g (-30.8, -18.8) |
| Lin et al. (2004b) | Kaohsiung and Taipei, Taiwan (n = 92,288) | 24-h avg: 15.86- 47.78 | Nearest monitor (within 3 km) | Entire pregnancy: 1.13 (0.92, 1.38) ^c T1: 1.02 (0.85, 1.22) ^c T2: 0.93 (0.78, 1.12) ^c T3: 1.05 (0.87, 1.26) ^c |
| Ha et al. (2001) | Seoul, Korea (n = 276,763) | 8-h avg: 22.4-23.3 ^b | Citywide avg | T1: 0.87 (0.81, 0.94) ^c T3: 1.05 (1.02, 1.08) ^c |

^aChange in birthweight per 10 ppb change in O₃

^bMedian

^cOdds ratios of LBW; Highest quartile of exposure compared to lowest quartile of exposure

^dRelative risk of LBW per 10 ppb change in O₃

T1 = First Trimester, T2 = Second Trimester, T3 = Third Trimester

NR: No quantitative results reported

1 [Table 7-4](#) provides a brief overview of the epidemiologic studies of birth weight. In
2 summary, only the Children's Health Study conducted in southern California ([Salam et](#)
3 [al., 2005](#)) provides strong evidence for an effect of ambient O₃ on birth weight. The study
4 by [Morello-Frosch et al. \(2010\)](#), also conducted in California, provides support for the
5 results of the Children's Health Study. Additional studies, conducted in the U.S., Canada,
6 Australia, Latin America, and Asia, provide limited and inconsistent evidence to support
7 the effect reported in the Children's Health Study. The toxicological literature on the
8 effect of O₃ on birth weight is sparse. In some studies, the reporting of birth weight may
9 be avoided because birth weight can be confounded by decreased litter size resulting
10 from an increased rate of pup resorption (aborted pups) in O₃ exposed dams. In one
11 toxicological study by [Haro and Paz \(1993\)](#), no differences in litter size were observed
12 and decreased birth weight in pups from dams who were exposed to 1ppm O₃ during
13 pregnancy (short-term exposure, ~22 days) was reported. A second animal toxicology
14 study recapitulated these finding with pregnant BALB/c mice that exposed to O₃
15 (1.2 ppm, short-term exposure, GD9-18) producing pups with significantly decreased
16 birth weights ([Sharkhuu et al., 2011](#)).

7.4.4 Preterm Birth

1 Preterm birth (PTB) is a syndrome ([Romero et al., 2006](#)) that is characterized by multiple
2 etiologies. It is therefore unusual to be able to identify an exact cause for each PTB. In
3 addition, PTB is not an adverse outcome in itself, but an important determinant of health
4 status (i.e., neonatal morbidity and mortality). Although some overlap exists for common
5 risk factors, different etiologic entities related to distinct risk factor profiles and leading
6 to different neonatal and postneonatal complications are attributed to PTB and measures
7 of fetal growth. Although both restricted fetal growth and PTB can result in LBW,
8 prematurity does not have to result in LBW or growth restricted babies.

9 A major issue in studying environmental exposures and PTB is selecting the relevant
10 exposure period, since the biological mechanisms leading to PTB and the critical periods
11 of vulnerability are poorly understood ([Bobak, 2000](#)). Short-term exposures proximate to
12 the birth may be most relevant if exposure causes an acute effect. However, exposure
13 occurring in early gestation might affect placentation, with results observable later in
14 pregnancy, or cumulative exposure during pregnancy may be the most important
15 determinant. The studies reviewed have dealt with this issue in different ways. Many
16 have considered several exposure metrics based on different periods of exposure. Often
17 the time periods used are the first month (or first trimester) of pregnancy and the
18 last month (or 6 weeks) prior to delivery. Using a time interval prior to delivery
19 introduces an additional problem since cases and controls are not in the same stage of
20 development when they are compared. For example, a preterm infant delivered at
21 36 weeks is a 32-week fetus 4 weeks prior to birth, while an infant born at term
22 (40 weeks) is a 36-week fetus 4 weeks prior to birth.

23 Recently, investigators have examined the association of PTB with both short-term
24 (i.e., hours, days, or weeks) and long-term (i.e., months or years) exposure periods. Time-
25 series studies have been used to examine the association between air pollution
26 concentrations during the days immediately preceding birth. An advantage of these time-
27 series studies is that this approach can remove the influence of covariates that vary across
28 individuals over a short period of time. Retrospective cohort and case-control studies
29 have been used to examine long-term exposure periods, often averaging air pollution
30 concentrations over months or trimesters of pregnancy.

31 Studies of PTB fail to show consistency in pollutants and periods during pregnancy when
32 an effect occurs. For example, while some studies find the strongest effects associated
33 with exposures early in pregnancy, others report effects when the exposure is limited to
34 the second or third trimester. However, the effect of air pollutant exposure during
35 pregnancy on PTB has a biological basis. There is an expanding list of possible

1 mechanisms that may explain the association between O₃ exposure and PTB (see
2 Section [5.4.2.4](#)).

3 Many studies of PTB compare exposure in quartiles, using the lowest quartile as the
4 reference (or control) group. No studies use a truly unexposed control group. If exposure
5 in the lowest quartile confers risk, than it may be difficult to demonstrate additional risk
6 associated with a higher quartile. Thus negative studies must be interpreted with caution.

7 Preterm birth occurs both naturally (idiopathic PTB), and as a result of medical
8 intervention (iatrogenic PTB). [Ritz et al. \(2007\)](#); [\(2000\)](#) excluded all births by Cesarean
9 section to limit their studies to idiopathic PTB. No other studies attempted to distinguish
10 the type of PTB, although air pollution exposure maybe associated with only one type.
11 This is a source of potential effect misclassification.

12 Generally, studies of air pollution and birth outcomes conducted in North America and
13 the United Kingdom have not identified an association between PTB and maternal
14 exposure to O₃. Most recently, [Darrow et al. \(2009\)](#) used vital record data to construct a
15 retrospective cohort of 476,489 births occurring between 1994 and 2004 in 5 central
16 counties of metropolitan Atlanta. Using a time-series approach, the authors examined
17 aggregated daily counts of PTB in relation to ambient levels of CO, NO₂, SO₂, O₃, PM₁₀,
18 PM_{2.5} and speciated PM measurements. This study investigated 3 gestational windows of
19 short- and long-term exposure: the final week of gestation (short-term exposure), and the
20 first month of gestation and the final 6 weeks of gestation (long-term exposure). The
21 authors did not observe associations of PTB with O₃ concentrations for any of the
22 exposure periods.

23 A number of U.S. studies were conducted in southern California, and report somewhat
24 inconsistent results. [Ritz et al. \(2000\)](#) evaluated the effect of air pollution (CO, NO₂, O₃,
25 PM₁₀) exposure during pregnancy on the occurrence of PTB in a cohort of 97,518
26 neonates born in southern California between 1989 and 1993. The authors use both short-
27 and long-term exposure windows, averaging pollutant measures taken at the closest air-
28 monitoring station over distinct periods, such as 1, 2, 4, 6, 8, 12, and 26 weeks before
29 birth and the whole pregnancy period. Additionally, they calculated average exposures
30 for the first and second months of pregnancy. The authors found no consistent effects
31 associated with O₃ concentration over any of the pregnancy periods in single or
32 multipollutant models. [Wilhelm and Ritz \(2005\)](#) extended previous analyses of PTB ([Ritz
33 et al., 2000](#); [Ritz and Yu, 1999](#)) in California to include 1994-2000. The authors
34 examined varying residential distances from monitoring stations to see if the distance
35 affected risk estimation, because effect attenuation may result from local pollutant
36 heterogeneity inadequately captured by ambient monitors. The authors analyzed the
37 association between long-term O₃ exposure during varying periods of pregnancy and

1 PTB, finding a positive association between O₃ levels in both the first trimester of
2 pregnancy (RR = 1.23 [95% CI: 1.06, 1.42] per 10 ppb increase in 24-h avg O₃) and the
3 first month of pregnancy (results for first trimester exposure were similar, but slightly
4 smaller, quantitative results not presented) in models containing all pollutants. No
5 association was observed between O₃ in the 6 weeks before birth and preterm delivery.
6 Finally, [Ritz et al. \(2007\)](#) conducted a case-control survey nested within a birth cohort
7 and assessed the extent to which residual confounding and exposure misclassification
8 impacted air pollution effect estimates. The authors calculated mean long-term exposure
9 levels for three gestational periods: the entire pregnancy, the first trimester, and the last
10 6 weeks before delivery. Though positive associations were observed for CO and PM_{2.5},
11 no consistent patterns of increase in the odds of PTB for O₃ or NO₂ were observed.

12 A study conducted in Canada evaluated the impacts of air pollution (including CO, NO₂,
13 NO, O₃, SO₂, PM_{2.5}, and PM₁₀) on PTBs (1999-2002) using spatiotemporal residential
14 exposure metrics by month of pregnancy (long-term exposure) in Vancouver, BC ([Brauer
15 et al., 2008](#)). The authors did not observe consistent associations with any of the
16 pregnancy average exposure metrics except for PM_{2.5} for PTB. The O₃ associations were
17 largely protective, and no quantitative results were presented for O₃. Additionally, [Lee et
18 al. \(2008c\)](#) used time-series techniques to investigate the associations of short-term
19 exposure to O₃ and PTB in London, England. In addition to exposure on the day of birth,
20 cumulative exposure up to 1 week before birth was investigated. The risk of PTB did not
21 increase with exposure to the levels of ambient air pollution experienced by this
22 population.

23 Conversely, studies conducted in Australia and China provide evidence for an association
24 between ambient O₃ and PTB. [Hansen et al. \(2006\)](#) reported that long-term exposure to
25 O₃ during the first trimester was associated with an increased risk of PTB (OR = 1.38,
26 [95% CI: 1.14, 1.69] per 10 ppb increase). Although the test for trend was significant due
27 to the strong effect in the highest quartile, there was not an obvious exposure-response
28 pattern across the quartiles of O₃ during the first trimester. The effect estimate was
29 diminished and lost statistical significance when PM₁₀ was included in the model
30 (OR = 1.23, [95% CI: 0.97, 1.59] per 10 ppb increase). Maternal exposure to O₃ during
31 the 90 days prior to birth showed a weak, positive association with PTB (OR = 1.09,
32 [95% CI: 0.85, 1.39] per 10 ppb increase). [Jalaludin et al. \(2007\)](#) found that O₃ levels in
33 the month and three months preceding birth had a statistically significant association with
34 PTB. Ozone levels in the first trimester of pregnancy were associated with increased risks
35 for PTBs (OR = 1.15 [95% CI: 1.05, 1.24] per 10 ppb increase in 1-h max O₃
36 concentration), and remained a significant predictor of PTB in copollutant models (ORs
37 between 1.07 and 1.10). [Jiang et al. \(2007\)](#) examined the effect of short- and long-term
38 exposure to air pollution on PTB, including risk in relation to levels of pollutants for a

1 single day exposure window with lags from 0 to 6 days before birth. An increase of
2 10 ppb of the 8-week avg of O₃ corresponded to 9.47% (95% CI: 0.70, 18.7%) increase in
3 PTBs. Increases in PTB were also observed for PM₁₀, SO₂, and NO₂. The authors did not
4 observe any significant effect of short-term exposure to outdoor air pollution on PTB
5 among the 1-day time windows examined in the week before birth.

6 Little data is available from toxicological studies; a study reported a nearly statistically
7 significant increase in pregnancy duration (short-term exposure) in mice when exposed to
8 0.8 or 1.2 ppm O₃. This phenomenon was most likely due to the anorexigenic effect of
9 relatively high O₃ concentrations ([Bignami et al., 1994](#)).

10 [Table 7-5](#) provides a brief overview of the epidemiologic studies of PTB. In summary,
11 the evidence is consistent when examining short-term exposure to O₃ during late
12 pregnancy and reports no association with PTB. However when long-term exposure to O₃
13 early in pregnancy is examined the results are inconsistent. Generally, studies conducted
14 in the U.S., Canada, and England find no association with O₃ and PTB, while studies
15 conducted in Australia and China report an O₃ effect on PTB.

Table 7-5 Brief summary of epidemiologic studies of PTB

| Study | Location Sample Size | Mean O ₃ (ppb) | Exposure assessment | Effect Estimate ^a (95% CI) |
|---|--|------------------------------|--|---|
| Darrow et al. (2009) | Atlanta, GA (n = 476,489) | 8-h max: 44.1 | Population-weighted spatial averages Nearest Monitor (within 4 miles) | First month: 0.98 (0.97, 1.00) Last week: 0.99 (0.98, 1.00) Last 6 weeks: 1.00 (0.98, 1.02) |
| Ritz et al. (2000) | California, U.S. (n = 97,158) | 8 h: 36.9 | <2 mi of monitor | First month: NR Last 6 weeks: NR |
| Wilhelm and Ritz (2005) | Los Angeles, CA (n = 106,483) | 1 h: 21.1- 22.2 | Varying distances to monitor | First month: 1.23 (1.06, 1.42) T1: NR T2: 1.38 (1.14, 1.66) Last 6 weeks: NR |
| Ritz et al. (2007) | Los Angeles, CA (n = 58,316) | 24-h avg: 22.5 | Nearest monitor to ZIP code | Entire pregnancy: NR T1: 0.93 (0.82, 1.06) Last 6 weeks: NR |
| Brauer et al. (2008) | Vancouver, BC, Canada (n = 70,249) | 24-h avg: 14 | Nearest Monitor (within 10 km) Inverse Distance Weighting (IDW) | Entire pregnancy: NR First 30 days of pregnancy: NR Last 30 days of pregnancy: NR T1: NR T3: NR |
| Lee et al. (2008c) | London, UK | 24-h avg: NR | 1 monitor | Lag 0: 1.00 (1.00, 1.01) |
| Hansen et al. (2006) | Brisbane, Australia (n = 28,200) | 8-h max: 26.7 | Citywide avg | T1: 1.39 (1.15, 1.70) T3: 1.09 (0.88, 1.39) |
| Jalaludin et al. (2007) | Sydney, Australia (n = 123,840) | 1-h max: 30.9 | Citywide avg and <5 km from monitor | First month: 1.04 (0.95, 1.13) T1: 1.15 (1.05, 1.24) T3: 0.98 (0.89, 1.07) Last month: 0.98 (0.88, 1.06) |
| Jiang et al. (2007) | Shanghai, China (n = 3,346 preterm births) | 8-h avg: 32.7 | Citywide avg | 4 wks before birth: 1.06 (1.00, 1.12) 6 wks before birth: 1.06 (0.99, 1.13) 8 wks before birth: 1.09 (1.01, 1.19) L0: NR (results presented in figure) L1: NR (results presented in figure) L2: NR (results presented in figure) L3: NR (results presented in figure) L4: NR (results presented in figure) L5: NR (results presented in figure) L6: NR (results presented in figure) |

^aRelative risk of PTB per 10 ppb change in O₃.

T1 = First Trimester, T2 = Second Trimester, T3 = Third Trimester.

L0 = Lag 0, L1= Lag 1, L2 = Lag 2, L3 = Lag 3, L4 = Lag 4, L5 = Lag 5, L6 = Lag 6.

NR: No quantitative results reported.

7.4.5 Fetal Growth

1 Low birth weight has often been used as an outcome measure because it is easily
2 available and accurately recorded on birth certificates. However, LBW may result from
3 either short gestation, or inadequate growth in utero. Most of the studies investigating air
4 pollution exposure and LBW limited their analyses to term infants to focus on inadequate
5 growth. A number of studies were identified that specifically addressed growth restriction
6 in utero by identifying infants who failed to meet specific growth standards. Usually
7 these infants had birth weight less than the 10th percentile for gestational age, using an
8 external standard. Many of these studies have been previously discussed, since they also
9 examined other reproductive outcomes (i.e., LBW or PTB).

10 Fetal growth is influenced by maternal, placental, and fetal factors. The biological
11 mechanisms by which air pollutants may influence the developing fetus remain largely
12 unknown. Several mechanisms have been proposed, and are the same as those
13 hypothesized for birth weight (see Section [5.4.2.4](#)). Additionally, in animal toxicology
14 studies, O₃ causes transient anorexia in exposed pregnant dams. This may be one of many
15 possible contributors to O₃-dependent decreased fetal growth.

16 A limitation of environmental studies that use birth weight as a proxy measure of fetal
17 growth is that patterns of fetal growth during pregnancy cannot be assessed. This is
18 particularly important when investigating pollutant exposures during early pregnancy as
19 birth weight is recorded many months after the exposure period. The insult of air
20 pollution may have a transient effect on fetal growth, where growth is hindered at one
21 point in time but catches up at a later point. For example, maternal smoking during
22 pregnancy can alter the growth rate of individual body segments of the fetus at variable
23 developmental stages, as the fetus experiences selective growth restriction and
24 augmentation ([Lampl and Jeanty, 2003](#)).

25 The terms small-for-gestational-age (SGA), which is defined as a birth weight <10th
26 percentile for gestational age (and often sex and/or race), and intrauterine growth
27 retardation (IUGR) are often used interchangeably. However, this definition of SGA does
28 have limitations. For example, using it for IUGR may overestimate the percentage of
29 “growth-restricted” neonates as it is unlikely that 10% of neonates have growth
30 restriction ([Wollmann, 1998](#)). On the other hand, when the 10th percentile is based on the
31 distribution of live births at a population level, the percentage of SGA among PTB is
32 most likely underestimated ([Hutcheon and Platt, 2008](#)). Nevertheless, SGA represents a
33 statistical description of a small neonate, whereas the term IUGR is reserved for those
34 with clinical evidence of abnormal growth. Thus all IUGR neonates will be SGA, but not
35 all SGA neonates will be IUGR ([Wollmann, 1998](#)). In the following section the terms
36 SGA and IUGR are referred to as each cited study used the terms.

1 Over the past decade a number of studies examined various metrics of fetal growth
2 restriction. [Salam et al. \(2005\)](#) assessed the effect of increasing O₃ concentrations on
3 IUGR in a population of infants born in California from 1975-1987 as part of the
4 Children's Health Study. The authors reported that maternal O₃ exposures averaged over
5 the entire pregnancy and during the third trimester were associated with increased risk of
6 IUGR. A 10-ppb difference in 24-h maternal O₃ exposure during the third trimester
7 increased the risk of IUGR by 11% (95% CI: 0, 20%). [Brauer et al. \(2008\)](#) evaluated the
8 impacts of air pollution (CO, NO₂, NO, O₃, SO₂, PM_{2.5}, PM₁₀) on SGA (1999-2002) using
9 spatiotemporal residential exposure metrics by month of pregnancy in Vancouver, BC.
10 The O₃ associations were largely protective (OR = 0.87, [95% CI: 0.81, 0.93] for a
11 10 ppb increase in inverse distance weighted SGA), and no additional quantitative results
12 were presented for O₃. [Liu et al. \(2007b\)](#) examined the association between IUGR among
13 singleton term live births and SO₂, NO₂, CO, O₃, and PM_{2.5} in 3 Canadian cities for the
14 period 1985-2000. No increase in the risk of IUGR in relation to exposure to O₃ averaged
15 over each month and trimester of pregnancy was noted.

16 Three studies conducted in Australia provide evidence for an association between
17 ambient O₃ and fetal growth restriction. [Hansen et al. \(2007\)](#) examined SGA among
18 singleton, full-term births in Brisbane, Australia in relation to ambient air pollution (bsp,
19 PM₁₀, NO₂, O₃) during pregnancy. They also examined head circumference and crown-
20 heel length in a subsample of term neonates. Trimester specific exposures to all pollutants
21 were not statistically significantly associated with a reduction in head circumference or
22 an increased risk of SGA. When monthly-specific exposures were examined, the authors
23 observed an increased risk of SGA associated with exposure to O₃ during month 4
24 (OR = 1.11 [95% CI: 1.00, 1.24] per 10 ppb increase). In a subsequent study, [Hansen et](#)
25 [al. \(2008\)](#) examined the possible associations between fetal ultrasonic measurements and
26 ambient air pollution (PM₁₀, O₃, NO₂, SO₂) during early pregnancy. This study had two
27 strengths: (1) fetal growth was assessed during pregnancy as opposed to at birth; and (2)
28 there was little delay between exposures and fetal growth measurements, which reduces
29 potential confounding and uses exposures that are concurrent with the observed growth
30 pattern of the fetus. Fetal ultrasound biometric measurements were recorded for biparietal
31 diameter (BPD), femur length, abdominal circumference, and head circumference. To
32 further improve exposure assessment, the authors restricted the samples to include only
33 scans from women for whom the centroid of their postcode was within 14 km of an air
34 pollution monitoring site. Ozone during days 31-60 was associated with decreases in all
35 of the fetal growth measurements, and a 1.78 mm reduction in abdomen circumference
36 per 10 ppb increase in O₃ concentration, though this effect did not persist in copollutant
37 models. The change in ultrasound measurements associated with O₃ during days 31-60 of
38 gestation indicated that increasing O₃ concentration decreased the magnitude of
39 ultrasound measurements for women living within 2 km of the monitoring site. The

1 relationship decreased toward the null as the distance from the monitoring sites increased.
2 When assessing effect modification due to SES, there was some evidence of effect
3 modification for most of the associations, with the effects of air pollution stronger in the
4 highest SES quartile. In the third study, [Mannes et al. \(2005\)](#) estimated the effects of
5 pollutant (PM₁₀, PM_{2.5}, NO₂, CO and O₃) exposure in the first, second and third trimesters
6 of pregnancy and risk of SGA in Sydney, Australia. Citywide average air pollutant
7 concentrations in the last month, third trimester, and first trimester of pregnancy had no
8 effect on SGA. Concentrations of O₃ in the second trimester of pregnancy had small but
9 adverse effects on SGA (OR = 1.10 [95% CI: 1.00, 1.14] per 10 ppb increment). This
10 effect disappeared when the analysis was limited to births with a maternal address within
11 5 km of a monitoring station (OR = 1.00 [95% CI: 0.60, 1.79] per 10 ppb increment).

12 Very little information from toxicological studies is available to address effects on fetal
13 growth. However, there is evidence to suggest that prenatal (short-term) exposure to O₃
14 can affect postnatal growth. A few studies reported that mice or rats exposed
15 developmentally (gestationally ± lactationally) to O₃ had deficits in body weight gain in
16 the postpartum period ([Bignami et al., 1994](#); [Haro and Paz, 1993](#); [Kavlock et al., 1980](#)).

17 [Table 7-6](#) provides a brief overview of the epidemiologic studies of fetal growth
18 restriction. In summary, the evidence is inconsistent when examining exposure to O₃ and
19 fetal growth restriction. Similar to PTB, studies conducted in Australia have reported an
20 effect of O₃ on fetal growth, whereas studies conducted in other areas generally have not
21 found such an effect. This may be due to the restriction of births to those within 2-14 km
22 of a monitoring station, as was done in the Australian studies.

Table 7-6 Brief summary of epidemiologic studies of fetal growth.

| Study | Location (Sample Size) | Mean O ₃ (ppb) | Exposure assessment | Effect Estimate ^a (95% CI) |
|--------------------------------------|--|---------------------------------------|--|---|
| Salam et al. (2005) | California, U.S. (n = 3901) | 24-h avg: 27.3 8 h: 50.6 | ZIP code level | Entire pregnancy: 1.16 (1.00, 1.32) T1: 1.00 (0.94, 1.11) T2: 1.06 (1.00, 1.12) T3: 1.11 (1.00, 1.17) |
| Brauer et al. (2008) | Vancouver, BC, Canada (n = 70,249) | 24-h avg: 14 | Nearest Monitor (within 10 km) Inverse Distance Weighting (IDW) | Entire pregnancy: NR First 30 days of pregnancy: NR Last 30 days of pregnancy: NR T1: NR T3: NR |
| Liu et al. (2007b) | Calgary, Edmonton, and Montreal, Canada (n = 16,430) | 24-h avg: 16.5 1-h max: 31.2 | Census Subdivision avg | Entire pregnancy: NR (results presented in figure) T1: NR (results presented in figure) T2: NR (results presented in figure) T3: NR (results presented in figure) |
| Hansen et al. (2007) | Brisbane, Australia (n = 26,617) | 8-h max: 26.7 | Citywide avg | T1: 1.01 (0.89, 1.15) T2: 1.00 (0.86, 1.17) T3: 0.83 (0.71, 0.97) |
| Hansen et al. (2008) | Brisbane, Australia (n = 15,623) | 8-h avg: 24.8 | Within 2 km of monitor | M1: -0.32 (-1.56, 0.91) ^b M2: -0.58 (-1.97, 0.80) ^b M3: 0.26 (-1.07, 1.59) ^b M4: 0.11 (-0.98, 1.21) ^b |
| Mannes et al. (2005) | Sydney, Australia (n = 138,056) | 1-h max: 31.6 | Citywide avg and <5 km from monitor | T1: 0.90 (0.48, 1.34) T2: 1.00 (0.60, 1.79) T3: 1.10 (0.66, 1.97) Last 30 days of pregnancy: 1.10 (0.74, 1.79) |

^aRelative risk of fetal growth restriction per 10 ppb change in O₃, unless otherwise noted.

^bMean change in fetal ultrasonic measure of head circumference recorded between 13 and 26 weeks gestation for a 10-ppb increase in maternal exposure to O₃ during early pregnancy

T1 = First Trimester, T2 = Second Trimester, T3 = Third Trimester

M1 = Month 1, M2 = Month 2, M3 = Month 3, M4 = Month 4

NR: No quantitative results reported

7.4.6 Postnatal Growth

1 Postnatal weight and height are routinely measured in children as indicators of growth
2 and somatic changes. Toxicological studies often follow these endpoints to ascertain if a
3 known exposure has an effect in the postnatal window, an effect which can be permanent.
4 Time-pregnant BALB/c mice were exposed to O₃ (0, 0.4, 0.8, or 1.2 ppm) GD9-18
5 (short-term exposure) with parturition at GD20-21 ([Sharkhuu et al., 2011](#)). As the
6 offspring aged, postnatal litter body weight continued to be significantly decreased in the
7 highest concentration (1.2 ppm) O₃ group at PND3 and PND7. When the pups were

1 weighed separately by sex at PND42, the males with the highest concentration of O₃
2 exposure (1.2 ppm, GD9-18) had significant decrements in body weight ([Sharkhuu et al.,](#)
3 [2011](#)).

4 Significant decrements in body weight at 4 weeks of age were reported in C57Bl/6 mice
5 that were exposed to postnatal O₃ (short-term exposure, PND2-28 exposure, 1 ppm O₃,
6 3 hours/day, 3 days/week) ([Auten et al., 2012](#)). Animals with co-exposure to in utero DE
7 (short-term exposure, dam GD9-GD17; inhalation 0.5 or 2.0 mg/m³ O₃; 4 h/day via
8 inhalation; or oropharyngeal aspiration DEPs, 2×/week) + postnatal O₃ (aforementioned
9 short-term exposure) also had significantly reduced body weight.

7.4.7 Birth Defects

10 Despite the growing body of literature evaluating the association between ambient air
11 pollution and various adverse birth outcomes, relatively few studies have investigated the
12 effect of temporal variations in ambient air pollution on birth defects. Heart defects and
13 oral clefts have been the focus of the majority of these recent studies, given the higher
14 prevalence than other birth defects and associated mortality. Mechanistically, air
15 pollutants could be involved in the etiology of birth defects via a number of key events
16 (see Section [5.4.2.4](#)).

17 Several studies have been conducted examining the relationship between O₃ exposure
18 during pregnancy and birth defects and reported a positive association with cardiac
19 defects. The earliest of these studies was conducted in southern California ([Ritz et al.,](#)
20 [2002](#)). This study evaluated the effect of air pollution on the occurrence of cardiac birth
21 defects in neonates and fetuses delivered in southern California in 1987-1993. Maternal
22 exposure estimates were based on data from the fixed site closest to the mother's ZIP
23 code area. When using a case-control design where cases were matched to 10 randomly
24 selected controls, results showed increased risks for aortic artery and valve defects
25 (OR = 1.56 [95% CI: 1.16, 2.09] per 10 ppb O₃), pulmonary artery and valve anomalies
26 (OR = 1.34 [95% CI: 0.96, 1.87] per 10 ppb O₃), and conotruncal defects (OR = 1.36
27 [95% CI: 0.91, 2.03] per 10 ppb O₃) in a dose-response manner with second-month O₃
28 exposure. A study conducted in Texas ([Gilboa et al., 2005](#)) looked at a similar period of
29 exposure but reported no association with most of the birth defects studied (O₃
30 concentration was studied using quartiles with the lowest representing <18 ppb and the
31 highest representing ≥ 31 ppb). The authors found slightly elevated odds ratios for
32 pulmonary artery and valve defects. They also detected an inverse association between O₃
33 exposure and isolated ventricular septal defects. Overall, this study provided some weak
34 evidence that air pollution increases the risk of cardiac defects. [Hansen et al. \(2009\)](#)

1 investigated the possible association between ambient air pollution concentrations
2 averaged over weeks 3-8 of pregnancy and the risk of cardiac defects. When analyzing all
3 births with exposure estimates for O₃ from the nearest monitor there was no indication for
4 an association with cardiac defects. There was also no adverse association when
5 restricting the analyses to only include births where the mother resided within 12 km of a
6 monitoring station. However, among births within 6 km of a monitor, a 10 ppb increase
7 in O₃ was associated with an increased risk of pulmonary artery and valve defects
8 (OR = 8.76 [95% CI: 1.80, 56.55]). As indicated by the very wide credible intervals,
9 there were very few cases in the sensitivity analyses for births within 6 km of a monitor,
10 and this effect could be a result of type I errors. [Dadvand et al. \(2011\)](#) investigated the
11 association between maternal exposure to ambient air pollution concentrations averaged
12 over weeks 3-8 of pregnancy and the occurrence of cardiac birth defects in England.
13 Similar to [Hansen et al. \(2009\)](#), they found no associations with maternal exposure to O₃
14 except for when the analysis was limited to those subjects residing within a 16 km
15 distance of a monitoring station (OR for malformations of pulmonary and tricuspid
16 valves=1.64 [95% CI: 1.04, 2.60] per 10 ppb increase in O₃).

17 Despite the association between O₃ and cardiac defects observed in the above studies, a
18 recent study did not observe an increased risk of cardiac birth defects associated with
19 ambient O₃ concentrations. The study, conducted in Atlanta, GA, examined O₃ exposure
20 during weeks 3-7 of pregnancy and reported no association with risk of cardiovascular
21 malformations ([Strickland et al., 2009](#)).

22 Several of these studies have also examined the relationship between O₃ exposure during
23 pregnancy and oral cleft defects. The study by [Ritz et al. \(2002\)](#) evaluated the effect of air
24 pollution on the occurrence of orofacial birth defects and did not observe strong
25 associations between ambient O₃ concentration and orofacial defects. They did report an
26 OR of 1.13 (95% CI: 0.90, 1.40) per 10 ppb during the second trimester for cleft lip with
27 or without cleft palate. Similarly, [Gilboa et al. \(2005\)](#) reported an OR of 1.09 (95% CI:
28 0.70, 1.69) for oral cleft defects when the fourth quartile was contrasted with the first
29 quartile of exposure during 3-8 weeks of pregnancy. [Hansen et al. \(2009\)](#) reported no
30 indication for an association with cleft defects and air pollution concentrations averaged
31 over weeks 3-8 of pregnancy. [Hwang and Jaakkola \(2008\)](#) conducted a population-based
32 case-control study to investigate exposure to ambient air pollution and the risk of cleft lip
33 with or without cleft palate in Taiwan. The risk of cleft lip with or without cleft palate
34 was increased in relation to O₃ levels in the first gestational month (OR = 1.17 [95% CI:
35 1.01, 1.36] per 10 ppb) and second gestational month (OR = 1.22 [95% CI: 1.03, 1.46]
36 per 10 ppb), but was not related to any of the other pollutants. In three-pollutant models,
37 the effect estimates for O₃ exposure were stable for the four different combinations of
38 pollutants and were all statistically significant. [Marshall et al. \(2010\)](#) compared estimated

1 exposure to ambient pollutants during early pregnancy (6 week period from 5 to 10
2 weeks into the gestational period) among mothers of children with oral cleft defects to
3 that among mothers of controls. The authors observed no consistent elevated associations
4 between any of the air pollutants examined and cleft malformations, though there was a
5 weak association between cases of cleft palate only and increasing O₃ concentrations.
6 This association increased when cases and controls were limited to those with residences
7 within 10 km of the closest O₃ monitor (OR = 2.2 [95% CI: 1.0, 4.9], comparing highest
8 quartile [>33 ppb] to lowest quartile [<15 ppb]).

9 A limited number of toxicological studies have examined birth defects in animals
10 exposed gestationally to O₃. [Kavlock et al. \(1979\)](#) exposed pregnant rats to O₃ for precise
11 periods during organogenesis. No significant teratogenic effects were found in rats
12 exposed 8 h/day to concentrations of O₃ varying from 0.44 to 1.97 ppm during early
13 (days 6-9), mid (days 9-12), or late (days 17 to 20) gestation, or the entire period of
14 organogenesis (days 6-15) (short-term exposures). Earlier research found eyelid
15 malformation following gestational and postnatal exposure to 0.2 ppm O₃ ([Veninga,
16 1967](#)).

17 [Table 7-7](#) provides a brief overview of the epidemiologic studies of birth defects. These
18 studies have focused on cardiac and oral cleft defects, and the results from these studies
19 are not entirely consistent. This inconsistency could be due to the absence of true
20 associations between O₃ and risks of cardiovascular malformations and oral cleft defects;
21 it could also be due to differences in populations, pollution levels, outcome definitions, or
22 analytical approaches. The lack of consistency of associations between O₃ and
23 cardiovascular malformations or oral cleft defects might be due to issues relating to
24 statistical power or measurement error. A recent meta-analysis of air pollution and
25 congenital anomalies concluded that there was no statistically significant increase in risk
26 of congenital anomalies and O₃ ([Vrijheid et al., 2011](#)). These authors note that
27 heterogeneity in the results of these studies may be due to inherent differences in study
28 location, study design, and/or analytic methods, and comment that these studies have not
29 employed some recent advances in exposure assessment used in other areas of air
30 pollution research that may help refine or reduce this heterogeneity.

Table 7-7 Brief summary of epidemiologic studies of birth defects

| Study | Outcomes Examined | Location (Sample Size) | Mean O ₃ (ppb) | Exposure Assessment | Exposure Window |
|---|---------------------------|--|---------------------------|-------------------------------------|--|
| Ritz et al. (2002) | Cardiac and Cleft Defects | Southern California (n = 3,549 cases; 10,649 controls) | 24-h avg: NR | Nearest Monitor (within 10 mi) | Month 1,2,3 Trimester 2,3 3-mo period prior to conception |
| Gilboa et al. (2005) | Cardiac and Cleft Defects | 7 Counties in TX (n = 5,338 cases; 4,580 controls) | 24-h avg: NR | Nearest Monitor | Weeks 3-8 of gestation |
| Hwang and Jaakkola (2008) | Oral Cleft Defects | Taiwan (n = 653 cases; 6,530 controls) | 24-h avg: 27.31 | Inverse Distance Weighting (IDW) | Months 1,2,3 |
| Strickland et al. (2009) | Cardiac Defects | Atlanta, GA (n = 3,338 cases) | 8-h max: 39.8-43.3 | Weighted citywide avg | Weeks 3-7 of gestation |
| Hansen et al. (2009) | Cardiac and Cleft Defects | Brisbane, Australia (n = 150,308 births) | 8-h max: 25.8 | Nearest Monitor | Weeks 3-8 of gestation |
| Marshall et al. (2010) | Oral Cleft Defects | New Jersey (n = 717 cases; 12,925 controls) | 24-h avg: 25 | Nearest Monitor (within 40 km) | Weeks 5-10 of gestation |
| Dadvand et al. (2011) | Cardiac Defects | Northeast England (n = 2,140 cases; 14,256 controls) | 24-h avg: 18.8 | Nearest Monitor | Weeks 3-8 of gestation ¹ |

7.4.8 Developmental Respiratory Effects

1 The issue of prenatal exposure has assumed increasing importance since ambient air
2 pollution exposures of pregnant women have been shown to lead to adverse pregnancy
3 outcomes, as well as to respiratory morbidity and mortality in the first year of life.
4 Growth and development of the respiratory system take place mainly during the prenatal
5 and early postnatal periods. This early developmental phase is thought to be very
6 important in determining long-term lung growth. Studies have recently examined this
7 emerging issue. Several studies were included in Section [7.2.1](#) and Section [7.2.3](#), and are
8 included here because they reported both prenatal and post-natal exposure periods.

9 [Mortimer et al. \(2008a\)](#); [\(2008b\)](#) examined the association of prenatal and lifetime
10 exposures to air pollutants with pulmonary function and allergen sensitization in a subset
11 of asthmatic children (ages 6-11) included in the Fresno Asthmatic Children's
12 Environment Study (FACES). Monthly means of pollutant levels for the years 1989-2000
13 were created and averaged separately across several important developmental time-
14 periods, including the entire pregnancy, each trimester, the first 3 years of life, the first
15 6 years of life, and the entire lifetime. The 8-h avg O₃ concentrations were approximately

1 50 ppb for each of the exposure metrics (estimated from figure). In the first analysis
2 ([Mortimer et al., 2008a](#)), negative effects on pulmonary function were found for exposure
3 to PM₁₀, NO₂, and CO during key neonatal and early life developmental periods. The
4 authors did not find a negative effect of exposure to O₃ among this cohort. In the second
5 analysis ([Mortimer et al., 2008b](#)), sensitization to at least one allergen was associated, in
6 general, with higher levels of CO and PM₁₀ during the entire pregnancy and second
7 trimester and higher PM₁₀ during the first 2 years of life. Lower exposure to O₃ during the
8 entire pregnancy or second trimester was associated with an increased risk of allergen
9 sensitization. Although the pollutant metrics across time periods are correlated, the
10 strongest associations with the outcomes were observed for prenatal exposures. Though it
11 may be difficult to disentangle the effect of prenatal and postnatal exposures, the models
12 from this group of studies suggest that each time period of exposure may contribute
13 independently to different dimensions of school-aged children's pulmonary function. For
14 4 of the 8 pulmonary-function measures (FVC, FEV₁, PEF, FEF₂₅₋₇₅), prenatal exposures
15 were more influential on pulmonary function than early-lifetime metrics, while, in
16 contrast, the ratio of measures (FEV₁/FVC and FEF₂₅₋₇₅/FVC) were most influenced by
17 postnatal exposures. When lifetime metrics were considered alone, or in combination
18 with the prenatal metrics, the lifetime measures were not associated with any of the
19 outcomes, suggesting the timing of the exposure may be more important than the overall
20 dose and prenatal exposures are not just markers for lifetime or current exposures.

21 [Clark et al. \(2010\)](#) investigated the effect of exposure to ambient air pollution in utero
22 and during the first year of life on risk of subsequent asthma diagnosis (incident asthma
23 diagnosis up to age 3-4) in a population-based nested case-control study. Air pollution
24 exposure for each subject based on their residential address history was estimated using
25 regulatory monitoring data, land use regression modeling, and proximity to stationary
26 pollution sources. An average exposure was calculated for the duration of pregnancy
27 (~15 ppb) and the first year of life (~14 ppb). In contrast to the [Mortimer et al. \(2008a\);](#)
28 [\(2008b\)](#) studies, the effect estimates for first-year exposure were generally larger than for
29 in utero exposures. However, similar to the Mortimer et al. studies, the observed
30 associations with O₃ were largely protective. Because of the relatively high correlation
31 between in utero and first-year exposures for many pollutants, it was difficult to discern
32 the relative importance of the individual exposure periods.

33 [Latzin et al. \(2009\)](#) examined whether prenatal exposure to air pollution was associated
34 with lung function changes in the newborn. Tidal breathing, lung volume, ventilation
35 inhomogeneity and eNO were measured in 241 unsedated, sleeping neonates (age=
36 5 weeks). The median of the 24-h avg O₃ concentrations averaged across the post-natal
37 period was ~44 ppb. Consistent with the previous studies, no association was found for
38 prenatal exposure to O₃ and lung function.

1 The new toxicological literature since the 2006 O₃ AQCD, covering respiratory changes
2 related to developmental O₃ exposure, reports ultrastructural changes in bronchiole
3 development, alterations in placental and pup cytokines, and increased pup airway hyper-
4 reactivity. These studies are detailed below.

5 Fetal rat lung bronchiole development is triphasic, comprised of the glandular phase
6 (measured at GD18), the canalicular phase (GD20), and the saccular phase (GD21). The
7 ultrastructural lung development in fetuses of pregnant rats exposed to 1-ppm O₃ (12
8 h/day, out to either GD18, GD20 or GD21) was examined by electron microscopy during
9 these three phases. In the glandular phase, bronchiolar columnar epithelial cells in fetuses
10 of dams exposed to O₃ had cytoplasmic damage and swollen mitochondria. Bronchial
11 epithelium at the canalicular phase in O₃ exposed pups had delayed maturation in
12 differentiation, i.e., glycogen abundance in secretory cells had not diminished as it should
13 with this phase of development. Congruent with this finding, delayed maturation of
14 tracheal epithelium following early neonatal O₃ exposure (1 ppm, 4-5 h/day for first week
15 of life) in lambs has been previously reported ([Mariassy et al., 1990](#); [Mariassy et al.,
16 1989](#)). Also at the canalicular phase, atypical cells were seen in the bronchiolar lumen of
17 O₃-exposed rat fetuses. Finally, in the saccular phase, mitochondrial degradation was
18 present in the non-ciliated bronchiolar cells of rats exposed in utero to O₃. In conclusion,
19 O₃ exposure of pregnant rats produced ultra-structural damage to near-term fetal
20 bronchiolar epithelium ([López et al., 2008](#)).

21 Exposure of laboratory animals to multiple airborne pollutants can differentially affect
22 pup physiology. One study showed that exposure of C57BL/6 mouse dams to 0.48 mg
23 PM intratracheally twice weekly for 3 weeks during pregnancy augmented O₃-induced
24 airway hyper-reactivity in juvenile offspring. Maternal PM exposure also significantly
25 increased placental cytokines above vehicle-instilled controls. Pup postnatal O₃ exposure
26 (1 ppm 3 h/day, every other day, thrice weekly for 4 weeks) induced significantly
27 increased cytokine levels (IL-1 β , TNF- α , KC, and IL-6) in whole lung versus postnatal
28 air exposed groups; this was further exacerbated with gestational PM exposure ([Auten et
29 al., 2009](#)). In further studies by the same laboratory, O₃-induced AHR was studied in
30 rodent offspring after dam gestational exposure to inhaled diesel exhaust ([Auten et al.,
31 2012](#)). Pregnant C57Bl/6 mice were exposed to diesel exhaust GD9-17 (0.5 or 2.0 mg/m³
32 O₃, 4h/day) via inhalation or in a separate set of animals via oropharyngeal aspiration of
33 freshly generated DEPs (2 \times /week). Postnatally, the offspring were exposed to O₃ starting
34 at PND2 (1 ppm O₃, 3 hours/day, 3 days/week for 4 weeks). Juvenile mice were then
35 subjected to measurements of pulmonary mechanisms (at 4 weeks of age and then at 8
36 weeks of age). Increased inflammation of the placenta and lungs of DE exposed fetuses
37 was reported at GD18. In animals with postnatal O₃ exposure alone, elevated
38 inflammation was seen with significant increased levels of BAL cytokines; these O₃-

1 related elevated levels were significantly exacerbated with prenatal DE exposure
2 (DE+O₃). At PND28, DE+O₃ exposed offspring had significant impairment of alveolar
3 development as measured with secondary alveolar crest development, a finding that was
4 absent in all other exposure groups (O₃ alone, DE alone). Postnatal O₃ exposure induced
5 AHR in methacholine challenged animals at 4 weeks of age and was exacerbated with the
6 higher dose of DE exposure (DE+O₃). At 8 weeks of age, O₃ exposed pups had persistent
7 AHR (+/-DE) that was significantly augmented in DE+O₃ pups. In summary, gestational
8 DE exposure induced an inflammatory response which, when combined with postnatal O₃
9 exposure impaired alveolar development, and caused an exacerbated and longer-lasting
10 O₃-induced AHR in offspring.

11 A series of experiments using infant rhesus monkeys repeatedly exposed to 0.5 ppm O₃
12 starting at one-month of age have examined the effect of O₃ alone or in combination with
13 an inhaled allergen on morphology and lung function ([Plopper et al., 2007](#)). Exposure to
14 O₃ alone or allergen alone produced small but not statistically significant changes in
15 baseline airway resistance and airway responsiveness, but the combined exposure to both
16 O₃ + antigen produced statistically significant and greater than additive changes in both
17 functional measurements. Additionally, cellular changes and significant structural
18 changes in the respiratory tract have been observed in infant rhesus monkeys exposed to
19 O₃ ([Fanucchi et al., 2006](#)). A more detailed description of these studies can be found in
20 Section [7.2.3](#) (Pulmonary Structure and Function), with mechanistic information found in
21 Section [5.4.2.4](#).

22 Lung immunological response in O₃ exposed pups was followed by analyzing BAL and
23 lung tissue. Sprague Dawley (SD) pups were exposed to a single 3h exposure of air or O₃
24 (0.6 ppm) on PND 13 ([Han et al., 2011](#)). Bronchoalveolar lavage (BAL) was performed
25 10 hours after the end of O₃ exposure. BALF polymorphonuclear leukocytes (PMNs) and
26 total BALF protein were significantly elevated in O₃ exposed pups. Lung tissue from O₃
27 exposed pups had significant elevations of manganese superoxide dismutase (SOD)
28 protein and significant decrements of extra-cellular SOD protein.

29 Various immunological outcomes were followed in offspring after their pregnant dams
30 (BALB/c mice) were exposed gestationally to O₃ (0, 0.4, 0.8, or 1.2 ppm, GD9-18)
31 ([Sharkhuu et al., 2011](#)). Delayed type hypersensitivity (DTH) was initiated with initial
32 BSA injection at 6 weeks of age and then challenge 7 days later. The normal edematous
33 response of the exposed footpad (thickness after BSA injection) was recorded as an
34 indicator of DTH. In female offspring, normal footpad swelling with BSA injection that
35 was seen in air exposed animals was significantly attenuated with O₃ exposure (0.8 and
36 1.2 ppm O₃), implying immune suppression of O₃ exposure specifically in DTH. Humoral
37 immunity was measured with the sheep red blood cell (SRBC) response. Animals

1 received primary immunization with SRBC and then blood was drawn for SRBC IgM
2 measurement. A SRBC booster was given 2 weeks later with blood collected 5 days after
3 booster for IgG measurement. Maternal O₃ exposure had no effect on humoral immunity
4 in the offspring as measured by IgG and IgM titers after SRBC primary and booster
5 immunizations ([Sharkhuu et al., 2011](#)).

6 Toxicity assessment and allergen sensitization was also assessed in these O₃ exposed
7 offspring. At PND42, animals were euthanized for analysis of immune and inflammatory
8 markers (immune proteins, inflammatory cells, T-cell populations in the spleen). A subset
9 of the animals was intra-nasally instilled or sensitized with ovalbumin on either PND2
10 and 3 or PND42 and 43. All animals were challenged with OVA on PND54, 55, and 56.
11 One day after final OVA challenge, lung function, lung inflammation and immune
12 response were determined. Offspring of O₃ exposed dams that were initially sensitized at
13 PND3 (early) or PND42 (late) were tested to determine the level of allergic sensitization
14 or asthma-like inflammation after OVA challenge. Female offspring sensitized early in
15 life developed significant eosinophilia (1.2 ppm O₃) and elevated serum OVA-specific
16 IgE (1.2 ppm O₃), which is a marker of airway allergic inflammation. The females that
17 were sensitized early also had significant decrements in BALF total cells, macrophages,
18 and lymphocytes (1.2 ppm O₃). Offspring that were sensitized later (PND42) in life did
19 not develop the aforementioned changes in BALF, but these animals did develop modest,
20 albeit significant neutropenia (0.8 and 1.2 ppm O₃) ([Sharkhuu et al., 2011](#)).

21 BALF cytology in non-sensitized animals was followed. BALF of offspring born to dams
22 exposed to O₃ was relatively unaffected (cytokines, inflammatory cell numbers/types) as
23 were splenic T-cell subpopulations. LDH was significantly elevated in BALF of females
24 whose mothers were exposed to 1.2 ppm during pregnancy ([Sharkhuu et al., 2011](#)). In
25 summary, the females born to mothers exposed to O₃ developed modest
26 immunocompromise. Males were unaffected ([Sharkhuu et al., 2011](#)).

27 Overall, animal toxicological studies have reported ultrastructural changes in bronchiole
28 development, alterations in placental and pup cytokines, and increased pup airway hyper-
29 reactivity related to exposure to O₃ during the developmental period. Epidemiologic
30 studies have found no association between prenatal exposure to O₃ and growth and
31 development of the respiratory system. Fetal origins of disease have received a lot of
32 attention recently, thus additional research to further explore the inconsistencies between
33 these two lines of evidence is warranted.

7.4.9 Developmental Central Nervous System Effects

1 The following sections describe the results of toxicological studies of O₃ and
2 developmental central nervous system effects. No epidemiologic studies of this
3 association have been published.

7.4.9.1 Laterality

4 Two reports of laterality changes in mice developmentally exposed to O₃ have been
5 reported in the literature. Mice developmentally exposed to 0.6 ppm O₃ (6 days before
6 breeding to weaning at PND21) showed a turning preference (left turns) distinct from air
7 exposed controls (clockwise turns) ([Dell'Omo et al., 1995](#)); in previous studies this
8 behavior in mice has been found to correlate with specific structural asymmetries of the
9 hippocampal mossy fiber projections ([Schöpke et al., 1991](#)). The 2006 O₃ AQCD
10 evidence for the effect of O₃ on laterality or handedness demonstrated that rats exposed to
11 O₃ during fetal and neonatal life showed limited, gender-specific changes in handedness
12 after exposure to the intermediate concentration of O₃ (only seen in female mice exposed
13 to 0.6 ppm O₃, and not in males at 0.6 ppm or in either sex of 0.3 or 0.9 ppm O₃ with
14 exposure from 6 days before breeding to PND26) ([Petruzzi et al., 1999](#)).

7.4.9.2 Brain Morphology and Neurochemical Changes

15 The nucleus tractus solitarius (NTS), a medullary area of respiratory control, of adult
16 animals exposed prenatally to 0.5 ppm O₃ (12h/day, ED5-eD20) had significantly less
17 tyrosine hydroxylase staining versus control ([Boussouar et al., 2009](#)). Tyrosine
18 hydroxylase is the rate-limiting enzyme for dopamine synthesis and serves as a precursor
19 for catecholamine synthesis; thus, decreased staining is used as a marker of dopaminergic
20 or catecholaminergic cell or activity loss in these regions and thus functions in neuronal
21 plasticity. After physical restraint stress, control animals respond at the histological level
22 with Fos activation, a marker of neuronal activity, and tyrosine hydroxylase activation in
23 the NTS, a response which is absent or attenuated in adult animals exposed prenatally to
24 0.5 ppm O₃ ([Boussouar et al., 2009](#)) when compared to control air exposed animals who
25 also were restrained. The O₃-exposed offspring in this study were cross-fostered to
26 control air exposed dams to avoid O₃-dependent dam related neonatal effects on offspring
27 outcomes (i.e., dam behavioral or lactational contributions to pup outcomes) ([Boussouar
28 et al., 2009](#)).

1 Developmental exposure to 0.3 or 0.6 ppm O₃ prior to mating pair formation through
2 GD17 induced significant increased levels of BDNF in the striatum of adult (PND140)
3 O₃ exposed offspring as compared to control air exposed animals; these O₃-exposed
4 animals also had significantly decreased level of NGF in the hippocampus versus control
5 ([Santucci et al., 2006](#)).

6 Changes in the pup cerebellum with prenatal 1 ppm O₃ exposure include altered
7 morphology ([Romero-Velazquez et al., 2002](#); [Rivas-Manzano and Paz, 1999](#)), decreased
8 total area ([Romero-Velazquez et al., 2002](#)), decreased number of Purkinje cells ([Romero-
9 Velazquez et al., 2002](#)), and altered monoamine neurotransmitter content with the
10 catecholamine system affected and the indoleamine system unaffected by O₃ ([Gonzalez-
11 Pina et al., 2008](#)).

7.4.9.3 Neurobehavioral Outcomes

12 O₃ administration to dams during pregnancy with or without early neonatal exposure has
13 been shown to contribute to multiple neurobehavioral outcomes in offspring that are
14 described in further detail below.

15 O₃ administration (0.4, 0.8 or 1.2 ppm O₃) during the majority of pregnancy (PD7-17) of
16 CD-1 mice did not affect pup behavioral outcomes including early behavioral ultrasonic
17 vocalizations and more permanent later measurements (PND60 or 61) including pup
18 activity, habituation and exploration and d-amphetamine-induced hyperactivity ([Bignami
19 et al., 1994](#)); these pups were all cross-fostered or reared on non- O₃ exposed dams.

20 Testing for aggressive behavior in mice continuously exposed to O₃ (0.3 or 0.6 ppm from
21 30 days prior to mating to GD17) revealed that mice had significantly increased
22 defensive/ submissive behavior (increased freezing posturing on the first day only of a
23 multiple-day exam) versus air exposed controls ([Santucci et al., 2006](#)). Similarly,
24 continuous exposure of adult animals to O₃ induced significant increases in fear behavior
25 and decreased aggression as measured by significantly decreased freezing behavior
26 ([Petruzzi et al., 1995](#)).

27 Developmentally exposed animals also had significantly decreased amount of time spent
28 nose sniffing other mice ([Santucci et al., 2006](#)); this social behavior deficit, decreased
29 sniffing time, was not found in an earlier study with similar exposures ([Petruzzi et al.,
30 1995](#)), but sniffing of specific body areas was measured in [Santucci et al. \(2006\)](#) and total
31 number of sniffs of the entire body was measured in [Petruzzi et al. \(1995\)](#). The two
32 toxicology studies exploring social behavior (sniffing) employ different study designs
33 and find opposite effects in animals exposed to O₃.

7.4.9.4 Sleep Aberrations after Developmental Ozone Exposure

1 The effect of gestational O₃ exposure (1 ppm O₃ daily for 12h/day, during dark period for
2 the entire pregnancy) on sleep patterns in rat offspring was followed using 24 h
3 polysomnographic recordings at 30, 60 and 90 days of age ([Haro and Paz, 1993](#)).
4 Ozone-exposed pups manifested with inverted sleep-wake patterns or circadian rhythm
5 phase-shift. Rat vigilance was characterized in wakefulness, slow wave sleep (SWS), and
6 paradoxical sleep (PS) using previously characterized criteria. The O₃ exposed offspring
7 spent longer time in the wakefulness state during the light period, more time in SWS
8 during the period of darkness, and showed significant decrements in PS. Chronic O₃
9 inhalation significantly decreased the duration of PS during both the light and dark
10 periods ([Haro and Paz, 1993](#)). These effects were consistent at all time periods measured
11 (30, 60 and 90 days of age). These sleep effects reported after developmental exposures
12 expand upon the existing literature on sleep aberrations in adult animals exposed to O₃
13 [rodents: ([Paz and Huitron-Resendiz, 1996](#); [Arito et al., 1992](#)); and cats: ([Paz and Bazan-
14 Perkins, 1992](#))]. A role for inhibition of cyclooxygenase-2 and the interleukins and
15 prostaglandins in the O₃-dependent sleep changes potentially exists with evidence from a
16 publication on indomethacin pretreatment attenuating O₃-induced sleep aberrations in
17 adult male animals ([Rubio and Paz, 2003](#)).

7.4.10 Early Life Mortality

18 Infants may be particularly at risk for the effects of air pollution. Within the first year of
19 life, infants develop rapidly; therefore their sensitivity may change within weeks or
20 months. During the neonatal and post-neonatal periods, the developing lung is highly
21 sensitive to environmental toxicants. The lung is not well developed at birth, with 80% of
22 alveoli being formed postnatally. An important question regarding the association
23 between O₃ and infant mortality is the critical window of exposure during development
24 for which infants are at risk. Several age intervals have been explored: neonatal
25 (<1 month); postneonatal (1 month to 1 year); and an overall interval for infants that
26 includes both the neonatal and postneonatal periods (<1 year). Within these various age
27 categories, multiple causes of deaths have been investigated, particularly total deaths and
28 respiratory-related deaths. The studies reflect a variety of study designs, exposure
29 periods, regions, and adjustment for confounders. As discussed below, a handful of
30 studies have examined the effect of ambient air pollution on neonatal and postneonatal
31 mortality, with the former the least studied. These studies varied somewhat with regard to
32 the outcomes and exposure periods examined and study designs employed.

7.4.10.1 Stillbirth

1 [Pereira et al. \(1998\)](#) investigated the association among daily counts of intrauterine
2 mortality (over 28 weeks of gestation) and air pollutant concentrations in Sao Paulo,
3 Brazil from 1991 through 1992. The association was strong for NO₂, but lesser for SO₂
4 and CO. These associations exhibited a short lag time, less than 5 days. No significant
5 association was detected between short-term O₃ exposure and intrauterine mortality.

7.4.10.2 Infant Mortality, Less than 1 Year

6 [Ritz et al. \(2006\)](#) linked birth and death certificates for infants who died between 1989
7 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South
8 Coast Air Basin of California. The authors examined short- and long-term exposure
9 periods 2 weeks, 1 month, 2 months, and 6 months before each case subject's death and
10 reported no association between ambient levels of O₃ and infant mortality. Similarly,
11 [Diaz et al. \(2004\)](#) analyzed the effects of extreme temperatures and short-term exposure
12 to air pollutants on daily mortality in children less than 1 year of age in Madrid, Spain,
13 from 1986 to 1997 and observed no statistically significant association between mortality
14 and O₃ concentrations. [Hajat et al. \(2007\)](#) analyzed time-series data of daily infant
15 mortality counts in 10 major cities in the UK to quantify any associations with short-term
16 changes in air pollution. When the results from the 10 cities were combined there was no
17 relationship between O₃ and infant mortality, even after restricting the analysis to just the
18 summer months.

19 Conversely, a time-series study of infant mortality conducted in the southwestern part of
20 Mexico City in the years 1993-1995 found that infant mortality was associated with
21 short-term exposure to NO₂ and O₃ 3-5 days before death, but not as consistently as with
22 PM. A 10-ppb increase in 24-h avg O₃ was associated with a 2.78% increase (95% CI:
23 0.29, 5.26%) in infant mortality (lag 3) ([Loomis et al., 1999](#)). This increase was
24 attenuated, although still positive when evaluated in a two-pollutant model with PM_{2.5}.
25 One-hour max concentrations of O₃ exceeded prevailing Mexican and international
26 standards nearly every day.

7.4.10.3 Neonatal Mortality, Less than 1 Month

27 Several studies have evaluated ambient O₃ concentrations and neonatal mortality and
28 observed no association. [Ritz et al. \(2006\)](#) linked birth and death certificates for infants
29 who died between 1989 and 2000 to evaluate the influence of outdoor air pollution on

1 infant death in the South Coast Air Basin of California. The authors examined short- and
2 long-term exposure periods 2 weeks, 1 month, 2 months, and 6 months before each case
3 subject's death and reported no association between ambient levels of O₃ and neonatal
4 mortality. [Hajat et al. \(2007\)](#) analyzed time-series data of daily infant mortality counts in
5 10 major cities in the UK to quantify any associations with short-term changes in air
6 pollution. When the results from the 10 cities were combined there was no relationship
7 between O₃ and neonatal mortality, even after restricting the analysis to just the summer
8 months. [Lin et al. \(2004a\)](#) assessed the impact of short-term changes in air pollutants on
9 the number of daily neonatal deaths in Sao Paulo, Brazil. The authors observed no
10 association between ambient levels of O₃ and neonatal mortality.

7.4.10.4 Postneonatal Mortality, 1 Month to 1 Year

11 A number of studies focused on the postneonatal period when examining the effects of O₃
12 on infant mortality. [Ritz et al. \(2006\)](#) linked birth and death certificates for infants who
13 died between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant
14 death in the South Coast Air Basin of California. The authors examined short- and long-
15 term exposure periods 2 weeks, 1 month, 2 months, and 6 months before each case
16 subject's death and reported no association between ambient levels of O₃ and
17 postneonatal mortality. [Woodruff et al. \(2008\)](#) evaluated the county-level relationship
18 between cause-specific postneonatal infant mortality and long-term early-life exposure
19 (first 2 months of life) to air pollutants across the U.S. Similarly, they found no
20 association between O₃ exposure and deaths from respiratory causes. In the U.K., [Hajat et](#)
21 [al. \(2007\)](#) analyzed time-series data of daily infant mortality counts in 10 major cities to
22 quantify any associations with short-term changes in air pollution. When the results from
23 the 10 cities were combined there was no relationship between O₃ and postneonatal
24 mortality, even after restricting the analysis to just the summer months. In Ciudad Juarez,
25 Mexico, [Romieu et al. \(2004a\)](#) examined the daily number of deaths between 1997 and
26 2001, estimating the modifying effect of SES on the risk of postneonatal mortality.
27 Ambient O₃ concentrations were not related to infant mortality overall, or in any of the
28 SES groups. In a follow-up study, [Carbajal-Arroyo et al. \(2011\)](#) evaluated the
29 relationship of 1-h daily max O₃ levels with postneonatal infant mortality in the
30 Mexico City Metropolitan Area between 1997 and 2005. Generally, short-term exposure
31 to O₃ was not significantly related to infant mortality. However, upon estimating the
32 modifying effect of SES on the risk of postneonatal mortality, the authors found that O₃
33 was statistically significantly related to respiratory mortality among those with low SES.
34 In a separate analysis, the effect of PM₁₀ was evaluated with O₃ level quartiles. PM₁₀
35 alone was related to a significant increase in all-cause mortality. The magnitude of this

1 effect remained the same when only the days when O₃ was in the lowest quartile were
2 included in the analyses. However, when only the days when O₃ was in the highest
3 quartile were included in the analyses, the magnitude of the PM₁₀ effect increased
4 dramatically (OR = 1.06 [95% CI: 0.909, 1.241] for PM₁₀ on days with O₃ in lowest
5 quartile; OR = 1.26 [95% CI: 1.08, 1.47] for PM₁₀ on days with O₃ in the highest quartile.
6 These results suggest that while O₃ alone may not have an effect on infant mortality, it
7 may serve to potentiate the observed effect of PM₁₀ on infant mortality.

8 [Tsai et al. \(2006\)](#) used a case-crossover analysis to examine the relationship between
9 short-term exposure to air pollution and postneonatal mortality in Kaohsiung, Taiwan
10 during the period 1994-2000. The risk of postneonatal deaths was 1.023 (95% CI: 0.564,
11 1.858) per 10-ppb increase in 24-h avg O₃. The confidence interval for this effect
12 estimate is very wide, likely due to the small number of infants that died each day,
13 making it difficult to interpret this result. Several other studies conducted in Asia did not
14 find any association between O₃ concentrations and infant mortality in the postneonatal
15 period. [Ha et al. \(2003\)](#) conducted a daily time-series study in Seoul, Korea to evaluate
16 the effect of short-term changes in ambient 8-h O₃ concentrations on postneonatal
17 mortality. [Son et al. \(2008\)](#) examined the relationship between air pollution and
18 postneonatal mortality from all causes among firstborn infants in Seoul, Korea during
19 1999-2003. [Yang et al. \(2006\)](#) used a case-crossover analysis to examine the relationship
20 between air pollution exposure and postneonatal mortality in Taipei, Taiwan for the
21 period 1994-2000. The authors observed no associations between ambient levels of O₃
22 and postneonatal mortality.

7.4.10.5 Sudden Infant Death Syndrome

23 The strongest evidence for an association between ambient O₃ concentrations and SIDS
24 comes from a study that evaluated the county-level relationship between SIDS and long-
25 term early-life exposure (first 2 months of life) to air pollutants across the U.S.
26 ([Woodruff et al., 2008](#)). The authors observed a 1.20 (95% CI: 1.09, 1.32) odds ratio for a
27 10-ppb increase in O₃ and deaths from SIDS. There was a monotonic increase in odds of
28 SIDS for each quartile of O₃ exposure compared with the lowest quartile (highest quartile
29 OR = 1.51; [95% CI: 1.17, 1.96]). In a multi-pollutant model including PM₁₀ or PM_{2.5},
30 CO and SO₂, the OR for SIDS and O₃ was not substantially lower than that found in the
31 single-pollutant model. When examined by season, the relationship between SIDS deaths
32 and O₃ was generally consistent across seasons with a slight increase for those babies
33 born in the summer. When stratified by birth weight, the OR for LBW babies was 1.27
34 (95% CI: 0.95, 1.69) per 10-ppb increase in O₃ and the OR for normal weight babies was
35 1.16 (95% CI: 1.01, 1.32) per 10-ppb increase in O₃.

Conversely, two additional studies reported no association between ambient levels of O₃ and SIDS. [Ritz et al. \(2006\)](#) linked birth and death certificates for infants who died between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South Coast Air Basin of California. The authors examined short- and long-term exposure periods 2 weeks, 1 month, 2 months, and 6 months before each case subject's death and reported no association between ambient levels of O₃ and SIDS. [Dales et al. \(2004\)](#) used time-series analyses to compare the daily mortality rates for SIDS and short-term air pollution concentrations in 12 Canadian cities during the period of 1984-1999. Increased daily rates of SIDS were associated with previous day increases in the levels of SO₂, NO₂, and CO, but not O₃ or PM_{2.5}.

[Table 7-8](#) provides a brief overview of the epidemiologic studies of infant mortality. These studies have focused on short-term exposure windows (e.g., 1-3 days) and long-term exposure windows (e.g., up to 6 months). Collectively, they provide no evidence for

Table 7-8 Brief summary of infant mortality studies.

| Study | Location | Mean O ₃ (ppb) | Exposure Assessment | Effect Estimate ^a (95% CI): |
|---------------------------------------|-----------------------|--|---------------------|---|
| Pereira et al. (1998) | Sao Paulo, Brazil | 1-h max: 33.8 | Citywide avg | L0-2: 1.00 (0.99, 1.01) |
| Diaz et al. (2004) | Madrid, Spain | 24-h avg: 11.4 | Citywide avg | NR |
| Loomis et al. (1999) | Mexico City, Mexico | 24-h avg: 44.1 1-h max: 163.5 | 1 monitor | L0: 0.99 (0.97, 1.02) L1: 0.99 (0.96, 1.01) L2: 1.00 (0.98, 1.03) L3: 1.03 (1.00, 1.05) L4: 1.01 (0.98, 1.03) L5: 1.02 (0.99, 1.04) L0-2: 1.02 (0.99, 1.05) |
| Ritz et al. (2006) | Southern California | 24-h avg: 21.9-22.1 | Nearest Monitor | 2 weeks before death: 1.03 (0.93, 1.14) 1 mo before death: NR 2 mo before death: 0.93 (0.89, 0.97) 6 mo before death: NR |
| Hajat et al. (2007) | 10 Cities in the UK | 24-h avg: 20.5-42.6 | Citywide avg | L0-2: 1.00 (0.96, 1.06) |
| Lin et al. (2004a) | Sao Paulo, Brazil | 24-h avg: 38.06 | Citywide avg | L0: 1.00 (0.99, 1.01) |
| Ha et al. (2003) | Seoul, South Korea | 8-h avg: 21.2 | Citywide avg | L0: 0.93 (0.90, 0.96) |
| Romieu et al. (2004a) | Ciudad Juarez, Mexico | 8-h avg: 43.43-55.12 | Citywide avg | L1: 0.96 (0.90, 1.03) L2: 0.97 (0.91, 1.04) L0-1 cum: 0.96 (0.89, 1.04) L0-2 cum: 0.94 (0.87, 1.02) |

| Study | Location | Mean O ₃ (ppb) | Exposure Assessment | Effect Estimate ^a (95% CI): |
|---|---------------------|---------------------------|---------------------|--|
| Carbajal-Arroyo et al. (2011) | Mexico City, Mexico | 1-h max: 103.0 | Citywide avg | L0: 1.00 (0.99, 1.00) L1: 0.99 (0.99, 0.99) L2: 0.99 (0.99, 1.00) L0-2: 0.99 (0.99, 1.00) |
| Son et al. (2008) | Seoul, South Korea | 8-ha avg: 25.61 | Citywide avg | L(NR): 0.984 (0.976, 0.992) ^b |
| Tsai et al. (2006) | Kaohsiung, Taiwan | 24-h avg: 23.60 | Citywide avg | L0-2 cum: 1.02 (0.56, 1.86) |
| Woodruff et al. (2008) | Nationwide, U.S. | 24-h avg: 26.6 | County wide avg | First 2 mo of life: 1.04 (0.98, 1.10) |
| Yang et al. (2006) | Taipei, Taiwan | 24-h avg: 18.14 | Citywide avg | L0-2 cum: 1.00 (0.62, 1.61) |
| Dales et al. (2004) | 12 Canadian cities | 24-h: 31.77 | Citywide avg | L0: NR L1: NR L2: NR L3: NR L4: NR L5: NR Multiday lags of 2-6 days: NR |

^aRelative risk of infant mortality per 10 ppb change in O₃

^bNo increment provided

L0 = Lag 0, L1 = Lag 1, L2 = Lag 2, L3 = Lag 3, L4 = Lag 4, L5 = Lag 5, L6 = Lag 6

NR: No quantitative results reported

Table 7-9 Summary of key reproductive and developmental toxicological studies.

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|--|--|----------------------|--|---|
| Sharkhuu et al. (2011) | Pregnant mice; BALB/c; F; GD9-18; effects in offspring | 0.4, 0.8, or 1.2 | Continuously for 10 consecutive days | Dams: Decreased number of dams reaching parturition. Offspring: (1)-Decreased birth weights. (2)-Decreased rate of postnatal growth (body weight). (3)-impaired delayed type hypersensitivity.(4)-No effect on humoral immunity. (5)-Significantly affected allergic airway inflammation markers (eosinophilia, IgE) in female offspring sensitized early in life. 6-BALF LDH significantly elevated in female offspring. |
| Bignami et al. (1994) | Pregnant CD-1 dams (PD7-17) | 0.4, 0.8 or 1.2 | Continuous | Reproductive success was not affected by O ₃ exposure (PD7-17, proportion of successful pregnancies, litter size, ex ratio, frequency of still birth, or neonatal mortality). Ozone acted as a transient anorexigen in pregnant dams. |
| Haro and Paz (1993) | Rat dams, Exposure over the entirety of pregnancy; | 1.0 | 12h/day during dark cycle | Decreased birth weight and postnatal body weight of offspring out to PND 90. Ozone-exposed pups manifested with inverted sleep-wake patterns or circadian rhythm phase-shift. |
| López et al. (2008) | Rats; Pregnant dams; GD1-GD18, GD20, or GD21. | 1.0 | (12 h/day, out to either GD18, GD20 or GD21) | O ₃ induced delayed maturation of near term rodent bronchioles, with ultra-structural damage to bronchiolar epithelium. |

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|---|--|----------------------|--|---|
| Auten et al. (2009) | C57BL/6 mouse pups | 1.0 | 3 h/day, every other day, thrice weekly for 4 weeks | Postnatal O ₃ exposure significantly increased lung inflammatory cytokine levels; this was further exacerbated with gestational PM exposure. |
| Plopper et al. (2007) | Infant rhesus monkeys | 0.5 | Postnatal, PND30-6month of age, 5 months of cyclic exposure, 5 days O ₃ followed by 9 days of filtered air, 8h/day. | Non-significant increases airway resistance and airway responsiveness with O ₃ or inhaled allergen alone. Allergen + O ₃ produced additive changes in both measures. |
| Fanucchi et al. (2006) | Infant male Rhesus monkeys, post-natal exposure | 0.5 | 5 months of episodic exposure, age 1 month-age 6 months, 5 days O ₃ followed by 9 days of filtered air, 8h/day. | Cellular changes and significant structural changes in the distal respiratory tract in infant rhesus monkeys exposed to O ₃ postnatally. |
| Dell'Omo et al. (1995) | CD-1 Mouse dams and pups | 0.6 | 6 days before breeding to weaning at PND21 | Laterality changes in offspring: Ozone exposed pups showed a turning preference (left turns) distinct from air exposed controls (clockwise turns) as adults. |
| Santucci et al. (2006) | CD-1 Mouse dams | 0.3 or 0.6 | Dam exposure prior to mating through GD17. | Developmental O ₃ caused increased defensive/submissive behavior in offspring. O ₃ exposed offspring also had significant elevations of striatal BDNF and hippocampal NGF v. air exposed controls. |
| Han et al. (2011) | Rat; Sprague Dawley, M & F; PND13 | 0.6 | 3 h, BALF examined 10h after O ₃ exposure | BALF polymorphonuclear leukocytes and total BALF protein were significantly elevated in O ₃ exposed pups. Lung tissue from O ₃ exposed pups had significant elevations of manganese superoxide dismutase (SOD) protein and significant decrements of extra-cellular SOD protein. |
| Campos-Bedolla et al. (2002) | Pregnant Rats; Sprague Dawley (GD5, GD10, or GD18) | 3.0 | 1 h on one day of gestation, uteri collected 16-18 h later | Ozone inhalation modifies the contractile response of the pregnant uterus. The O ₃ exposed pregnant uteri had significant increases in the maximum response to acetylcholine stimulation at GD5 and 10; they also had a significant increase in maximal response to oxytocin at GD 5. |
| Kavlock et al. (1980) | CD-1 mice; (pregnancy day 7-17) | 0.4, 0.8 and 1.2 | Continuous, pregnancy day 7-17 | O ₃ induced decrements in postnatal body weight gain. When O ₃ was co-administered with sodium salicylate, O ₃ synergistically increased the rate of pup resorption (1.0 ppm GD9-12). |
| Jedlinska-Krakowska et al. (2006) | 5 month old male Wistar Hannover rats | 3.0 | 0.5 ppm, 5h/day for 50 days | Histopathological evidence of impaired spermatogenesis (round spermatids/ 21 spermatocytes, giant spermatid cells, and focal epithelial desquamation with denudation to the 22 basement membrane). Vitamin E exposure concomitant with O ₃ protected against pathological changes but Vitamin C did not. |

7.4.11 Summary and Causal Determination

1 The 2006 O₃ AQCD concluded that the limited number of studies that investigated O₃
2 demonstrated no associations between O₃ and birth outcomes, with the possible exception
3 of birth defects. The current review included an expanded body of evidence on the
4 associations between O₃ and reproductive and developmental effects. Recent
5 epidemiologic and toxicological studies provide evidence for an effect of prenatal
6 exposure to O₃ on pulmonary structure and function, including lung function changes in
7 the newborn, incident asthma, ultrastructural changes in bronchiole development,

1 alterations in placental and pup cytokines, and increased pup airway hyper-reactivity.
2 Also, there is limited toxicological evidence for an effect of prenatal and early life
3 exposure on central nervous system effects, including laterality, brain morphology,
4 neurobehavioral abnormalities, and sleep aberration. Recent epidemiologic studies have
5 begun to explore the effects of O₃ on sperm quality, and provide limited evidence for
6 decrements in sperm concentration, while there is limited toxicological evidence for
7 testicular degeneration associated with O₃.

8 While the collective evidence for many of the birth outcomes examined is generally
9 inconsistent (including birth defects), there are several well-designed, well-conducted
10 studies that indicate an association between O₃ and adverse outcomes. For example, as
11 part of the southern California Children's Health Study, [Salam et al. \(2005\)](#) observed a
12 concentration-response relationship of decreasing birth weight with increasing O₃
13 concentrations averaged over the entire pregnancy that was clearest above the 30-ppb
14 level (see [Figure 7-4](#)). Similarly, [Hansen et al. \(2008\)](#) utilized fetal ultrasonic
15 measurements and found a change in ultrasound measurements associated with O₃ during
16 days 31-60 of gestation indicated that increasing O₃ concentration decreased an
17 ultrasound measurement for women living within 2 km of the monitoring site.

18 The weight of evidence does not indicate that prenatal or early life O₃ concentrations are
19 associated with infant mortality. Collectively, there is limited though positive
20 toxicological evidence for O₃-induced developmental effects, including effects on
21 pulmonary structure and function and central nervous system effects. Limited
22 epidemiologic evidence for an effect on prenatal O₃ exposure on respiratory development
23 provides coherence with the effects observed in toxicological studies. There is also
24 limited epidemiologic evidence for an association with O₃ concentration and decreased
25 sperm concentration. A recent toxicological study provides limited evidence for a
26 possible biological mechanism (histopathology showing impaired spermatogenesis) for
27 such an association. Additionally, though the evidence for an association between O₃
28 concentrations and adverse birth outcomes is generally inconsistent, there are several
29 influential studies that indicate an association with reduced birth weight and restricted
30 fetal growth.

31 Some of the key challenges to interpretation of these study results include the difficulty in
32 assessing exposure as most studies use existing monitoring networks to estimate
33 individual exposure to ambient air pollution (see [Section 4.6](#)); the inability to control for
34 potential confounders such as other risk factors that affect birth outcomes (e.g., smoking);
35 evaluating the exposure window (e.g., trimester) of importance; integrating the results
36 from both short- and long-term exposure periods; integrating the results across a variety

1 of reproductive and developmental outcomes; and limited evidence on the physiological
2 mechanism of these effects.

3 Taking into consideration the positive evidence for developmental and reproductive
4 outcomes from toxicological and epidemiological studies, and the few influential birth
5 outcome studies, the evidence **is suggestive of a causal relationship between**
6 **exposures to O₃ and reproductive and developmental effects.**

7.5 Central Nervous System Effects

7.5.1 Effects on the Brain and Behavior

7 The 2006 O₃ AQCD included toxicological evidence that acute exposures to O₃ are
8 associated with alterations in neurotransmitters, motor activity, short and long term
9 memory, and sleep patterns. Additionally, histological signs of neurodegeneration have
10 been observed. Reports of headache, dizziness, and irritation of the nose with O₃
11 exposure are common complaints in humans, and some behavioral changes in animals
12 may be related to these symptoms rather than indicative of neurotoxicity. Research in the
13 area of O₃-induced neurotoxicity has notably increased over the past few years, and
14 recent studies examining the effects of long-term exposure have demonstrated
15 progressive damage in various regions of the brains of rodents in conjunction with altered
16 behavior. Evidence from epidemiologic studies has been more limited. A recently
17 published epidemiologic study examined the association between O₃ concentration and
18 neurobehavioral effects. [Chen and Schwartz \(2009\)](#) utilized data from the NHANES III
19 cohort to study the relationship between O₃ concentrations (mean annual O₃
20 concentration 26.5 ppb) and neurobehavioral effects among adults aged 20-59 years.
21 Annual O₃ concentration was determined using inverse distance weighting for county of
22 residence and adjacent counties (for more information on inverse distance weighting and
23 other methods for exposure assessment, see Section [4.5.1](#) and [4.6](#)). The authors observed
24 an association between annual O₃ concentration and tests measuring coding ability
25 (symbol-digit substitution test) and attention/short-term memory (serial-digit learning
26 test). Each 10-ppb increase in annual O₃ concentration corresponded to an aging-related
27 cognitive performance decline of 3.5 yr for coding ability and 5.3 years for
28 attention/short-term memory. These associations persisted in both crude and adjusted
29 models. There was no association between O₃ concentration and reaction time tests. The
30 authors concluded that overall, there is an association between long-term O₃
31 concentration and reduced performance on neurobehavioral tests.

1 A number of recent toxicological studies demonstrate various perturbations in neurologic
2 function or histology with long-term exposure to O₃, including changes similar to those
3 observed in neurodegenerative disorders such as Parkinson's and Alzheimer's disease
4 pathologies in relevant regions of the brain ([Table 7-10](#)). The central nervous system is
5 very sensitive to oxidative stress, due in part to its high content of polyunsaturated fatty
6 acids, high rate of oxygen consumption, and low antioxidant enzyme capacity. Oxidative
7 stress has been identified as one of the pathophysiological mechanisms underlying
8 neurodegenerative disease ([Simonian and Coyle, 1996](#)), and it is believed to play a role in
9 altering hippocampal function, which causes cognitive deficits with aging ([Vanguilder
10 and Freeman, 2011](#)). A particularly common finding in studies of O₃-exposed rats is lipid
11 peroxidation in the brain, especially in the hippocampus, which is important for higher
12 cognitive function including contextual memory acquisition. Performance in passive
13 avoidance learning tests is impaired when the hippocampus is injured. For example, in a
14 subchronic study, exposure of rats to 0.25 ppm O₃ (4 h/day) for 15-90 days caused a
15 complex array of responses, including a time-dependent increase in lipid peroxidation
16 products and immunohistochemical changes in the hippocampus that were correlated
17 with decrements in passive avoidance behavioral tests ([Rivas-Arancibia et al., 2010](#)).
18 Changes included increased numbers of activated microglia, a sign of inflammation, and
19 progressive neurodegeneration. Notably, continued exposure tends to bring about
20 progressive, cumulative damage, as shown by this study ([Rivas-Arancibia et al., 2010](#))
21 and others ([Santiago-López et al., 2010](#); [Guevara-Guzmán et al., 2009](#); [Angoa-Pérez et
22 al., 2006](#)). The effects of O₃ on passive avoidance test performance were particularly
23 evident at 90 days for both short- and long-term memory. The greatest extent of cell loss
24 was also observed at this time point, whereas lipid peroxidation did not increase much
25 beyond 60 days of exposure.

26 The substantia nigra is another region of the brain affected by O₃, and seems particularly
27 sensitive to oxidative stress because the metabolism of dopamine, central to its function,
28 is an oxidative process perturbed by redox imbalance. Oxidative stress has been
29 implicated in the premature death of substantia nigra dopamine neurons in Parkinson's
30 disease. Progressive damage has been found in the substantia nigra of male rats after 15,
31 30, and 60 days of exposure to 0.25 ppm O₃ for 4 h/day. [Santiago-López et al. \(2010\)](#)
32 observed a reduction dopaminergic neurons within the substantia nigra over time, with a
33 complete loss of normal morphology in the remaining cells and virtually no dopamine
34 immunoreactivity at 60 days. This was accompanied by an increase in p53 levels and
35 nuclear translocation, a process associated with programmed cell death. Similarly,
36 [Angoa-Pérez et al. \(2006\)](#) have shown progressive lipoperoxidation in the substantia
37 nigra and a decrease in nigral neurons in ovariectomized female rats exposed to 0.25 ppm
38 O₃, 4h/day, for 7 - 60 days. Lipid peroxidation effectively doubled between the 30 and
39 60 day time points. Total nigral cell number was also diminished to the greatest extent at

1 60 days, and cell loss was particularly evident in the tyrosine hydroxylase positive cell
2 population (90%), indicating a selective loss of dopamine neurons or a loss of dopamine
3 pathway functionality.

4 The olfactory bulb also undergoes oxidative damage in O₃-exposed animals, in some
5 cases altering olfactory-dependent behavior. Lipid peroxidation was observed in the
6 olfactory bulbs of ovariectomized female rats exposed to 0.25 ppm O₃ (4 h/day) for 30 or
7 60 days ([Guevara-Guzmán et al., 2009](#)). O₃ also induced decrements in a selective
8 olfactory recognition memory test, which were significantly greater at 60 days compared
9 to 30 days, and the authors note that early deficits in odor perception and memory are
10 components of human neurodegenerative diseases. The decrements in olfactory memory
11 did not appear to be due to damaged olfactory perception based on other tests early on,
12 but by 60 days deficits in olfactory perception had emerged.

13 Memory deficits and associated morphological changes can be attenuated by
14 administration of α -tocopherol ([Guerrero et al., 1999](#)), taurine ([Rivas-Arancibia et al.,](#)
15 [2000](#)), and estradiol ([Guevara-Guzmán et al., 2009](#); [Angoa-Pérez et al., 2006](#)), all of
16 which have antioxidant properties. In the study by [Angoa-Pérez et al. \(2006\)](#) described
17 above, estradiol seemed particularly effective at protecting against lipid peroxidation and
18 nigral cell loss at 60 days compared to shorter exposure durations. The same was true for
19 amelioration of decrements in olfactory recognition memory ([Guevara-Guzmán et al.,](#)
20 [2009](#)), although protection against lipid peroxidation was similar for the 30 and 60 day
21 exposures.

22 CNS effects have also been demonstrated in adult mice whose only exposure to O₃
23 occurred while in utero, a period particularly critical for brain development. [Santucci et](#)
24 [al. \(2006\)](#) investigated behavioral effects and gene expression after in utero exposure of
25 mice to 0.3 or 0.6 ppm O₃. Exposure began 30 days prior to mating and continued
26 throughout gestation. Testing of adult animals demonstrated increased
27 defensive/submissive behavior and reduced social investigation were observed in both the
28 0.3 and 0.6 ppm O₃ groups. Changes in gene expression of brain-derived neurotrophic
29 factor (BDNF, increased in striatum) and nerve growth factor (NGF, decreased in
30 hippocampus) accompanied these behavioral changes. BDNF and NGF are involved in
31 neuronal organization and the growth, maintenance, and survival of neurons during early
32 development and in adulthood. This study and two others using short-term exposures
33 demonstrate that CNS effects can occur as a result of in utero exposure to O₃, and
34 although the mode of action of these effects is not known, it has been suggested that
35 circulating lipid peroxidation products may play a role ([Boussouar et al., 2009](#)).
36 Importantly, these CNS effects occurred in rodent models after in utero only exposure to
37 (semi-) relevant concentrations of O₃.

Table 7-10 Central nervous system effects of long-term ozone exposure in rats.

| Study | Model | O ₃ (ppm) | Exposure Duration | Effects |
|---|---|----------------------|--|--|
| Angoa-Pérez et al. (2006) | Rat; Wistar; F; Weight: 300 g; Ovariectomized | 0.25 | 7 to 60 days, 4 h/day, 5 days/week | Long-term estradiol treatment protected against O ₃ -induced oxidative damage to nigral dopamine neurons, lipid peroxidation, and loss of tyrosine hydrolase-immunopositive cells. |
| Guevara-Guzmán et al. (2009) | Rat; Wistar; F; Weight: 264 g; Ovariectomized | 0.25 | 30 and 60 days, 4h/day | Long-term estradiol treatment protected against O ₃ -induced oxidative stress and decreases in α and β estrogen receptors and dopamine β-hydroxylase in olfactory bulb, and deficits in olfactory social recognition memory and chocolate recognition. |
| Rivas-Arancibia et al. (2010) | Rat; Wistar; M; Weight: 250-300 g | 0.25 | 15 to 90 days, 4h/day | Ozone produced significant increases in lipid peroxidation in the hippocampus, and altered the number of p53 positive immunoreactive cells, activated and phagocytic microglia, GFAP immunoreactive cells, double cortine cells, and short- and long-term memory-retention latency |
| Santiago-López et al. (2010) | Rat; Wistar; M; Weight: 250-300 g | 0.25 | 15, 30, and 60 days, 4 h/day | Progressive loss of dopamine reactivity in the substantia nigra, along with morphological changes. Increased p53 levels and nuclear translocation. |
| Santucci et al. (2006) | Mice; CD-1; M; 18 weeks old | 0.3; 0.6 | Females continuously exposed from 30 days prior to breeding until GD17 | Upon behavioral challenge with another male, there was a significant increase in defensive and freezing postures and decrease in the frequency of nose-sniffing. These behavioral changes were accompanied by a significant increase in BDNF in the striatum and a decrease of NGF in the hippocampus. |

7.5.2 Summary and Causal Determination

1 The 2006 O₃ AQCD included toxicological evidence that acute exposures to O₃ are
2 associated with alterations in neurotransmitters, motor activity, short and long term
3 memory, and sleep patterns. Additionally, histological signs of neurodegeneration have
4 been observed. However, evidence regarding chronic exposure and neurobehavioral
5 effects was not available. Recent research in the area of O₃-induced neurotoxicity has
6 included several long-term exposure studies. Notably, the first epidemiologic study to
7 examine the relationship between O₃ exposure and neurobehavioral effects observed an
8 association between annual O₃ levels and an aging-related cognitive performance decline
9 in tests measuring coding ability and attention/short-term memory. This observation is
10 supported by studies in rodents which demonstrate progressive oxidative stress and
11 damage in the brain and associated decrements in behavioral tests, including those
12 measuring memory, after subchronic exposure to 0.25 ppm O₃. Additionally,

1 neurobehavioral changes are evident in animals whose only exposure to O₃ occurred in
2 utero. Collectively, the limited epidemiologic and toxicological evidence is coherent and
3 **suggestive of a causal relationship between O₃ exposure and CNS effects.**

7.6 Carcinogenic and Genotoxic Potential of Ozone

7.6.1 Introduction

4 The radiomimetic and clastogenic qualities of O₃, combined with its ability to stimulate
5 proliferation of cells in the respiratory tract, have suggested that O₃ could act as a
6 carcinogen. However, toxicological studies of tumorigenesis in the rodent lung have
7 yielded mixed and often confusing results, and the epidemiologic evidence is equally
8 conflicted. The 2006 O₃ AQCD concluded that, “the weight of evidence from recent
9 animal toxicological studies and a very limited number of epidemiologic studies do not
10 support ambient O₃ as a pulmonary carcinogen”¹ ([U.S. EPA, 2006b](#)).

11 Multiple epidemiologic studies reported in the 2006 O₃ AQCD examined the association
12 between O₃ concentration and cancer. The largest of these studies, by [Pope et al. \(2002\)](#),
13 included 500,000 adults from the American Cancer Society’s (ACS) Cancer Prevention II
14 study. In this study, no association was observed between O₃ concentration and lung
15 cancer mortality. The Adventist Health Study of Smog (AHSMOG) also examined the
16 association between O₃ concentration and lung cancer mortality ([Abbey et al., 1999](#)).
17 There was a positive association between O₃ concentrations and lung cancer mortality
18 among men. No association was reported for women. Another study using the AHSMOG
19 cohort assessed the risk of incident lung cancer ([Beeson et al., 1998](#)). Among males, an
20 association with incidence of lung cancer was observed with increasing O₃
21 concentrations. When stratified by smoking status, the association persisted among never
22 smokers but was null for former smokers. No association was detected for females. The
23 Six Cities Study examined various air pollutants and mortality but did not specifically
24 explore the association between O₃ concentrations and lung cancer mortality due to low
25 variability in O₃ concentrations across the cities ([Dockery et al., 1993](#)). An ecologic study
26 performed in Sao Paulo City, Brazil examined the correlations between O₃ concentrations
27 in four of the city districts and incident cancer of the larynx and lung reported in 1997
28 ([Pereira et al., 2005](#)). A correlation between the average number of days O₃
29 concentrations exceeded air quality standards from 1981 to 1990 and cancer incidence
30 was present for larynx cancer but not for lung cancer.

¹ The toxicological evidence is presented in detail in Table 6-18 on page 6-116 of the 1996 O₃ AQCD and Table AX5-13 on page AX5-43 of the 2006 O₃ AQCD.

1 Early toxicological research demonstrated lung adenoma¹ acceleration in mice with daily
2 exposure to 1 ppm over 15 months ([Stokinger, 1962](#)). Later work demonstrated a
3 significant increase in lung tumor numbers in one strain of mouse (A/J) but not another
4 after exposure to 0.3-0.8 ppm O₃ ([Last et al., 1987](#); [Hassett et al., 1985](#)). The A/J mouse
5 strain is known to have a high incidence of spontaneous adenomas, and further studies
6 using this strain found a statistically significant increase in lung tumor incidence after a
7 9-month exposure to 0.5 ppm and incidence and multiplicity after a 5 month exposure to
8 0.12 ppm with a 4-month recovery period ([Witschi et al., 1999](#)). However, these findings
9 were discounted by the study authors due to the lack of a clear concentration-response,
10 and results from the Hassett et al. 1985 and Last et al. 1987 studies were retrospectively
11 deemed spurious based on what appeared to be unusually low spontaneous tumor
12 incidences in the control groups ([Witschi, 1991](#)). A study of carcinogenicity of O₃ by the
13 National Toxicology Program ([NTP, 1994](#)) reported increased incidences of
14 alveolar/bronchiolar adenoma or carcinoma (combined) in female B6C3F₁ mice exposed
15 over 2 years to 1.0 ppm O₃, but not 0.12 or .5 ppm. No effect was detected in male mice.
16 For a lifetime exposure to 0.5 or 1.0 ppm O₃, an increase in the number of female mice
17 with adenomas (but not carcinomas or total neoplasms) was found. The number of total
18 neoplasms was also unaffected in male mice, but there was a marginally increased
19 incidence of carcinoma in males exposed to 0.5 and 1.0 ppm. Thus there was equivocal
20 evidence of carcinogenic activity in male mice and some evidence of carcinogenic
21 activity of O₃ in females. Experimental details of the NTP mouse study are available in
22 Table 6-19 on page 6-121 ([U.S. EPA, 1996o](#)) of the 1996 O₃ AQCD.

23 In Fischer-344/N rats (50 of each sex per group), neither a 2-year nor lifetime exposure to
24 O₃ ranging from 0.12 to 1.0 ppm was found to be carcinogenic ([Boorman et al., 1994](#);
25 [NTP, 1994](#)). However, a marginally significant carcinogenic effect of 0.2 ppm O₃ was
26 reported in a study of male Sprague-Dawley rats exposed for 6 months (n = 50)
27 ([Monchaux et al., 1996](#)). These two studies also examined co-carcinogenicity of O₃ with
28 NNK² ([Boorman et al., 1994](#)) or a relatively high dose of radon ([Monchaux et al., 1996](#)),
29 finding no enhancement of NNK related tumors and a slight non-significant increase in
30 tumor incidence after combined exposure with radon, respectively. Another study
31 exploring co-carcinogenicity was conducted in hamsters. Not only was there no
32 enhancement of chemically induced tumors in the peripheral lung or nasal cavity, but
33 results suggested that O₃ could potentially delay or inhibit tumor development ([Witschi et](#)
34 [al., 1993](#)). Thus there is no concrete evidence that O₃ can act as a co-carcinogen.

¹ NOTE: Although adenomas are benign, over time they may progress to become malignant, at which point they are called adenocarcinomas. Adenocarcinoma is the predominant lung cancer subtype in most countries, and is the only lung cancer found in nonsmokers. From page 8-33 of the 1970 O₃ AQCD: "No true lung cancers have been reported, however, from experimental exposures to either O₃ alone or any other combination or ingredient of photochemical oxidants."

² 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

1 Immune surveillance is an important defense against cancer, and it should be noted that
2 natural killer (NK) cells, which destroy tumor cells in the lung, appear to be inhibited by
3 higher concentrations of O₃ and either unaffected or stimulated at lower concentrations
4 (Section [6.2.5.4](#), Infection and Adaptive Immunity). This aspect of tumorigenesis adds
5 yet another layer of complexity which may be reflected by conflicting results across
6 studies.

7 The following sections will examine epidemiologic studies of cancer incidence and
8 mortality and toxicological studies that have been published since the 2006 O₃ AQCD.
9 An epidemiologic study has been published with cancer as the outcome; most
10 epidemiologic studies examine markers of exposure.

7.6.2 Lung Cancer Incidence and Mortality

11 A recent re-analysis of the full ACS CPSII cohort by the Health Effects Institute is the
12 only epidemiologic study that has explored the association between O₃ concentration and
13 cancer mortality since the last O₃ AQCD. [Krewski et al. \(2009\)](#) conducted an extended
14 follow-up of the cohort (1982-2000). Mean O₃ concentration [obtained from the
15 Aerometric Information Retrieval System (AIRS) for 1980] were 22.91 ppb for the full
16 year and 30.15 ppb for the summer months (April-September). No association was
17 reported between lung cancer mortality and O₃ concentration (HR = 1.00 [95% CI:
18 0.96-1.04] per 10 ppb O₃). Additionally, no association was observed when the analysis
19 was restricted to the summer months. There was also no association present in a sub-
20 analysis of the cohort examining the relationship between O₃ concentration and lung
21 cancer mortality in the Los Angeles area.

22 Since the 2006 O₃ AQCD, two toxicological studies have examined potential
23 carcinogenicity of O₃ ([Kim and Cho, 2009a, b](#)). Looking across both studies, which used
24 the same mouse strain as the National Toxicology Program study described above ([NTP,](#)
25 [1994](#)), 0.5 ppm O₃ alone or in conjunction with chemical tumor inducers did not enhance
26 lung tumor incidence in males or females. However, a 10% incidence of oviductal
27 carcinoma was observed in mice exposed to 0.5 ppm O₃ for 16 weeks. The implications
28 of this observation are unclear, particularly in light of the lack of statistical information
29 reported. Additionally, there is no mention of oviductal carcinoma after 32 weeks of
30 exposure, and no oviductal carcinoma was observed after one year of exposure. The NTP
31 study did not report any increase in tumors at extrapulmonary sites.

7.6.3 DNA Damage

1 The potential for genotoxic effects relating to O₃ exposure was predicted from the
2 radiomimetic properties of O₃. The decomposition of O₃ in water produces OH and HO₂
3 radicals, the same species that are generally considered to be the biologically active
4 products of ionizing radiation. Ozone has been observed to cause degradation of DNA in
5 a number of different models and bacterial strains. The toxic effects of O₃ have been
6 generally assumed to be confined to the tissues directly in contact with the gas, such as
7 the respiratory epithelium. Due to the highly reactive nature of O₃, little systemic
8 absorption is predicted. [Zelac et al. \(1971a\)](#); [\(1971b\)](#), however, reported a significant
9 increase in chromosome aberrations in peripheral blood lymphocytes from Chinese
10 hamsters exposed to 0.2 ppm for 5 hours. Other in vivo exposure studies found increased
11 DNA strand breaks in respiratory cells from guinea pigs ([Feng et al., 1997](#)) and mice
12 ([Bornholdt et al., 2002](#)) but only with exposure to higher concentrations of O₃ (1 ppm for
13 72 hours and 1 or 2 ppm for 90 minutes, respectively). In other studies there were no
14 observations of chromosomal aberrations in germ cells, but mutagenic effects have been
15 seen in offspring of mice exposed to 0.2 ppm during gestation (blepharophimosis or
16 dysplasia of the eyelids). The overall evidence for mutagenic activity from in vitro
17 studies is positive, and in the National Toxicology Program report described above, O₃
18 was found to be mutagenic in Salmonella, with and without S9 metabolic activation. No
19 recent toxicological studies of DNA damage have become available since the 2006 O₃
20 AQCD.

21 A number of epidemiologic studies looked at the association between O₃ and DNA and
22 cellular level damages. These changes may be relevant to mechanisms leading to cancers
23 development and serve as early indicators of elevated risk of mutagenicity.

24 Two studies performed in California examined cytogenetic damage in relation to O₃
25 exposures. [Huen et al. \(2006\)](#) examined cytogenetic damage among African American
26 children and their mothers in Oakland, CA. Increased O₃ (mean monthly 8-h O₃
27 concentrations ranged from about 30 ppb in April to 14 ppb in November) was associated
28 with increased cytogenetic damage (micronuclei frequency among lymphocytes and
29 buccal cells) even after adjustment for household/personal smoking status and distance-
30 weighted traffic density. [Chen et al. \(2006a\)](#) recruited college students at the University
31 of California, Berkeley who reported never smoking and compared their levels of
32 cytogenetic damage (micronuclei frequency from buccal cells) in the spring and fall.
33 Cytogenetic damage was greater in the fall, which the authors attributed to the increase in
34 O₃ over the summer. However, O₃ levels over 2, 7, 10, 14, or 30 days (concentrations not
35 given) before collection of buccal cells did not correlate with cytogenetic damage.
36 Estimated lifetime O₃ exposure was also not correlated with cytogenetic damage.

1 Additionally, the authors exposed a subset of the students (n = 15) to 200 ppb O₃ for
2 4 hours while the students exercised intermittently. Ozone was found to be associated
3 with an increase in cytogenetic damage in degenerated cells but not in normal cells
4 9-10 days after exposure. Increased cytogenetic damage was also noted in peripheral
5 blood lymphocytes collected 18 hours after exposure.

6 A study performed in Mexico recruited 55 male workers working indoors (n = 27) or
7 outdoors (n = 28) in Mexico City or Puebla, Mexico in order to study the relationship
8 between O₃ and DNA damage (detected from peripheral blood samples using the Comet
9 assay) ([Tovalin et al., 2006](#)). The median estimated daily O₃ concentrations were
10 estimated to be 28.5 ppb for outdoor workers and 5.1 ppb for indoor workers in
11 Mexico City and 36.1 ppb for outdoor workers and 19.5 ppb for indoor workers in
12 Puebla. Overall, a positive correlation between O₃ levels and DNA damage was
13 observed. However, when examining the relationship by city and workplace, only DNA
14 damage in outdoor workers in Mexico City remained correlated with O₃ levels.

15 Three studies examining the relationship between O₃ concentration and DNA-level
16 damage have been performed in Europe. The largest of these studies was the GenAir
17 case-control study, which was nested within the European Prospective Investigation into
18 Cancer and Nutrition (EPIC) study, and included individuals recruited between 1993 and
19 1998 from ten European countries. Only non-smokers (must not have smoked for at least
20 10 years prior to enrollment) were enrolled in the study. The researchers examined DNA
21 adduct levels (DNA bonded to cancer-causing chemicals) and their relationship with O₃
22 concentrations (concentrations not given) ([Peluso et al., 2005](#)). A positive association was
23 seen between DNA adduct levels and O₃ concentrations from 1990-1994 but not O₃
24 concentrations from 1995-1999. In adjusted analyses with DNA adduct levels
25 dichotomized as high and low (detectable versus non-detectable), the OR was 1.97
26 (95% CI: 1.08, 3.58) when comparing the upper tertile of O₃ concentration to the lower
27 two tertiles. Two other European studies were conducted in Florence, Italy. The most
28 recent of these enrolled individuals from the EPIC study into a separate study between
29 March and September of 1999 ([Palli et al., 2009](#)). The purpose of the study was to
30 examine oxidative DNA damage (determined by Comet assay using blood lymphocytes)
31 in association with varying periods of O₃ exposure. The researchers observed that longer
32 periods of high O₃ concentrations (values not given) were more strongly correlated with
33 oxidative DNA damage than shorter periods of time (i.e., the rho [p-value] was 0.26
34 [0.03] for 0-10 days and 0.35 [0.002] for 0-90 days). This correlation was stronger among
35 men compared to women. The correlations for all time periods had p-values <0.05 for ex-
36 and never-smokers. For current smokers, the correlation was only observed among time
37 periods ≤ 25 days. When adjusted for age, gender, smoking history, traffic pollution
38 exposure, period of blood draw, and area of residence, the association between O₃

1 concentrations and oxidative DNA damage was positive for O₃ concentrations 0-60 days,
2 0-75 days, and 0-90 days prior to blood draw. Positive, statistically significant
3 associations were not observed among shorter time periods. The other study performed in
4 Florence recruited healthy volunteers who reported being non-smokers or light smokers
5 ([Giovannelli et al., 2006](#)). The estimated O₃ concentrations during the study ranged from
6 approximately 4-40 ppb for 3-day averages, 5-35 ppb for 7-day averages, and
7 7.5-32.5 ppb for 30-day averages. Ozone concentrations were correlated with DNA
8 strand breaks (measured from blood lymphocytes) over longer exposure periods (p-value:
9 0.002 at 30 days, p-value: 0.04 at 7 days; p-value: 0.17 at 3 days). This association was
10 robust to control for temperature, solar radiation, gender, and age. No association was
11 seen between O₃ concentrations and measures of oxidative DNA damage at 3, 7, or
12 30 days.

7.6.4 Summary and Causal Determination

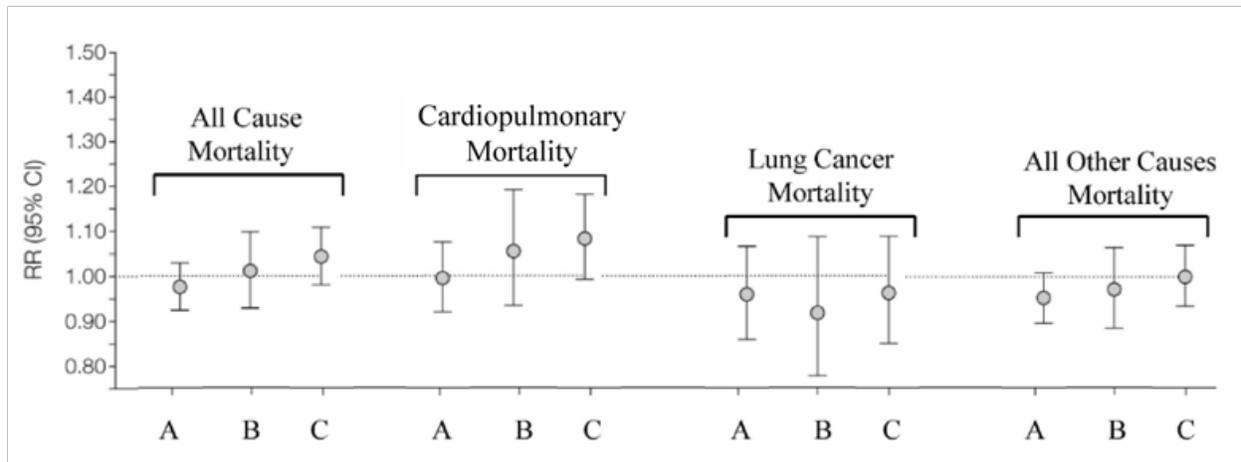
13 The 2006 O₃ AQCD reported that evidence did not support ambient O₃ as a pulmonary
14 carcinogen. Since the 2006 O₃ AQCD, very few epidemiologic and toxicological studies
15 have been published that examine O₃ as a carcinogen, but collectively, study results
16 indicate that O₃ may contribute to DNA damage. O₃ concentrations in most
17 epidemiologic studies were measured using air monitoring data. For more information on
18 long-term exposure assessment, see Section 4.6.3.2 Overall, the evidence **is inadequate**
19 **to determine if a causal relationship exists between ambient O₃ exposures and**
20 **cancer.**

7.7 Mortality

21 A limited number of epidemiologic studies have assessed the relationship between long-
22 term exposure to O₃ and mortality in adults. The 2006 O₃ AQCD concluded that an
23 insufficient amount of evidence existed “to suggest a causal relationship between chronic
24 O₃ exposure and increased risk for mortality in humans” ([U.S. EPA, 2006b](#)). In addition
25 to the infant mortality studies discussed in Section [7.4.10](#), additional studies have been
26 conducted among adults since the last review; an ecologic study that finds no association
27 between mortality and O₃, several re-analyses of the ACS cohort, one of which
28 specifically points to a relationship between long-term O₃ exposure and an increased risk
29 of respiratory mortality, and a study of four cohorts of persons with potentially
30 predisposing conditions. These studies supplement the evidence from long-term cohort
31 studies characterized in previous reviews of O₃, and are summarized here briefly.

1 In the Harvard Six Cities Study ([Dockery et al., 1993](#)), adjusted mortality rate ratios were
2 examined in relation to long-term mean O₃ concentrations in six cities: Topeka, KS; St.
3 Louis, MO; Portage, WI; Harriman, TN; Steubenville, OH; and Watertown, MA. Mean
4 O₃ concentrations from 1977 to 1985 ranged from 19.7 ppb in Watertown to 28.0 ppb in
5 Portage. Long-term mean O₃ concentrations were not found to be associated with
6 mortality in the six cities. However, the authors noted that “The small differences in O₃
7 levels among the (six) cities limited the power of the study to detect associations between
8 mortality and O₃ levels.” In addition, while total and cardio-pulmonary mortality were
9 considered in this study, respiratory mortality was not specifically considered.

10 In a subsequent large prospective cohort study of approximately 500,000 U.S. adults,
11 [Pope et al. \(2002\)](#) examined the effects of long-term exposure to air pollutants on
12 mortality (American Cancer Society, Cancer Prevention Study II). All-cause,
13 cardiopulmonary, lung cancer and other mortality risk estimates for long-term O₃
14 exposure are shown in [Figure 7-5](#). While consistently positive associations were not
15 observed between O₃ and mortality (effect estimates labeled A in [Figure 7-5](#)), the
16 mortality risk estimates were larger in magnitude when analyses considered more
17 accurate exposure metrics, increasing when the entire period was considered (effect
18 estimates labeled B in [Figure 7-5](#)) and becoming marginally significant when the
19 exposure estimate was restricted to the summer months (July to September; effect
20 estimates labeled C in [Figure 7-5](#)), especially when considering cardiopulmonary deaths.
21 In contrast, consistent positive and significant effects of PM_{2.5} were observed for both
22 lung cancer and cardio-pulmonary mortality.



| | Years of Data Collection | Number of Metropolitan Areas | Number of Participants (in thousands) | 1-h max O ₃ Mean (SD) |
|---|--------------------------|------------------------------|---------------------------------------|----------------------------------|
| A | 1980-1981 | 134 | 559 | 47.9 (11.0) |
| B | 1982-1998 | 119 | 525 | 45.5 (7.3) |
| C | 1982-1998 (July – Sept) | 134 | 557 | 59.7 (12.8) |

Source: Reprinted with permission of American Medical Association [Pope et al. \(2002\)](#).

Figure 7-5 Adjusted ozone-mortality relative risk estimates (95% CI) by time period of analysis per subject-weighted mean ozone concentration in the Cancer Prevention Study II by the American Cancer Society.

1 A study by [Abbey et al. \(1999\)](#) examined the effects of long-term air pollution exposure,
 2 including O₃, on all-cause (n = 1,575), cardiopulmonary (n = 1,029), nonmalignant
 3 respiratory (n = 410), and lung cancer (n = 30) mortality in the long-term prospective
 4 Adventist Health Study of Smog (AHSMOG) of 6,338 nonsmoking, non-Hispanic white
 5 individuals living in California. A particular strength of this study was the extensive
 6 effort devoted to assessing long-term air pollution exposures, including interpolation to
 7 residential and work locations from monitoring sites over time and space. No associations
 8 with long-term O₃ exposure were observed for all cause, cardiopulmonary, and
 9 nonmalignant respiratory mortality. In a follow-up, [Chen et al. \(2005\)](#) utilized data from
 10 the AHSMOG study and reported no evidence of associations between long-term O₃
 11 exposure (mean O₃ concentration 26.2 ppb) and fatal coronary heart disease. Thus, no
 12 association of chronic O₃ exposure with mortality outcomes has been detected in this
 13 study.

14 [Lipfert et al. \(2003\)](#); [\(2000\)](#) reported positive effects on all-cause mortality for peak O₃
 15 exposures (95th percentile levels) in the U.S. Veterans Cohort study of approximately
 16 50,000 middle-aged men recruited with a diagnosis of hypertension. The actual analysis

1 involved smaller subcohorts based on exposure and mortality follow-up periods. Four
2 separate exposure periods were associated with three mortality follow-up periods. For
3 concurrent exposure periods, peak O₃ was positively associated with all-cause mortality,
4 with a 9.4% (95% CI: 0.4, 18.4) excess risk per mean 95th percentile O₃ less estimated
5 background level (not stated). “Peak” refers, in this case, to the 95th percentile of
6 the hourly measurements, averaged by year and county. In a further analysis, [Lipfert et al.](#)
7 [\(2003\)](#) reported the strongest positive association for concurrent exposure to peak O₃ for
8 the subset of subjects with low diastolic blood pressure during the 1982 to 1988 period.
9 Two more recent studies of this cohort focused specifically on traffic density ([Lipfert et](#)
10 [al., 2006a; 2006b](#)). [Lipfert et al. \(2006b\)](#) concluded that: “Traffic density is seen to be a
11 significant and robust predictor of survival in this cohort, more so than ambient air
12 quality, with the possible exception of O₃,” reporting a significant O₃ effect even with
13 traffic density included in the model: RR = 1.080 per 40 ppb peak O₃ (95% CI: 1.019,
14 1.146). However, in [Lipfert et al. \(2006a\)](#), which considers only the EPA Speciation
15 Trends Network (STN) sites, O₃ drops to non-significant predictor of total mortality for
16 this cohort. The authors acknowledge that: “Peak O₃ has been important in analyses of
17 this cohort for previous periods, but in the STN data set, this variable has limited range
18 and somewhat lower values and its small coefficient of variation results in a relatively
19 large standard error.” The restriction to subjects near STN sites likely reduced the power
20 of this analysis, though the size of the remaining subjects considered was not reported in
21 this paper. In addition, these various Veterans Cohort studies considered only total
22 mortality, and did not consider mortality on a by-cause basis.

23 An ecological study in Brisbane, Australia used a geospatial approach to analyze the
24 association of long-term exposure to gaseous air pollution with cardio-respiratory
25 mortality, in the period 1996-2004 ([Wang et al., 2009c](#)). A generalized estimating
26 equations model was employed to investigate the impact of NO₂, O₃ and SO₂, but PM
27 was not addressed. The results indicated that long-term exposure to O₃ was not associated
28 with cardio-respiratory mortality, but the fact that this study considered only one city, and
29 that the range of O₃ exposure across that city (23.7-35.6 ppb) was low and slight in
30 variation in comparison to the range of other pollutants across the city, limited study
31 power. In addition, confounding factors (e.g., smoking) could not be addressed at the
32 individual level in this ecological study. Respiratory mortality was not evaluated
33 separately.

34 A recent study by Zanobetti and Schwartz examined whether year-to-year variations in
35 8-h mean daily O₃ concentrations for the summer (May-September) around their city-
36 specific long-term trend were associated with year-to-year variations in mortality around
37 its long-term trend. This association was examined among Medicare participants with
38 potentially predisposing conditions, including COPD, diabetes, CHF, and MI, defined as

1 patients discharged alive after an emergency admission for one of these four conditions.
2 The analyses was repeated in 105 cities using available data from 1985 through 2006, and
3 the results were combined using methods previously employed by these authors
4 ([Zanobetti et al., 2008](#); [Zanobetti and Schwartz, 2007](#)). This study design eliminated
5 potential confounding by factors that vary across city, which is a common concern in
6 most air pollution cohort studies, and also avoided both confounding by cross-sectional
7 factors that vary by city and the short-term factors that confound daily time-series studies,
8 but are not present in annual analyses. The average 8-h mean daily summer O₃
9 concentrations ranged from 15.6 ppb (Honolulu, HI) to 71.4 ppb (Bakersfield, CA) for
10 the 105 cities. The authors observed associations between yearly fluctuations in summer
11 O₃ concentrations and mortality in each of the four cohorts; the hazard ratios (per 10 ppb
12 increment) were 1.12 (95% CI: 1.06, 1.17) for the CHF cohort, 1.19 (95% CI 1.12, 1.25)
13 for the MI cohort, 1.14 (95% CI: 1.10, 1.21) for the diabetes cohort, and 1.14 (95% CI:
14 1.08, 1.19) for the COPD cohort. A key advantage to this study is that fluctuations from
15 summer to summer in O₃ concentrations around long-term level and trend in a specific
16 city are unlikely to be correlated with most other predictors of mortality risk; except for
17 temperature, which was controlled for in the regression. Key limitations of the study were
18 the inability to control for PM_{2.5}, since it was not reliably measured in these cities until
19 1999, and the inability to separate specific causes of death (e.g., respiratory,
20 cardiovascular), since Medicare does not provide the underlying cause of death.

21 In the most recent follow-up analyses of the ACS cohort ([Jerrett et al., 2009](#); [Smith et al.,](#)
22 [2009a](#)), the effects of long-term exposure to O₃ were evaluated alone, as well as in
23 copollutant models with PM_{2.5} and components of PM_{2.5}. [Jerrett et al. \(2009\)](#) utilized the
24 ACS cohort with data from 1977 through 2000 (mean O₃ concentration ranged from 33.3
25 to 104.0 ppb) and subdivided cardiopulmonary deaths into respiratory and cardiovascular,
26 separately, as opposed to combined into one category, as was done by [Pope et al. \(2002\)](#).
27 Increases in exposure to O₃ were associated with an elevated risk of death from
28 cardiopulmonary, cardiovascular, ischemic heart disease, and respiratory causes.
29 Consistent with study hypotheses, inclusion of PM_{2.5} concentrations measured in
30 1999-2000 (the earliest years for which it was available) as a copollutant attenuated the
31 association with O₃ for all end points except death from respiratory causes, for which a
32 significant association persisted ([Table 7-11](#)). The association between increased O₃
33 concentrations and increased risk of death from respiratory causes was insensitive to the
34 use of a random-effects survival model allowing for spatial clustering within the
35 metropolitan area and state of residence, and adjustment for several ecologic variables
36 considered individually. Subgroup analyses showed that temperature and region of
37 country, but not sex, age at enrollment, body-mass index, education, or PM_{2.5}
38 concentration, modified the effects of O₃ on the risk of death from respiratory causes
39 (i.e., risks were higher at higher temperature, and in the Southeast, Southwest, and Upper

Midwest). Ozone threshold analyses indicated that the threshold model was not a better fit to the data ($p > 0.05$) than a linear representation of the overall O₃-mortality association. Overall, this new analysis indicates that long-term exposure to PM_{2.5} increases risk of cardiac death, while long-term exposure to O₃ is specifically associated with an increased risk of respiratory death, and suggests that combining cardiovascular and respiratory causes of mortality into one category for analysis may obscure any effect that O₃ may have on respiratory-related causes of mortality.

Table 7-11 Relative risk (and 95% CI) of death attributable to a 10-ppb change in the ambient ozone concentration.

| Cause of Death | O ₃ (96 MSAs) ^a | O ₃ (86 MSAs) ^a | O ₃ +PM _{2.5} (86 MSAs) ^a |
|------------------------|---------------------------------------|---------------------------------------|--|
| Any Cause | 1.001 (0.996, 1.007) | 1.001 (0.996, 1.007) | 0.989 (0.981, 0.996) |
| Cardiopulmonary | 1.014 (1.007, 1.022) | 1.016 (1.008, 1.024) | 0.992 (0.982, 1.003) |
| Respiratory | 1.029 (1.010, 1.048) | 1.027 (1.007, 1.046) | 1.040 (1.013, 1.067) |
| Cardiovascular | 1.011 (1.003, 1.023) | 1.014 (1.005, 1.023) | 0.983 (0.971, 0.994) |
| Ischemic Heart Disease | 1.015 (1.003, 1.026) | 1.017 (1.006, 1.029) | 0.973 (0.958, 0.988) |

^aOzone concentrations were measured from April to September during the years from 1977 to 2000, with follow-up from 1982 to 2000; changes in the concentration of PM_{2.5} of 10 µg/m³ were recorded for members of the cohort in 1999 and 2000.

Source: Reprinted with permission of Massachusetts Medical Society ([Jerrett et al., 2009](#)).

In a similar analysis, [Smith et al. \(2009a\)](#) used data from 66 Metropolitan Statistical Areas (MSAs) in the ACS cohort to examine the association of O₃ concentrations during the warm season and all-cause and cardiopulmonary mortality. Mortality effects were estimated in single pollutant and copollutant models, adjusting for two PM_{2.5} constituents, sulfate, and EC. When all-cause mortality was investigated, there was a 0.8% (95% CI: -0.31, 1.9) increase associated with a 10 ppb increase in O₃ concentration. This association was diminished when sulfate or EC were included in the model. There was a 2.48% (95% CI: 0.74, 4.3) increase in cardiopulmonary mortality associated with a 10 ppb increase in O₃ concentration. The cardiopulmonary association was robust to adjustment for sulfate, and diminished, though still positive, after adjustment for EC (1.63% increase; 95% CI: -0.41, 3.7). [Smith et al. \(2009a\)](#) did not specifically separate out cardiovascular and respiratory causes of death from the cardiopulmonary category, as was done by [Jerrett et al. \(2009\)](#).

7.7.1 Summary and Causal Determination

The The 2006 O₃ AQCD concluded that an insufficient amount of evidence existed “to suggest a causal relationship between chronic O₃ exposure and increased risk for

1 mortality in humans” ([U.S. EPA, 2006b](#)). Several additional studies have been conducted
2 since the last review that evaluate cause-specific and total mortality. An ecologic study
3 conducted in Australia observed no association between cardiopulmonary mortality and
4 O₃ ([Wang et al., 2009c](#)). Two reanalyses of the ACS cohort were conducted; one
5 provides weak evidence for an association with cardiopulmonary mortality ([Smith et al.,
6 2009a](#)) while the other specifically points to a relationship between long-term O₃
7 exposure and an increased risk of respiratory mortality ([Jerrett et al., 2009](#)). Most
8 recently, a study of four cohorts of Medicare enrollees with potentially predisposing
9 conditions observed associations between O₃ and total mortality among each of the
10 cohorts ([Zanobetti and Schwartz, 2011](#)).

11 When considering the entire body of evidence, there is limited support for an association
12 with long-term exposure to ambient O₃ and total mortality. There is inconsistent evidence
13 for an association between long-term exposure to ambient O₃ and cardiopulmonary
14 mortality, with several analyses from the ACS cohort reporting some positive
15 associations ([Smith et al., 2009a](#); [Pope et al., 2002](#)) while other studies reported no
16 association ([Wang et al., 2009c](#); [Abbey et al., 1999](#); [Dockery et al., 1993](#)). The strongest
17 evidence for an association between long-term exposure to ambient O₃ concentrations
18 and mortality is derived from associations reported in the [Jerrett et al. \(2009\)](#) study for
19 respiratory mortality that remained robust after adjusting for PM_{2.5} concentrations.
20 Finally, a recent analysis reported associations of ambient O₃ concentrations and total
21 mortality in potentially at-risk populations in the Medicare Cohort ([Zanobetti and
22 Schwartz, 2011](#)), while earlier studies generally report no associations with total
23 mortality ([Lipfert et al., 2006a](#); [Lipfert et al., 2003](#); [Pope et al., 2002](#); [Abbey et al., 1999](#);
24 [Dockery et al., 1993](#)). Studies of cardiopulmonary and total mortality provide limited
25 evidence for an association with long-term exposure to ambient O₃ concentrations. The
26 study by [Jerrett et al. \(2009\)](#) observes an association between long-term exposure to
27 ambient O₃ concentrations and respiratory mortality remained robust after adjusting for
28 PM_{2.5} concentrations. Coherence and biological plausibility for this observation is
29 provided by evidence from epidemiologic, controlled human exposure, and animal
30 toxicological studies for the effects of short- and long-term exposure to O₃ on respiratory
31 effects (See Sections 6.2 and 7.2). Respiratory mortality is a relatively small portion of
32 total mortality [about 7.6% of all deaths in 2010 were due to respiratory causes ([Murphy
33 et al., 2012](#))], thus it is not surprising that the respiratory mortality signal may be difficult
34 to detect in studies of cardiopulmonary or total mortality. Based on the recent evidence
35 for respiratory mortality along with limited evidence for total and cardiopulmonary
36 mortality, the evidence **is suggestive of a causal relationship between long-term O₃
37 exposures and total mortality.**

7.8 Overall Summary

1 The evidence reviewed in this chapter describes the recent findings regarding the health
2 effects of long-term exposure to ambient O₃ concentrations. [Table 7-12](#) provides an
3 overview of the causal determinations for each of the health categories evaluated.

Table 7-12 Summary of causal determinations for long-term exposures to ozone.

| Health Category | Causal Determination |
|--|---|
| Respiratory Effects | Likely to be a causal relationship |
| Cardiovascular Effects | Suggestive of a causal relationship |
| Reproductive and Developmental Effects | Suggestive of a causal relationship |
| Central Nervous System Effects | Suggestive of a causal relationship |
| Carcinogenicity and Genotoxicity | Inadequate to infer a causal relationship |
| Total Mortality | Suggestive of a causal relationship |

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8 POPULATIONS POTENTIALLY AT INCREASED RISK FOR OZONE-RELATED HEALTH EFFECTS

1 Interindividual variation in human responses to air pollution exposure can result in some
2 groups being at increased risk for detrimental effects in response to ambient exposure to
3 an air pollutant. The NAAQS are intended to provide an adequate margin of safety for
4 both the population as a whole and those potentially at increased risk for health effects in
5 response to ambient air pollution (Preface to this ISA). To facilitate the identification of
6 populations and lifestages at greater risk for air pollutant related health effects, studies
7 have evaluated factors that may contribute to the susceptibility and/or vulnerability of an
8 individual to air pollutants. The definitions of susceptibility and vulnerability have been
9 found to vary across studies, but in most instances “susceptibility” refers to biological or
10 intrinsic factors (e.g., lifestage, sex, preexisting disease/conditions) while “vulnerability”
11 refers to non-biological or extrinsic factors (e.g., socioeconomic status [SES]) ([U.S. EPA,
12 2010c, 2009d](#)). In some cases, the terms “at-risk” and “sensitive” populations have been
13 used to encompass these concepts more generally. The main goal of this evaluation is to
14 identify and understand those factors that result in a population or lifestage being at
15 increased risk of an air pollutant-related health effect, not to categorize the factors. To
16 this end, previous ISAs and reviews ([Sacks et al., 2011](#); [U.S. EPA, 2010c, 2009d](#)) have
17 used “susceptible populations” to encompass these various factors. In this chapter,
18 “at-risk” is the all-encompassing term used for groups with specific factors that increase
19 the risk of an air pollutant (e.g., O₃)-related health effects in a population.

20 Individuals, and ultimately populations, could experience increased risk for air pollutant
21 induced health effects via multiple avenues. A group with intrinsically increased risk
22 would have some factor(s) that increases risk for an effect through a biological
23 mechanism. In general, people in this category would have a steeper concentration-
24 risk relationship, compared to those not in the category. Potential factors that are often
25 considered intrinsic include genetic background and sex. A group of people could also
26 have extrinsically increased risk, which would be through an external, non-biological
27 factor. Examples of extrinsic factors include SES and diet. Some groups are at risk of
28 increased internal dose at a given exposure concentration, which includes individuals
29 that have a greater dose of delivered pollutant because of breathing pattern. This
30 category would include persons who work outdoors or exercise outdoors. In addition,
31 some outdoor workers could have greater exposure (concentration x time), regardless
32 of the delivered dose. Finally, there are those who might be placed at increased risk
33 for experiencing a greater exposure by being exposed at a higher concentration. For

1 example, groups of people exposed to higher air pollutant concentrations due to less
2 availability/use of home air conditioners (i.e., more open windows on high O₃ days).

3 Some factors described above are multifaceted and may influence the risk of an air
4 pollutant related health effect through a combination of avenues. For example, SES may
5 affect access to medical care, which itself may contribute to the presence of preexisting
6 diseases and conditions considered as intrinsic factors. Additionally, children tend to
7 spend more time outdoors at higher levels of activity than adults, which leads to
8 increased intake dose and exposure, but they also have biological (i.e., intrinsic)
9 differences when compared to adults.

10 The emphasis of this chapter is to identify and understand the factors that potentially
11 increase the risk of O₃-related health effects, regardless of whether the increased risk is
12 due to intrinsic factors, extrinsic factors, increased dose/exposure or a combination, due
13 to the often connected pathways between factors. The following sections examine factors
14 that potentially lead to increased risk of O₃-related health effects and characterize the
15 overall weight of evidence for each factor. Most of the factors are related to greater health
16 effects given a specific dose but there is also discussion of increased internal dose and/or
17 exposure at a given concentration integrated throughout the sections (i.e., lifestage,
18 outdoor workers, and air conditioning use).

Approach to Classifying Potential At-Risk Factors

19 To identify factors that potentially lead to some populations being at greater risk to air
20 pollutant related health effects, the evidence across relevant scientific disciplines
21 (i.e., exposure sciences, dosimetry, controlled human exposure, toxicology, and
22 epidemiology) was evaluated. In this systematic approach, the collective evidence is used
23 to examine coherence of effects across disciplines and determine biological plausibility.
24 By first focusing on studies (i.e., epidemiologic or controlled human exposure) that
25 conduct stratified analyses it is possible to identify factors that may result in some
26 populations being at greater risk of an air pollutant related health effect. These types of
27 studies allow for an evaluation of populations exposed to similar air pollutant (e.g., O₃)
28 concentrations within the same study design. Experimental studies also provide important
29 lines of evidence in the evaluation of factors that may lead to increased risk of an air
30 pollutant related-health effect. Toxicological studies conducted using animal models of
31 disease and controlled human exposure studies that examine individuals with underlying
32 disease or genetic polymorphisms may provide evidence in the absence of stratified
33 epidemiologic analyses. Additionally these studies can provide support for coherence
34 with the health effects observed in epidemiologic studies as well as an understanding of
35 biological plausibility. The collective results across the scientific disciplines comprise the

1 overall weight of evidence that is used to determine whether a specific factor results in a
2 population being at increased risk of an air pollutant related health effect.

3 Building on the causal framework discussed in detail in the Preamble and used
4 throughout the ISA, conclusions are made regarding the strength of evidence for each
5 factor that may contribute to increased risk of an O₃-related health effect based on the
6 evaluation and synthesis of evidence across scientific disciplines. The conclusions drawn
7 considered the “Aspects to Aid in Judging Causality” discussed in Table 1 of the
8 Preamble. The categories considered for evaluating the potential increased risk of an air
9 pollutant-related health effect are “adequate evidence,” “suggestive evidence,”
10 “inadequate evidence,” and “evidence of no effect.” They are described in more detail in
11 [Table 8-1](#).

Table 8-1 Classification of Evidence for Potential At-Risk Factors.

| Health Effects | |
|-----------------------|--|
| Adequate evidence | There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable this includes coherence across disciplines. Evidence includes multiple high-quality studies. |
| Suggestive evidence | The collective evidence suggests that a factor results in a population or lifestage being at increased risk of an air pollutant-related health effect relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines. |
| Inadequate evidence | The collective evidence is inadequate to determine if a factor results in a population or lifestage being at increased risk of an air pollutant-related health effect relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency and/or statistical power to permit a conclusion to be drawn. |
| Evidence of no effect | There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable this includes coherence across disciplines. Evidence includes multiple high-quality studies. |

12 This chapter evaluates the various factors indicated in the literature that may result in a
13 population being at increased risk of an O₃-related health effect. For further detail on the
14 epidemiologic, controlled human exposure, and toxicological studies included in this
15 chapter, see Chapters 5, 6, and 7.

8.1 Genetic Factors

16 The potential effects of air pollution on individuals with specific genetic characteristics
17 have been examined; studies often target polymorphisms in already identified candidate
18 susceptibility genes or in genes whose protein products are thought to be involved in the
19 biological mechanism underlying the health effect of an air pollutant ([Sacks et al., 2011](#)).
20 As a result, multiple studies that examined the effect of short- and long-term O₃ exposure
21 on respiratory function have focused on whether various gene profiles lead to an

1 increased risk of O₃-related health effects. For more details on the function and mode of
2 action of the genetic factors discussed in this section, see Section [5.4.2.1](#). Additionally, a
3 limited number of toxicological studies have examined the joint effects of nutrition and
4 genetics. Details on these toxicological studies of nutrition and genetics can be found in
5 Section [5.4.2.3](#).

6 Multiple genes, including glutathione S-transferase Mu 1 (GSTM1) and tumor necrosis
7 factor- α (TNF- α) were evaluated in the 2006 O₃ AQCD and found to have a “potential
8 role... in the innate susceptibility to O₃” ([U.S. EPA, 2006b](#)). Epidemiologic, controlled
9 human exposure, and toxicological studies performed since the 2006 O₃ AQCD have
10 continued to examine the roles of GSTM1 and TNF- α in modifying O₃-related health
11 effects and have examined other gene variants that may also increase risk. Due to small
12 sample sizes, many controlled human exposure studies are limited in their ability to test
13 genes with low frequency minor alleles and therefore, some genes important for
14 O₃-related health effects may not have been examined in these types of studies. A
15 summary of effect measure modification findings from epidemiologic and controlled
16 human exposure studies discussed in this section is included as [Table 8-2](#).

Table 8-2 Summaries of results from epidemiologic and controlled human exposures studies of modification by genetic variants.

| Gene variant | Comparison group | Health outcome /population | Effect modification of association for the gene variant | Reference |
|------------------------------|--------------------------|---|---|---|
| GSTM1 null | GSTM1 positive | Respiratory symptoms among asthmatic children | ↑ | Romieu et al. (2006) |
| GSTP1 Val/Val | GSTP1 Ile/Ile or Ile/Val | Respiratory symptoms among asthmatic children | ↑ | |
| GSTP1 Ile/Ile or Ile/Val | GSTP1 Val/Val | Lung function among asthmatic children | ↓ | |
| GSTP1 Ile/Val or Val/Val | GSTP1 Ile/Ile | Lung function among adults | ↓ | Alexeeff et al. (2008) |
| HMOX1 S/L or L/L | HMOX1 S/S | Lung function among adults | ↓ | |
| NQO1 wildtype and GSTM1 null | Other combinations | Lung function among healthy adults with exercise | ↓ | Bergamaschi et al. (2001) |
| NQO1 wildtype and GSTM1 null | Other combinations | Lung function among mild-to-moderate asthmatics with moderate exercise | = | Vagaggini et al. (2010) |
| NQO1 wildtype and GSTM1 null | Other combinations | Inflammatory responses among mild-to-moderate asthmatics with moderate exercise | = | |
| GSTM1 null | GSTM1 positive | Lung function among healthy adults with intermittent moderate exercise | = | Kim et al. (2011) |
| GSTM1 null | GSTM1 positive | Inflammatory responses among healthy adults with intermittent moderate exercise | = | |
| GSTM1 null | GSTM1 positive | Lung function among asthmatic children | ↓ | Romieu et al. (2004b) |
| GSTM1 null | GSTM1 positive | Lung function among healthy adults with intermittent moderate exercise | = | Alexis et al. (2009) |
| GSTM1 null | GSTM1 positive | Inflammatory changes among healthy adults with intermittent moderate exercise | ↑ | |

1 Epidemiologic studies that examined the effects of short-term exposure to O₃ on lung
2 function included analyses of potential gene-environment interactions. [Romieu et al.](#)
3 [\(2006\)](#) reported an association between O₃ and respiratory symptoms that were larger
4 among children with GSTM1 null or glutathione S-transferase P 1 (GSTP1) Val/Val
5 genotypes compared with children with GSTM1 positive or GSTP1 Ile/Ile or Ile/Val
6 genotypes, respectively. However, results suggested that O₃-associated decreases in lung
7 function may be greater among children with GSTP1 Ile/Ile or Ile/Val compared to
8 GSTP1 Val/Val. [Alexeeff et al. \(2008\)](#) reported greater O₃-related decreases in lung
9 function among GSTP1 Val/Val adults than those with GSTP1 Ile/Ile or GSTP1 Ile/Val
10 genotypes. In addition, they detected greater O₃-associated decreases in lung function for
11 adults with long GT dinucleotide repeats in heme-oxygenase-1 (HMOX1) promoters.

1 Several controlled human exposure studies have reported that genetic polymorphisms of
2 antioxidant enzymes may modulate pulmonary function and inflammatory responses to
3 O₃ challenge. Healthy carriers of NAD(P)H quinone oxidoreductase 1 (NQO1) wild type
4 (wt) in combination with GSTM1 null genotype had greater decreases in lung function
5 parameters with exposure to O₃ ([Bergamaschi et al., 2001](#)). [Vagaggini et al. \(2010\)](#)
6 exposed mild-to-moderate asthmatics to O₃ during moderate exercise. In subjects with
7 NQO1 wt and GSTM1 null, there was no evidence of changes in lung function or
8 inflammatory responses to O₃. [Kim et al. \(2011\)](#) also recently conducted a study among
9 young adults, about half of whom were GSTM1-null and half of whom were
10 GSTM1-sufficient. They detected no difference in the FEV₁ responses to O₃ exposure by
11 GSTM1 genotype and did not examine NQO1. In another study that examined GSTM1
12 but not NQO1, asthmatic children with GSTM1 null genotype ([Romieu et al., 2004b](#))
13 were reported to have greater decreases in lung function in relation to O₃ exposure.
14 Additionally, supplementation with antioxidants (Vitamins C and E) had a slightly more
15 beneficial effect among GSTM1 null children (for more on modification by diet, see
16 Section [8.4.1](#)).

17 In a study of healthy volunteers with GSTM1 sufficient (n = 19; 24 ± 3) and GSTM1 null
18 (n = 16; 25 ± 5) genotypes exposed to 400 ppb O₃ for 2 hours with exercise, [Alexis et al.](#)
19 [\(2009\)](#) found genotype effects on inflammatory responses but not lung function responses
20 to O₃. At 4 hours post-O₃ exposure, individuals with either GSTM1 genotype had
21 statistically significant increases in sputum neutrophils with a tendency for a greater
22 increase in GSTM1 sufficient than GSTM1 nulls. At 24 hours postexposure, neutrophils
23 had returned to baseline levels in the GSTM1 sufficient individuals. In the GSTM1 null
24 subjects, neutrophil levels increased from 4 to 24 hours and were significantly greater
25 than both baseline levels and levels at 24 hours in the GSTM1 sufficient individuals. In
26 addition, O₃ exposure increased the expression of the surface marker CD14 in airway
27 neutrophils of GSTM1 null subjects compared with GSTM1 sufficient subjects. CD14
28 and TLR4 are co-receptors for endotoxin, and signaling through this innate immune
29 pathway has been shown to be important for a number of biological responses to O₃
30 exposure in toxicological studies ([Garantziotis et al., 2010](#); [Hollingsworth et al., 2010](#);
31 [Hollingsworth et al., 2004](#); [Kleeberger et al., 2000](#)). [Alexis et al. \(2009\)](#) also
32 demonstrated decreased numbers of airway macrophages at 4 and 24 hours following O₃
33 exposure in GSTM1 sufficient subjects. Airway macrophages in GSTM1 null subjects
34 were greater in number and found to have greater oxidative burst and phagocytic
35 capability following O₃ exposure than those of GSTM1 sufficient subjects. Airway
36 macrophages and dendritic cells from GSTM1 null subjects exposed to O₃ expressed
37 higher levels of the surface marker HLA-DR, again suggesting activation of the innate
38 immune system. Since there was no FA control in the [Alexis et al. \(2009\)](#) study, effects
39 of the exposure other than O₃ cannot be ruled out. In general, the findings between these

1 studies are inconsistent. It is possible that different genes may be important for different
2 phenotypes. Additional studies, which include appropriate controls, are needed to clarify
3 the influence of genetic polymorphisms on O₃ responsiveness in humans.

4 In general, toxicological studies have reported differences in cardiac and respiratory
5 effects after O₃ exposure among different mouse strains, which alludes to differential risk
6 among individuals due to genetic variability ([Tankersley et al., 2010](#); [Chuang et al., 2009](#);
7 [Hamade and Tankersley, 2009](#); [Hamade et al., 2008](#)). Thus strains of mice which are
8 prone to or resistant to O₃-induced effects have been used to systematically identify
9 candidate genes that may increase risk of O₃-related health effects. Genome wide linkage
10 analyses have identified quantitative trait loci for O₃-induced lung inflammation and
11 hyperpermeability on chromosome 17 ([Kleeberger et al., 1997](#)) and chromosome 4
12 ([Kleeberger et al., 2000](#)), respectively, using recombinant inbred strains of mice. More
13 specifically, these studies found that TNF (protein product is the inflammatory cytokine
14 TNF- α) and Tlr4 (protein product is TLR4, involved in endotoxin responses) were
15 candidate susceptibility genes ([Kleeberger et al., 2000](#); [Kleeberger et al., 1997](#)). The TNF
16 receptors 1 and 2 have also been found to play a role in injury, inflammation, and airway
17 hyperreactivity in studies of O₃-exposed knockout mice ([Cho et al., 2001](#)). In addition to
18 Tlr4, other innate immune pattern recognition signaling pathway genes, including Tlr2
19 and Myd88, appear to be important in responses to O₃, as demonstrated by [Williams et al.](#)
20 ([2007b](#)). A role for the inflammatory cytokine IL-6 has been demonstrated in
21 gene-deficient mice with respect to inflammation and injury, but not AHR ([Johnston et](#)
22 [al., 2005](#); [Yu et al., 2002](#)). Mice deficient in IL-10, an anti-inflammatory cytokine,
23 demonstrated increased pulmonary inflammation in response to O₃ exposure ([Backus et](#)
24 [al., 2010](#)). Thus genes related to innate immune signaling and pro- and anti-inflammatory
25 genes are important for O₃-induced responses.

26 Altered O₃ responses between mouse strains could be due to genetic variability in nuclear
27 factor erythroid 2-related factor 2 (Nrf-2), suggesting a role for genetic differences in
28 altering the formation of ROS ([Hamade et al., 2010](#); [Cho and Kleeberger, 2007](#)).
29 Additionally, some studies have reported O₃-related effects to vary by Inf-1 and Inf-2
30 quantitative trait loci ([Tankersley and Kleeberger, 1994](#)) and a gene coding for Clara cell
31 secretory protein (CCSP) ([Broeckaert et al., 2003](#); [Wattiez et al., 2003](#)). Other
32 investigations in inbred mouse strains found that differences in expression of certain
33 proteins, such as CCSP ([Broeckaert et al., 2003](#)) and MARCO ([Dahl et al., 2007](#)), are
34 responsible for phenotypic characteristics, such as epithelial permeability and scavenging
35 of oxidized lipids, respectively, which confer sensitivity to O₃.

36 Nitric oxide (NO), derived from activated macrophages, is produced upon exposure to O₃
37 and is thought to participate in lung damage. Mice deficient in the gene for inducible

1 nitric oxide synthase (NOS2/NOSII/iNOS) are partially protected against lung injury
2 ([Kleeberger et al., 2001](#)), and it appears that O₃-induced iNOS expression is tied to the
3 TLR4 pathway described above. Similarly, iNOS deficient mice do not produce reactive
4 nitrogen intermediates after O₃ exposure, in contrast to their wild-type counterparts, and
5 also produce less PGE2 comparatively ([Fakhrzadeh et al., 2002](#)). These gene-deficient
6 mice were protected from O₃-induced lung injury and inflammation. In contrast, another
7 study using a similar exposure concentration but longer duration of exposure found that
8 iNOS deficient mice were more susceptible to O₃-induced lung damage ([Kenyon et al.,
9 2002](#)). Therefore it is unclear whether inducible nitric oxide synthase plays a protective
10 role or mediates damage.

11 [Voynow et al. \(2009\)](#) have shown that NQO1 deficient mice, like their human
12 counterparts, are resistant to O₃-induced AHR and inflammation. NQO1 catalyzes the
13 reduction of quinones to hydroquinones, and is capable of both protective detoxification
14 reactions and redox cycling reactions resulting in the generation of reactive oxygen
15 species. Reduced production of inflammatory mediators and cells and blunted AHR were
16 observed in NQO1 null mice after exposure to 1 ppm O₃ for 3 hours. These results
17 correlated with those from in vitro experiments in which human bronchial epithelial cells
18 treated with an NQO1 inhibitor exhibited reduced inflammatory responses to exposure to
19 0.4 ppm O₃ for 5 hours. This study may provide biological plausibility for the increased
20 biomarkers of oxidative stress and increased pulmonary function decrements observed in
21 O₃-exposed individuals bearing both the wild-type NQO1 gene and the null GSTM1 gene
22 ([Bergamaschi et al., 2001](#)).

23 The role of TNF- α signaling in O₃-induced responses has been previously established
24 through depletion experiments, but a more recent toxicological study investigated the
25 effects of combined O₃ and PM exposure in transgenic TNF overexpressing mice.
26 [Kumarathasan et al. \(2005\)](#) found that subtle effects of these pollutants were difficult to
27 identify in the midst of the severe pathological changes caused by constitutive TNF- α
28 overexpression. However, there was evidence that TNF transgenic mice were more
29 susceptible to O₃/PM-induced oxidative stress, and they exhibited elevation of a serum
30 creatine kinase after pollutant exposure, which may suggest potential systemic or cardiac
31 related effects. Differential susceptibility to O₃ among inbred strains of animals does not
32 seem to be dose dependent since absorption of ¹⁸O in various strains of mice did not
33 correlate with resistance or sensitivity ([Vancza et al., 2009](#)).

34 Defects in DNA repair mechanisms may also confer increased risk of O₃-related health
35 effects. Cockayne syndrome, a rare autosomal recessive disorder in humans, is
36 characterized by UV sensitivity abnormalities, neurological abnormalities, and premature
37 aging. The same genetic defect in mice (Csb^{-/-}) makes them sensitive to oxidative

1 stressors, including O₃. [Kooter et al. \(2007\)](#) demonstrated that Csb^{-/-} mice produced
2 significantly more TNF-α after exposure to 0.8 ppm O₃ than their wild-type counterparts.
3 However, there were no statistically significant differences in other markers of
4 inflammation or lung injury between the two strains of mice.

5 Overall, for variants in multiple genes there is suggestive evidence for potential
6 involvement in populations being potentially more at-risk than others to the effects of O₃
7 exposure on health. Controlled human exposure and epidemiologic studies have reported
8 some evidence of O₃-related increases in respiratory symptoms or decreases in lung
9 function with variants including GSTM1, GSTP1, HMOX1 and NQO1, although the
10 results are not consistent across studies and gene variants. Future studies of these and
11 other genes in human populations will be important for determining the role of each
12 genotype and its effect on risk as well as finding coherence across the disciplines. NQO1
13 deficient mice were found to be resistant to O₃-induced AHR and inflammation,
14 providing biological plausibility for results of studies in humans. Additionally, studies of
15 rodents have identified a number of other genes that may affect O₃-related health
16 outcomes, including genes related to innate immune signaling and pro- and
17 anti-inflammatory genes, which have not been investigated in human studies.

8.2 Preexisting Disease/Conditions

18 Individuals with certain preexisting diseases are likely to constitute an at-risk population.
19 This may be the result of individuals with a preexisting disease/condition having less
20 reserve than healthy individuals, so although the absolute change may be the same, the
21 health consequences are different. Previous O₃ AQCDs concluded that some people with
22 preexisting pulmonary disease, especially asthma, are among those at increased risk of an
23 O₃-related health effect. Extensive toxicological evidence indicates that altered
24 physiological, morphological and biochemical states typical of respiratory diseases may
25 render people at risk of an additional oxidative burden induced by O₃ exposure. In
26 addition, a number of epidemiologic studies found that some individuals with respiratory
27 diseases are at increased risk of O₃-related effects. The majority of the studies identified
28 in previous AQCDs focused on whether preexisting respiratory diseases result in
29 increased risk of O₃-related health effects, with a limited number of studies examining
30 other preexisting diseases, such as cardiovascular.

31 Studies identified since the completion of the 2006 O₃ AQCD that examined whether
32 preexisting diseases and conditions lead to increased risk of O₃-induced health effects
33 were identified and are summarized below. [Table 8-3](#) displays the prevalence rates of
34 some of these conditions categorized by age and region among adults in the U.S.

1 population; data for children, when available, are presented within the following sections.
 2 Substantial proportions of the U.S. population are affected by these conditions and
 3 therefore may represent a potentially large at-risk population. While these diseases and
 4 conditions represent biological or intrinsic factors that could lead to increased risk, the
 5 pathways to their development may have intrinsic or extrinsic origins.

Table 8-3 Prevalence of respiratory diseases, cardiovascular diseases, and diabetes among adults by age and region in the U.S.

| Chronic Disease/Condition | Adults | | | | | | | | |
|---------------------------|------------------|-------|-------|-------|------|-----------|---------|-------|------|
| | N (in thousands) | Age | | | | Region | | | |
| | | 18-44 | 45-64 | 65-74 | 75+ | Northeast | Midwest | South | West |
| Respiratory Diseases | | | | | | | | | |
| Asthma ^a | 16,380 | 7.2 | 7.5 | 7.8 | 6.4 | 7.7 | 8.0 | 5.9 | 8.4 |
| COPD | | | | | | | | | |
| Chronic Bronchitis | 9,832 | 3.2 | 5.5 | 5.9 | 5.3 | 3.4 | 4.8 | 5.2 | 2.9 |
| Emphysema | 3,789 | 0.2 | 2.0 | 5.7 | 5.0 | 1.2 | 1.9 | 1.9 | 1.3 |
| Cardiovascular Diseases | | | | | | | | | |
| All Heart Disease | 26,628 | 4.6 | 12.3 | 26.7 | 39.2 | 11.3 | 12.7 | 12.2 | 9.9 |
| Coronary Heart Disease | 14,428 | 1.1 | 6.7 | 16.9 | 26.7 | 5.7 | 6.5 | 7.3 | 4.9 |
| Hypertension | 56,159 | 8.7 | 32.5 | 54.4 | 61.1 | 22.9 | 24.1 | 27.1 | 20.6 |
| Diabetes | 18,651 | 2.3 | 12.1 | 20.4 | 17.3 | 4.5 | 7.6 | 9.0 | 7.7 |

^aAsthma prevalence is reported for "still has asthma."

Source: Pleis et al. (2009); National Center for Health Statistics.

8.2.1 Influenza/Infections

6 Recent studies have indicated that underlying infections may increase the risk of O₃-
 7 related health effects because O₃ exposure likely impairs host defenses, which may
 8 increase the body's response to an infectious agent. However, there is little epidemiologic
 9 or experimental evidence that infection or influenza itself renders an individual at greater
 10 risk of an O₃-induced health effect. A study of hospitalizations in Hong Kong reported
 11 that increased levels of influenza intensity resulted in increased excess risk of respiratory
 12 disease hospitalizations related to O₃ exposure (Wong et al., 2009). In addition, a study of
 13 lung function in asthmatic children reported decreases in lung function with increased
 14 short-term O₃ exposure for those with upper respiratory infections but not for those
 15 without infections (Lewis et al., 2005). Toxicological studies provide biological
 16 plausibility for the increase in O₃-induced health effects observed in epidemiologic
 17 studies that examined infections by way of studies that demonstrated that exposure to

0.08 ppm O₃ increased streptococcus-induced mortality, regardless of whether O₃ exposure preceded or followed infection ([Miller et al., 1978](#); [Coffin and Gardner, 1972](#); [Coffin et al., 1967](#)). Overall, the epidemiologic and experimental evidence supports the potential for increased risk to be conferred by an infection but the number of studies is limited. There have only been a few epidemiologic studies and these studies examine different outcomes (respiratory-related hospital admissions or lung function) and different modifiers (influenza or respiratory infection). In some of the toxicological studies, the O₃ exposure came before the infection. Therefore, evidence is inadequate to determine if influenza/infections increase the risk of O₃-related health effects.

8.2.2 Asthma

Previous O₃ AQCDs identified individuals with asthma as a population at increased risk of O₃-related health effects. Within the U.S., approximately 7.3% of adults have reported currently having asthma ([Pleis et al., 2009](#)), and 9.5% of children have reported currently having asthma ([Bloom et al., 2008](#)). For more detailed prevalence by age, see [Table 8-4](#).

Table 8-4 Prevalence of asthma by age in the U.S.

| Age (years) | N (in thousands) | Percent |
|-------------|------------------|---------|
| 0-4 | 1,276 | 6.2 |
| 5-11 | 3,159 | 11.2 |
| 12-17 | 2,518 | 10.2 |
| 18-44 | 7,949 | 7.2 |
| 45-64 | 5,768 | 7.5 |
| 65-74 | 1,548 | 7.8 |
| 75+ | 1,116 | 6.4 |

^aAsthma prevalence is reported for “still has asthma”

Source: Statistics for adults: [Pleis et al. \(2009\)](#); statistics for children: [Bloom et al. \(2008\)](#); National Center for Health Statistics.

Multiple epidemiologic studies included within this ISA have evaluated the potential for increased risk of O₃-related health effects among individuals with asthma. A study of lifeguards in Texas reported decreased lung function with short-term O₃ exposure among both individuals with and without asthma, however, the decrease was greater among those with asthma ([Thaller et al., 2008](#)). A Mexican study of children ages 6-14 detected an association between short-term O₃ exposure and wheeze, cough, and bronchodilator use among asthmatics but not non-asthmatics, although this may have been the result of a small non-asthmatic population ([Escamilla-Nuñez et al., 2008](#)). A study of modification

1 by airway hyperresponsiveness (AHR) (a condition common among asthmatics) reported
2 greater short-term O₃-associated decreases in lung function in elderly individuals with
3 AHR, especially among those who were obese ([Alexeeff et al., 2007](#)). However, no
4 evidence for increased risk was found in a study performed among children in Mexico
5 City that examined the effect of short-term O₃ exposure on respiratory health ([Barraza-
6 Villarreal et al., 2008](#)). In this study, a positive association was reported for airway
7 inflammation among asthmatic children, but the observed association was similar in
8 magnitude to that of non-asthmatics. Similarly, a study of children in California reported
9 an association between O₃ concentration and exhaled nitric oxide fraction (FeNO) that
10 persisted both among children with and without asthma as well as those with and without
11 respiratory allergy ([Berhane et al., 2011](#)). Finally, [Khatri et al. \(2009\)](#) found no
12 association between short-term O₃ exposure and altered lung function for either asthmatic
13 or non-asthmatic adults, but did note a decrease in lung function among individuals with
14 allergies.

15 Evidence for difference in effects among asthmatics has been observed in studies that
16 examined the association between O₃ exposure and altered lung function by asthma
17 medication use. A study of children with asthma living in Detroit reported a greater
18 association between short-term O₃ and lung function for corticosteroid users compared
19 with noncorticosteroid users ([Lewis et al., 2005](#)). Conversely, another study found
20 decreased lung function among noncorticosteroid users compared to corticosteroid users,
21 although in this study, a large proportion of non-users were considered to be persistent
22 asthmatics ([Hernández-Cadena et al., 2009](#)). Lung function was not related to short-term
23 O₃ exposure among corticosteroid users and non-users in a study taking place during the
24 winter months in Canada ([Liu et al., 2009a](#)). Additionally, a study of airway
25 inflammation reported a counterintuitive inverse association with O₃ of similar magnitude
26 for all groups of corticosteroid users and non-users ([Qian et al., 2009](#)).

27 Controlled human exposure studies that have examined the effects of O₃ on individuals
28 with asthma and healthy controls are limited. Based on studies reviewed in the 1996 and
29 2006 O₃ AQCDs, subjects with asthma appeared to be at least as sensitive to acute effects
30 of O₃ in terms of FEV₁ and inflammatory responses as healthy non-asthmatic subjects.
31 For instance, [Horstman et al. \(1995\)](#) observed that mild-to-moderate asthmatics, on
32 average, experienced double the O₃-induced FEV₁ decrement of healthy subjects (19%
33 versus 10%, respectively, p = 0.04). Moreover, a statistically significant positive
34 correlation between FEV₁ responses to O₃ exposure and baseline lung function was
35 observed in individuals with asthma, i.e., responses increased with severity of disease.
36 [Kreit et al. \(1989\)](#) performed a short duration study in which asthmatics also showed a
37 considerable larger average O₃-induced FEV₁ decrement than the healthy controls (25%
38 vs. 16%, respectively) following exposure to O₃ with moderate-heavy exercise. [Alexis et](#)

1 [al. \(2000\)](#) and [Jorres et al. \(1996\)](#) also reported a tendency for slightly greater FEV₁
2 decrements in asthmatics than healthy subjects. Minimal evidence exists suggesting that
3 individuals with asthma have smaller O₃-induced FEV₁ decrements than healthy subjects
4 (3% versus 8%, respectively) ([Mudway et al., 2001](#)). However, the asthmatics in that
5 study also tended to be older than the healthy subjects, which could partially explain their
6 lesser response since FEV₁ responses to O₃ exposure diminish with age. Individuals with
7 asthma also had more neutrophils in the BALF (18 hours postexposure) than similarly
8 exposed healthy individuals ([Peden et al., 1997](#); [Scannell et al., 1996](#); [Basha et al., 1994](#)).
9 Furthermore, a study examining the effects of O₃ on individuals with atopic asthma and
10 healthy controls reported that greater numbers of neutrophils, higher levels of cytokines
11 and hyaluronan, and greater expression of macrophage cell-surface markers were
12 observed in induced sputum of atopic asthmatics compared with healthy controls
13 ([Hernandez et al., 2010](#)). Differences in O₃-induced epithelial cytokine expression were
14 noted in bronchial biopsy samples from asthmatics and healthy controls ([Bosson et al.,](#)
15 [2003](#)). Cell-surface marker and cytokine expression results, and the presence of
16 hyaluronan, are consistent with O₃ having greater effects on innate and adaptive
17 immunity in these asthmatic individuals (see Section [5.4.2.2](#)). In addition, studies have
18 demonstrated that O₃ exposure leads to increased bronchial reactivity to inhaled allergens
19 in mild allergic asthmatics ([Kehrl et al., 1999](#); [Jorres et al., 1996](#)) and to the influx of
20 eosinophils in individuals with pre-existing allergic disease ([Vagaggini et al., 2002](#);
21 [Peden et al., 1995](#)). Taken together, these results point to several mechanistic pathways
22 which could account for the increased risk of O₃-related health effects in subjects with
23 asthma (see Section [5.4.2.2](#)).

24 Toxicological studies provide biological plausibility for greater effects of O₃ among those
25 with asthma or AHR. In animal toxicological studies, an asthmatic phenotype is modeled
26 by allergic sensitization of the respiratory tract. Many of the studies that provide evidence
27 that O₃ exposure is an inducer of AHR and remodeling utilize these types of animal
28 models. For example, a series of experiments in infant rhesus monkeys have shown these
29 effects, but only in monkeys sensitized to house dust mite allergen ([Fanucchi et al., 2006](#);
30 [Joad et al., 2006](#); [Schelegle et al., 2003](#)). Similarly, [Funabashi et al. \(2004\)](#) demonstrated
31 changes in pulmonary function in mice exposed to O₃, and [Wagner et al. \(2007\)](#)
32 demonstrated enhanced inflammatory responses in rats exposed to O₃, but only in
33 animals sensitized to allergen. In general, it is the combined effects of O₃ and allergic
34 sensitization which result in measurable effects on pulmonary function. In a bleomycin
35 induced pulmonary fibrosis model, exposure to 250 ppb O₃ for 5 days increased
36 pulmonary inflammation and fibrosis, along with the frequency of bronchopneumonia in
37 rats. Thus, short-term exposure to O₃ may enhance damage in a previously injured lung
38 ([Oyarzún et al., 2005](#)).

1 In the 2006 O₃ AQCD, the potential for individuals with asthma to have greater risk of
2 O₃-related health effects was supported by a number of controlled human exposure
3 studies, evidence from toxicological studies, and a limited number of epidemiologic
4 studies. Overall, in the recent epidemiologic literature some, but not all, studies report
5 greater risk of health effects among individuals with asthma. Studies examining effect
6 measure modification of the relationship between short-term O₃ exposure and altered
7 lung function by corticosteroid use provided limited and inconsistent evidence of
8 O₃-related health effects. Additionally, recent studies of behavioral responses have found
9 that studies do not take into account individual behavioral adaptations to forecasted air
10 pollution levels (such as avoidance and reduced time outdoors), which may underestimate
11 the observed associations in studies that examined the effect of O₃ exposure on
12 respiratory health ([Neidell and Kinney, 2010](#)). This could explain some inconsistency
13 observed among recent epidemiologic studies. The evidence from controlled human
14 exposure studies provides support for increased decrements in FEV₁ and greater
15 inflammatory responses to O₃ in individuals with asthma than in healthy individuals
16 without a history of asthma. The collective evidence for increased risk of O₃-related
17 health effects among individuals with asthma from controlled human exposure studies is
18 supported by recent toxicological studies which provide biological plausibility for
19 heightened risk of asthmatics to respiratory effects due to O₃ exposure. Evidence
20 indicating O₃-induced respiratory effects among individuals with asthma is further
21 supported by additional studies of O₃-related respiratory effects (Section [6.2](#)). Overall,
22 there is adequate evidence for asthmatics to be a potentially at-risk population based on
23 the substantial, consistent evidence among controlled human exposure studies and
24 coherence from epidemiologic and toxicological studies.

8.2.3 Chronic Obstructive Pulmonary Disease (COPD)

25 In the U.S. over 4% of adults report having chronic bronchitis and almost 2% report
26 having emphysema, both of which are classified as COPD ([Pleis et al., 2009](#)).

27 A recent study reported no association between O₃ exposure and lung function regardless
28 of whether the study participant had COPD or other preexisting diseases (asthma or IHD)
29 ([Lagorio et al., 2006](#)).

30 [Peel et al. \(2007\)](#) found that individuals with COPD were at increased risk of
31 cardiovascular ED visits in response to short-term O₃ exposure compared to healthy
32 individuals in Atlanta, GA. The authors reported that short-term O₃ exposure was
33 associated with higher odds of an emergency department (ED) visit for peripheral and
34 cerebrovascular disease among individuals with COPD compared to individuals without

1 COPD. However, preexisting COPD did not increase the odds of hospitalization for all
2 CVD outcomes (i.e., IHD, dysrhythmia, or congestive heart failure). In an additional
3 study performed in Taiwan, individuals with and without COPD had higher odds of
4 congestive heart failure associated with O₃ exposure on warm days ([Lee et al., 2008a](#)). As
5 discussed in Section [6.3](#), most studies reported no overall association between O₃
6 concentration and CVD morbidity.

7 Recent epidemiologic evidence indicates that persons with COPD may have increased
8 risk of O₃-related cardiovascular effects, but little information is available on whether
9 COPD leads to an increased risk of O₃-induced respiratory effects. Overall, this small
10 number of studies provides inadequate evidence to determine whether COPD results in
11 increased risk of O₃-related health effects.

8.2.4 Cardiovascular Disease (CVD)

12 Cardiovascular disease has become increasingly prevalent in the U.S., with about 12% of
13 adults reporting a diagnosis of heart disease ([Table 8-3](#)). A high prevalence of other
14 cardiovascular-related conditions has also been observed, such as hypertension which is
15 prevalent among approximately 24% of adults. In the 2006 O₃ AQCD, little evidence was
16 available regarding whether preexisting CVD contributed to increased risk of O₃-related
17 health effects. Recent epidemiologic studies have examined cardiovascular-related
18 diseases as modifiers of the O₃-outcome associations; however, no recent evidence is
19 available from controlled human exposure studies or toxicological studies.

20 [Peel et al. \(2007\)](#) compared the associations between short-term O₃ exposure and
21 cardiovascular ED visits in Atlanta, GA among multiple comorbid conditions. The
22 authors found no evidence of increased risk of cardiovascular ED visits in individuals
23 previously diagnosed with dysrhythmia, congestive heart failure, or hypertension
24 compared to healthy individuals. Similarly, a study in France examined the association
25 between O₃ concentrations and ischemic cerebrovascular events (ICVE) and myocardial
26 infarction (MI) and the influence of multiple vascular risk factors on any observed
27 associations ([Henrotin et al., 2010](#)). The association between O₃ exposure and ICVE was
28 elevated for individuals with multiple risk factors, specifically individuals with diabetes
29 or hypertension. For the association between O₃ and MI, increased odds were apparent
30 only for those with hypercholesterolemia. In a study conducted in Taiwan, a positive
31 association was observed for O₃ on warm days and congestive heart failure hospital
32 admissions, but the association did not differ between individuals with/without
33 hypertension or with/without dysrhythmia ([Lee et al., 2008a](#)). Another study in Taiwan
34 reported that the association between O₃ levels and ED visits for arrhythmias were greater

1 on warm days among those with congestive heart failure compared to those without
2 congestive heart failure; however, the estimate and 95% CIs for those without congestive
3 heart failure is completely contained within the 95% CI of those with congestive heart
4 failure ([Chiu and Yang, 2009](#)).

5 Although not studied extensively, a study has examined the increased risk of O₃-related
6 changes in blood markers for individuals with CVD. There was a greater association
7 between O₃ exposure and some, but not all, blood inflammatory markers among
8 individuals with a history of CVD ([Liao et al., 2005](#)). [Liao et al. \(2005\)](#) found that
9 increased fibrinogen was positively associated with short-term O₃ exposure but this
10 association was present only among individuals with a history of CVD. No association
11 was observed among those without a history of CVD. However, for another biomarker
12 (vWF), CVD status did not modify the positive association with short-term O₃ exposure
13 ([Liao et al., 2005](#)).

14 Mortality studies provide some evidence for a potential increase in O₃-induced mortality
15 in individuals with preexisting atrial fibrillation and atherosclerosis. In a study of 48 U.S.
16 cities, increased risk of mortality with short-term O₃ exposure was observed only among
17 individuals with secondary atrial fibrillation ([Medina-Ramón and Schwartz, 2008](#)). No
18 association was observed for short-term O₃ exposure and mortality in a study of
19 individuals with diabetes with or without CVD prior to death; however, there was some
20 evidence of increased risk of mortality during the warm season if individuals had diabetes
21 and atherosclerosis compared to only having diabetes ([Goldberg et al., 2006](#)).

22 Finally, although not extensively examined, a study explored whether a preexisting CVD
23 increased the risk of an O₃-induced respiratory effect. [Lagorio et al. \(2006\)](#) examined the
24 effect of O₃ exposure on lung function among participants with a variety of preexisting
25 diseases, including IHD. No association was observed regardless of whether the
26 participant had IHD.

27 Overall, most short-term exposure studies did not report increased O₃-related
28 cardiovascular morbidity for individuals with preexisting CVD. However, as discussed in
29 Section 6.3, most studies reported no overall association between O₃ concentration and
30 CV morbidity. Thus, it is likely the association would be null regardless of the
31 stratification. A limited number of studies examined whether cardiovascular disease
32 modifies the association between O₃ and respiratory effects. There was some evidence
33 that cardiovascular disease increases the risk of O₃-related mortality but again the number
34 of studies was limited. Currently, evidence is inadequate to classify CVD as a potential
35 at-risk factor for O₃-related health effects. Future research among those with CVD
36 compared to those without will increase the understanding of potential increased risk of
37 O₃-related health effects among this group.

8.2.5 Diabetes

1 The literature has not extensively examined whether individuals with diabetes (about 8%
2 of U.S. adults) are potentially at increased risk of O₃-related health effects. In a study of
3 short-term O₃ exposure and cardiovascular ED visits in Atlanta, GA, no association was
4 observed for individuals with or without diabetes ([Peel et al., 2007](#)). A similar study
5 conducted in Taiwan reported a positive association between O₃ exposure on warm days
6 and hospital admissions for congestive heart failure; however, no modification of the
7 association by diabetes was observed ([Lee et al., 2008a](#)). Finally, in a study of O₃
8 exposure and ED visits for arrhythmia in Taiwan, there was no evidence of effect
9 measure modification by diabetes on warm or cool days ([Chiu and Yang, 2009](#)).
10 Currently, the limited number of epidemiologic studies as well as the lack of controlled
11 human exposure or toxicological studies provides inadequate evidence to indicate
12 whether diabetes results in a potentially increased risk of O₃-related health effects.

8.2.6 Hyperthyroidism

13 Hyperthyroidism has been identified in toxicological studies as a potential factor that may
14 lead to increased risk of O₃-related health effects but has not yet been explored in
15 epidemiologic or controlled human exposure studies. Lung damage and inflammation due
16 to oxidative stress may be modulated by thyroid hormones. Compared to controls,
17 hyperthyroid rats exhibited elevated levels of BAL neutrophils and albumin after a 4-hour
18 exposure to O₃, indicating O₃-induced inflammation and damage. Hyperthyroidism did
19 not affect production of reactive oxygen or nitrogen species, but BAL phospholipids were
20 increased, indicating greater activation of Type II cells and surfactant protein production
21 compared to normal rats ([Huffman et al., 2006](#)). Thus, this study provides some
22 underlying evidence, which suggests that individuals with hyperthyroidism may represent
23 an at-risk population; however, overall the lack of additional studies provides inadequate
24 evidence to determine whether hyperthyroidism results in potentially increased risk of
25 O₃-related health effects.

8.3 Sociodemographic Factors

8.3.1 Lifestage

26 The 1996 and 2006 O₃ AQCDs identified children, especially those with asthma, and
27 older adults as at-risk populations. These previous AQCDs reported clinical evidence that

1 children have greater spirometric responses to O₃ than middle-aged and older adults ([U.S.](#)
2 [EPA, 1996a](#)). Similar results were observed for symptomatic responses and O₃ exposure.
3 Among older adults, most studies reported in the 2006 O₃ AQCD reported greater effects
4 of short-term O₃ exposure and mortality compared to other age groups ([U.S. EPA,](#)
5 [2006b](#)). Evidence published since the 2006 O₃ AQCD, summarized below, further
6 supports these findings.

8.3.1.1 Children

7 The 2000 Census reported that 28.6% of the U.S. population was under 20 years of age,
8 with 14.1% under the age of 10 ([SSDAN CensusScope, 2010a](#)). Children's respiratory
9 systems are undergoing lung growth until about 18-20 years of age and are therefore
10 thought to be intrinsically more at risk for O₃-induced damage ([U.S. EPA, 2006b](#)). It is
11 generally recognized that children spend more time outdoors than adults, and therefore
12 would be expected to have higher exposure to O₃ than adults. The ventilation rates also
13 vary between children and adults, particularly during moderate/heavy activity. Children
14 aged 11 years and older and adults have higher absolute ventilation rates than children
15 aged 1 -11 years. However, children have higher ventilation rates relative to their lung
16 volumes, which tends to increase dose normalized to lung surface area. Exercise intensity
17 has a substantial effect on ventilation rate, with high intensity activities resulting in nearly
18 double the ventilation rate during moderate activity among children and those adults less
19 than 31 years of age. For more information on time spent outdoors and ventilation rate
20 differences by age group, see Section [4.4.1](#).

21 The 1996 O₃ AQCD, reported clinical evidence that children, adolescents, and young
22 adults (<18 years of age) appear, on average, to have nearly equivalent spirometric
23 responses to O₃ exposure, but have greater responses than middle-aged and older adults
24 ([U.S. EPA, 1996a](#)). Symptomatic responses (e.g., cough, shortness of breath, pain on
25 deep inspiration) to O₃ exposure, however, appear to increase with age until early
26 adulthood and then gradually decrease with increasing age ([U.S. EPA, 1996a](#)). For
27 subjects aged 18-36 years, [McDonnell et al. \(1999b\)](#) reported that symptom responses
28 from O₃ exposure also decrease with increasing age. Complete lung growth and
29 development is not achieved until 18-20 years of age in women and the early 20s for
30 men; pulmonary function is at its maximum during this time as well. Additionally, PBPK
31 modeling reported lung regional extraction of O₃ to be higher in infants compared to
32 adults. This is thought to be due to the smaller nasal and pulmonary regions' surface area
33 in children under the age of 5 years compared to the total airway surface area observed in
34 adults ([Sarangapani et al., 2003](#)).

1 Recent epidemiologic studies have examined different age groups and their risk to
2 O₃-related respiratory hospital admissions and ED visits. A study in Cyprus of short-term
3 O₃ concentrations and respiratory hospital admissions detected possible effect measure
4 modification by age with a larger association among individuals <15 years of age
5 compared with those >15 years of age. However, this difference was only apparent with a
6 2-day lag ([Middleton et al., 2008](#)). Similarly, a Canadian study of asthma-eD visits
7 reported the strongest O₃-related associations among 5 to 14 year-olds compared to the
8 other age groups (ages examined 0-75+) ([Villeneuve et al., 2007](#)). Greater O₃-associated
9 risk in asthma-related ED visits were also reported among children (<15 years) as
10 compared to adults (15 to 64 years) in a study from Finland ([Halonen et al., 2009](#)). A
11 study of New York City hospital admissions demonstrated an increase in the association
12 between O₃ exposure and asthma-related hospital admissions for 6 to 18 year-olds
13 compared to those <6 years old and those >18 years old ([Silverman and Ito, 2010](#)). When
14 examining long-term O₃ exposure and asthma hospital admissions among children,
15 associations were determined to be larger among children 1 to 2 years old compared to
16 children 2 to 6 years old ([Lin et al., 2008b](#)). A few studies reported positive associations
17 among both children and adults and no modification of the effect by age. A study
18 performed in Hong Kong examined O₃ exposure and asthma-related hospital admissions
19 for ages 0 to 14, 15 to 65, and >65 ([Ko et al., 2007](#)). The researchers reported that the
20 association was greater among the 0 to 14 and 14 to 65 age groups compared to the >65
21 age group. Another study looking at asthma-related ED visits and O₃ exposure in Maine
22 reported positive associations for all age groups (ages 2 to 65) ([Paulu and Smith, 2008](#)).
23 Effects of O₃ exposure on asthma hospitalizations among both children and adults (<18
24 and ≥ 18 years old) were demonstrated in a study in Washington, but only children (<18
25 years of age) had statistically significant results at lag day 0, which the authors wrote,
26 “suggests that children are more immediately responsive to adverse effects of O₃
27 exposure” ([Mar and Koenig, 2009](#)).

28 The evidence reported in epidemiologic studies is supported by recent toxicological
29 studies which observed O₃-induced health effects in immature animals. Early life
30 exposures of multiple species of laboratory animals, including infant monkeys, resulted
31 in changes in conducting airways at the cellular, functional, ultra-structural, and
32 morphological levels. [Carey et al. \(2007\)](#) conducted a study of O₃ exposure in infant
33 rhesus macaques, whose respiratory tract closely resemble that of humans. Monkeys were
34 exposed either acutely for 5 days to 0.5 ppm O₃, or episodically for 5 biweekly cycles
35 alternating 5 days of 0.5 ppm O₃ with 9 days of filtered air, designed to mimic human
36 exposure (70 days total). All monkeys acutely exposed to O₃ had moderate to marked
37 necrotizing rhinitis, with focal regions of epithelial exfoliation, numerous infiltrating
38 neutrophils, and some eosinophils. The distribution, character, and severity of lesions in
39 episodically exposed infant monkeys were similar to that of acutely exposed animals.

1 Neither exposure protocol for the infant monkeys produced mucous cell metaplasia
2 proximal to the lesions, an adaptation observed in adult monkeys exposed continuously to
3 0.3 ppm O₃ in another study ([Harkema et al., 1987a](#)). Functional (increased airway
4 resistance and responsiveness with antigen + O₃ co-exposure) and cellular changes in
5 conducting airways (increased numbers of inflammatory eosinophils) were common
6 manifestations of exposure to O₃ among both the adult and infant monkeys ([Plopper et
7 al., 2007](#)). In addition, the lung structure of the conducting airways in the infant monkeys
8 was stunted by O₃ and this aberrant development was persistent 6 months postexposure.
9 This developmental endpoint was not, of course, studied in the adult monkey experiments
10 ([Fanucchi et al., 2006](#)). Thus, some functional and biochemical effects were similar
11 between the infant and adult monkeys exposed to O₃, but because the study designs did
12 not include concentration-response experiments, it is not possible to determine whether
13 the infant monkeys were more at risk for the effects of O₃.

14 Similarly, rat fetuses exposed to O₃ in utero had ultrastructural changes in bronchiolar
15 epithelium when examined near the end of gestation ([López et al., 2008](#)). In addition,
16 exposure of mice to mixtures of air pollutants early in development affected pup lung
17 cytokine levels (TNF, IL-1, KC, IL-6, and MCP-1) ([Auten et al., 2009](#)). In utero exposure
18 of animals to PM augmented O₃-induced airway hyper-reactivity in these pups as
19 juveniles.

20 Age may affect the inflammatory response to O₃ exposure. In comparing neonatal mice to
21 adult mice, increased bronchoalveolar lavage (BAL) neutrophils were observed in four
22 strains of neonates 24 hours after exposure to 0.8 ppm O₃ for 5 hours ([Vancza et al.,
23 2009](#)). Three of these strains also exhibited increased BAL protein, although the two
24 endpoints were not necessarily consistently correlated in a given strain. In some strains,
25 however, adults were responsive, indicating a strain-age interaction. Measurement of ¹⁸O
26 determined that the observed strain- and age-dependent differences were not due to
27 absorbed O₃ dose. Using electron microscopy, [Bils \(1970\)](#) studied the lungs of mice of
28 different ages (4 days or 1 to 2 months) exposed to 0.6 to 1.3 ppm O₃ for 6 to 7 h/day for
29 1 to 2 days and noted swelling of the alveolar epithelial lining cells without intra-alveolar
30 edema. Swelling of endothelial cells and occasional breaks in the basement membrane
31 were observed. These effects were most evident in younger mice exposed for 2 days.
32 Toxicological studies reported that the difference in effects among younger lifestage test
33 animals may be due to age-related changes in endogenous antioxidants and sensitivity to
34 oxidative stress. A recent study demonstrated that 0.25 ppm O₃ exposure differentially
35 altered expression of metalloproteinases in the skin of young (8 weeks old) and aged
36 (18 months old) mice, indicating age-related susceptibility to oxidative stress ([Fortino et
37 al., 2007](#)). [Valacchi et al. \(2007\)](#) found that aged mice had more Vitamin E in their
38 plasma but less in their lungs compared to young mice, which may affect their pulmonary

1 antioxidant defenses. [Servais et al. \(2005\)](#) found higher levels of oxidative damage
2 indicators in immature (3 weeks old) and aged (20 months old) rats compared to adult
3 rats, the latter which were relatively resistant to an intermittent 7-day exposure to
4 0.5 ppm O₃. Immature rats exhibited a higher ventilation rate, which may have increased
5 exposure. Additionally, a series of toxicological studies reported an association between
6 O₃ exposure and bradycardia that was present among young but not older mice ([Hamade
7 et al., 2010](#); [Tankersley et al., 2010](#); [Hamade and Tankersley, 2009](#); [Hamade et al., 2008](#)).
8 Regression analysis revealed an interaction between age and strain on heart rate, which
9 implies that aging may affect heart rate differently among mouse strains ([Tankersley et
10 al., 2010](#)). The authors proposed that the genetic differences between the mice strains
11 could be altering the formation of ROS, which tends to increase with age, thus
12 modulating the changes in cardiopulmonary physiology after O₃ exposure.

13 The previous and recent human clinical and toxicological studies reported evidence of
14 increased risk from O₃ exposure for younger ages, which provides coherence and
15 biological plausibility for the findings from epidemiologic studies. Although there was
16 some inconsistency, generally, the epidemiologic studies reported larger associations for
17 respiratory hospital admissions and ED visits for children than adults. The interpretation
18 of these studies is limited by the lack of consistency in comparison age groups and
19 outcomes examined. Toxicological studies observed O₃-induced health effects in
20 immature animals, including infant monkeys, though the effects were not consistently
21 greater in young animals than adults. However, overall, the epidemiologic, controlled
22 human exposure, and toxicological studies provide substantial and consistent evidence
23 within and across disciplines. Therefore, there is adequate evidence to conclude that
24 children are potentially at increased risk of O₃-related health effects.

8.3.1.2 Older Adults

25 Older adults may be at greater risk of health effects associated with O₃ exposure through
26 a variety of intrinsic pathways. In addition, older adults may differ in their exposure and
27 internal dose. Older adults were outdoors for a slightly longer proportion of the day than
28 adults aged 18-64 years. Older adults also have somewhat lower ventilation rates than
29 adults aged 31 - less than 61 years. For more information on time spent outdoors and
30 ventilation rate differences by age group, see Section [4.4.1](#). The gradual decline in
31 physiological processes that occur with aging may lead to increased risk of O₃-related
32 health effects ([U.S. EPA, 2006a](#)). Respiratory symptom responses to O₃ exposure appears
33 to increase with age until early adulthood and then gradually decrease with increasing age
34 ([U.S. EPA, 1996a](#)), which may put older adults at increased risk by withstanding
35 continued O₃ exposure and thus not seeking relief and avoiding exposure. In addition,

1 older adults, in general, have a higher prevalence of preexisting diseases, with the
2 exception of asthma, compared to younger age groups and this may also lead to increased
3 risk of O₃-related health effects (see [Table 8-3](#) that gives preexisting rates by age). With
4 the number of older Americans increasing in upcoming years (estimated to increase from
5 12.4% of the U.S. population to 19.7% between 2000 to 2030, which is approximately
6 35 million and 71.5 million individuals, respectively) this group represents a large
7 population potentially at risk of O₃-related health effects ([SSDAN CensusScope, 2010a](#);
8 [U.S. Census Bureau, 2010](#)).

9 The majority of recent studies reported greater effects of short-term O₃ exposure and
10 mortality among older adults, which is consistent with the findings of the 2006 O₃
11 AQCD. A study conducted in 48 cities across the U.S. reported larger effects among
12 adults ≥ 65 years old compared to those <65 years ([Medina-Ramón and Schwartz, 2008](#)).
13 Further investigation of this study population revealed a trend of O₃-related mortality risk
14 that gets larger with increasing age starting at age 50 ([Zanobetti and Schwartz, 2008a](#)). A
15 study of 7 urban centers in Chile reported similar results, with greater effects in adults
16 ≥ 65 years old, however the effects were smaller among those ≥ 85 years old compared to
17 those in the 75 to 84 years old age range ([Cakmak et al., 2007](#)). More recently, a study
18 conducted in the same area reported similar associations between O₃ exposure and
19 mortality in adults aged <64 years old and 65 to 74 years old, but the risk was increased
20 among older age groups ([Cakmak et al., 2011](#)). A study performed in China reported
21 greater effects in populations ≥ 45 years old (compared to 5 to 44 year-olds), with
22 statistically significant effects present only among those ≥ 65 years old ([Kan et al., 2008](#)).
23 An Italian study reported higher risk of all-cause mortality associated with increased O₃
24 concentrations among individuals ≥ 85 years old as compared to those 35 to 84 years old.
25 Those 65 to 74 and 75 to 84 years old did not show a greater increase in risk compared to
26 those aged 35 to 64 years ([Stafoggia et al., 2010](#)). The Air Pollution and Health: A
27 European and North American Approach (APHENA) project examined the association
28 between O₃ exposure and mortality for those <75 and ≥ 75 years of age. In Canada, the
29 associations for all-cause and cardiovascular mortality were greater among those
30 ≥ 75 years old in the summer-only and all-year analyses. Age groups were not compared
31 in the analysis for respiratory mortality in Canada. In the U.S., the association for
32 all-cause mortality was slightly greater for those <75 years of age compared to those ≥ 75
33 years old in summer-only analyses. No consistent pattern was observed for CVD
34 mortality. In Europe, slightly larger associations for all-cause mortality were observed in
35 those <75 years old in all-year and summer-only analyses. Larger associations were
36 reported among those <75 years for CVD mortality in all-year analyses, but the reverse
37 was true for summer-only analyses ([Katsouyanni et al., 2009](#)).

1 Multiple epidemiologic studies of O₃ exposure and hospital admissions were stratified by
2 age groups. A positive association was reported between short-term O₃ exposure and
3 respiratory hospital admissions for adults ≥ 65 years old but not for those adults aged 15
4 to 64 years ([Halonen et al., 2009](#)). In the same study, no association was observed
5 between O₃ concentration and respiratory mortality among those ≥ 65 years old or those
6 15 to 64 years old; however, an inverse association between O₃ concentration and
7 cardiovascular mortality was present among individuals ≥ 65 years old but not among
8 individuals <65 years old. This inverse association among those ≥ 65 years old persisted
9 when examining hospital admissions for coronary heart disease. A study of CVD-related
10 hospital visits in Bangkok, Thailand reported an increase in percent change for hospital
11 visits with previous day and cumulative 2-day O₃ levels among those ≥ 65 years old,
12 whereas no association was present for individuals less than 65 years of age ([Buadong et
13 al., 2009](#)). No association was observed for current day or cumulative 3-day averages in
14 any age group. A study examining O₃ and hospital admissions for CVD-related health
15 effects reported no association for individuals aged 15 to 64 or individuals aged ≥ 65
16 years, although one lag-time did show an inverse effect for coronary heart disease among
17 elderly that was not present among 15 to 64 year-olds ([Halonen et al., 2009](#)). However, as
18 discussed in the Section on CVD hospital admissions ([6.3.2.7](#)), results were inconsistent
19 and often null so it is plausible that no association would be observed regardless of age.
20 No modification by age (40 to 64 year-olds versus >64 years old) was observed in a study
21 from Brazil examining O₃ levels and COPD ED visits ([Arbex et al., 2009](#)).

22 Biological plausibility for differences by age is provided by toxicological studies. O₃
23 exposure resulted in an increase in left ventricular chamber dimensions at end diastole
24 (LVEDD) in young and old mice, whereas decreases in left ventricular posterior wall
25 thickness at end systole (PWTES) were only observed among older mice ([Tankersley et
26 al., 2010](#)). Other toxicological studies also indicate increased risk in older animals for
27 additional endpoints, including neurological and immune. The hippocampus, one of the
28 main regions affected by age-related neurodegenerative diseases, may be more sensitive
29 to oxidative damage in aged rats. In a study of young (47 days) and aged (900 days) rats
30 exposed to 1 ppm O₃ for 4 hours, O₃-induced lipid peroxidation occurred to a greater
31 extent in the striatum of young rats, whereas it was highest in the hippocampus in aged
32 rats ([Rivas-Arancibia et al., 2000](#)). In young mice, healing of skin wounds is not
33 significantly affected by O₃ exposure ([Lim et al., 2006](#)). However, exposure to 0.5 ppm
34 O₃ for 6 h/day significantly delays wound closure in aged mice.

35 Although some outcomes reported mixed findings regarding an increase in risk for older
36 adults, recent epidemiologic studies report consistent positive associations between short-
37 term O₃ exposure and mortality in older adults. The evidence from mortality studies is
38 consistent with the results reported in the 2006 O₃ AQCD and is supported by

1 toxicological studies providing biological plausibility for increased risk of effects in older
2 adults. Also, older adults may be experiencing increased exposure compared to younger
3 adults. Overall, adequate evidence is available indicating that older adults are potentially
4 at increased risk of O₃-related health effects based on the substantial and consistent
5 evidence within epidemiologic studies on O₃ exposure and mortality and the coherence
6 with toxicological studies.

8.3.2 Sex

7 The distribution of males and females in the U.S. is similar. In 2000, 49.1% of the U.S.
8 population was male and 50.9% were female. However, this distribution does vary by age
9 with a greater prevalence of females ≥ 65 years old compared to males ([SSDAN](#)
10 [CensusScope, 2010a](#)). The 2006 O₃ AQCD did not report evidence of differences
11 between the sexes in health responses to O₃ exposure ([U.S. EPA, 2006b](#)). Recent
12 epidemiologic studies have evaluated the effects of short-term and long-term exposure to
13 O₃ on multiple health endpoints stratified by sex.

14 A study in Maine that examined short-term O₃ concentrations and asthma ED visits
15 detected greater effects among males ages 2 to 14 years and among females ages 15 to 34
16 years compared to males and females in the same age groups (no difference was detected
17 for males and females aged 35 to 64) ([Paulu and Smith, 2008](#)). A Canadian study
18 reported no associations between short-term O₃ and respiratory infection hospital
19 admissions for either boys or girls under the age of 15 ([Lin et al., 2005](#)), whereas another
20 Canadian study reported a slightly higher but non-statistically significant increase in
21 respiratory hospital admissions for males (mean ages 47.6 to 69.0 years) ([Cakmak et al.,](#)
22 [2006b](#)). A recent study from Hong Kong examining individuals of all ages reported no
23 effect measure modification by sex for overall respiratory disease hospital admissions,
24 but did detect a greater excess risk of hospital admissions for COPD among females
25 compared to males ([Wong et al., 2009](#)). Similarly a study in Brazil found higher effect
26 estimates for COPD ED visits among females compared to males ([Arbex et al., 2009](#)).
27 Higher levels of respiratory hospital admissions with greater O₃ concentrations was also
28 observed for females in a study of individuals living in Cyprus ([Middleton et al., 2008](#)).
29 A study of lung function unrelated to hospital admissions and ED visits was conducted
30 among lifeguards in Texas and reported decreased lung function with increased O₃
31 exposure among females but not males ([Thaller et al., 2008](#)). This study included
32 individuals aged 16 to 27 years, and the majority of participants were male. A New York
33 study found no evidence of effect measure modification of the association between
34 long-term O₃ exposure and asthma hospital admissions among males and females
35 between 1 and 6 years old ([Lin et al., 2008b](#)).

1 In addition to examining the potential modification of O₃ associations with respiratory
2 outcomes by sex, studies also examined cardiovascular-related outcomes specifically
3 hospital admissions and ED visits. All of these studies reported no effect modification by
4 sex with some studies reporting null associations for both males and females ([Wong et
5 al., 2009](#); [Middleton et al., 2008](#); [Villeneuve et al., 2006a](#)) and one study reporting a
6 positive associations for both sexes ([Cakmak et al., 2006a](#)). A French study examining
7 the associations between O₃ concentrations and risk of ischemic strokes (not limited to
8 ED visits or hospital admissions) reported no association for either males or females with
9 lags of 0, 2, or 3 days ([Henrotin et al., 2007](#)). A positive association was reported for
10 males with a lag of 1 day, but this association was null for females. The authors noted
11 that men in the study had much higher rates of current and former smoking than women
12 (67.4% versus 9.3%). Additionally, cardiovascular hospital admissions and ED visits
13 overall have demonstrated inconsistent and null results (Section [6.3.2.7](#)). The lack of
14 effect measure modification by sex may be indicative of the lack of association, not the
15 lack of effect of sex.

16 A biomarker study investigating the effects of O₃ concentrations on high-sensitivity
17 C-reactive protein (hs-CRP), fibrinogen, and white blood cell (WBC) count, reported
18 observations for various lag times ranging from 0 to 7 days ([Steinvil et al., 2008](#)). Most
19 of the associations were null for males and females although one association between O₃
20 and fibrinogen was positive for males and null for females (lag day 4); however, this
21 positive association was null or negative when other pollutants were included in the
22 model. One study examining correlations between O₃ levels and oxidative DNA damage
23 examined results stratified by sex. In this study [Palli et al. \(2009\)](#) reported stronger
24 correlations for males than females, both during short-term exposure (less than 30 days)
25 and long-term exposure (0-90 days). However, the authors commented that this
26 difference could have been partially explained by different distributions of exposure to
27 traffic pollution at work.

28 A few studies have examined the association between short-term O₃ concentrations and
29 mortality stratified by sex and, in contrast with studies of other endpoints, were more
30 consistent in reporting elevated risks among females. These studies, conducted in the
31 U.S. ([Medina-Ramón and Schwartz, 2008](#)), Italy ([Stafoggia et al., 2010](#)), and Asia ([Kan
32 et al., 2008](#)), reported larger effect estimates in females compared to males. In the U.S.
33 study, the elevated risk of mortality among females was greater specifically among those
34 ≥ 60 years old ([Medina-Ramón and Schwartz, 2008](#)). However, a recent study in Chile
35 reported similar associations between O₃ exposure and mortality among both men and
36 women ([Cakmak et al., 2011](#)). A long-term O₃ exposure study of respiratory mortality
37 stratified their results by sex and reported relative risks of 1.01 (95% CI: 0.99, 1.04) for
38 males and 1.04 (95% CIs 1.03, 1.07) for females ([Jerrett et al., 2009](#)).

1 Experimental research provided a further understanding of the underlying mechanisms
2 that may explain a possible differential risk in O₃-related health effects among males and
3 females. Several studies have suggested that physiological differences between sexes
4 may predispose females to greater effects from O₃. In females, lower plasma and nasal
5 lavage fluid (NLF) levels of uric acid (most prevalent antioxidant), the initial defense
6 mechanism of O₃ neutralization, may be a contributing factor ([Housley et al., 1996](#)).
7 Consequently, reduced absorption of O₃ in the upper airways of females may promote its
8 deeper penetration. Dosimetric measurements have shown that the absorption distribution
9 of O₃ is independent of sex when absorption is normalized to anatomical dead space
10 ([Bush et al., 1996](#)). Thus, a differential removal of O₃ by uric acid seems to be minimal.
11 In general, the physiologic response of young healthy females to O₃ exposure appears
12 comparable to the response of young males ([Hazucha et al., 2003](#)). A few studies have
13 examined changes in O₃ responses during various menstrual cycle phases. Lung function
14 response to O₃ was enhanced during the follicular phase of the menstrual cycle compared
15 to the luteal phase in a small study of women ([Fox et al., 1993](#)). However, [Seal et al.](#)
16 ([1996](#)) later reported no effect of menstrual cycle phase in their analysis of responses
17 from 150 women, but conceded that the methods used by [Fox et al. \(1993\)](#) more precisely
18 defined the menstrual cycle phase. Another study also reported no difference in responses
19 among females during the follicular and luteal phases of their cycle ([Weinmann et al.,](#)
20 [1995c](#)). Additionally, in this study the responses in women were comparable to those
21 reported for men in the study. In a toxicological study, small differences in effects by sex
22 were seen in adult mice with respect to pulmonary inflammation and injury after a 5-h
23 exposure to 0.8 ppm O₃, and although adult females were generally more at risk, these
24 differences were strain-dependent, with some strains exhibiting greater risk in males
25 ([Vancza et al., 2009](#)). The most obvious sex difference was apparent in lactating females,
26 which incurred the greatest lung injury or inflammation among several of the strains.

27 Overall, results have varied, with recent evidence for increased risk for O₃-related health
28 effects present for females in some studies and males in other studies. Most studies
29 examining the associations O₃ and mortality report females to be at greater risk than
30 males, but minimal evidence is available regarding a difference between the sexes for
31 other outcomes. Inconsistent findings were reported on whether effect measure
32 modification exists by sex for respiratory and cardiovascular hospital admissions and ED
33 visits, although there is some indication that females are at increased risk of O₃-related
34 respiratory hospital admissions and ED visits. While O₃-related effects may occur in both
35 men and women, there is suggestive evidence exists indicating that females are at
36 potentially increased risk of O₃-related health effects as there are consistent findings
37 among epidemiologic studies of mortality.

8.3.3 Socioeconomic Status

1 SES is often represented by personal or neighborhood SES, which is comprised of a
2 variety of components such as educational attainment, household income, health
3 insurance status, and other such factors. SES is often indicative of such things as access
4 to healthcare, quality of housing, and pollution gradient to which people are exposed.
5 One or a combination of these components could modify the risk of O₃-related health
6 effects. Based on the 2000 Census data, 12.4% of Americans live in poverty (poverty
7 threshold for family of four was \$17,463) ([SSDAN CensusScope, 2010c](#)). Although
8 included below, studies stratifying by SES that are conducted outside the U.S. may not be
9 comparable to those studies from within the U.S. Having low SES in another country
10 may be different than having low SES in the U.S. based on SES definitions, population
11 composition, and/or conditions in that country.

12 Multiple epidemiologic studies have reported individuals of low SES to have increased
13 risk for the effects of short-term O₃ exposure on respiratory hospital admissions and ED
14 visits. In New York State, larger associations between long-term O₃ exposure and asthma
15 hospital admissions were observed among children of mothers who did not graduate from
16 high school, whose births were covered by Medicaid/self-paid, or who were living in
17 poor neighborhoods compared to children whose mothers graduated from high school,
18 whose births were covered by other insurance, or who were not living in poor
19 neighborhoods, respectively ([Lin et al., 2008b](#)). In addition, a study conducted across 10
20 cities in Canada found the largest association between O₃ exposure and respiratory
21 hospital admissions was among those with an educational level less than grade 9, but no
22 consistent trend in the effect was seen across quartiles of income ([Cakmak et al., 2006b](#)).
23 A Canadian study reported inverse effects of O₃ on respiratory hospital admissions and
24 ED visits for all levels of SES, measured by average census tract household income
25 ([Burra et al., 2009](#)). A study performed in Korea examined the association between O₃
26 concentrations and asthma hospital admissions and reported larger effect estimates in
27 areas of moderate and low SES compared with areas of high SES (SES was based on
28 average regional insurance rates) ([Lee et al., 2006](#)).

29 The examination of the potential effects of SES on O₃-related cardiovascular health
30 effects is relatively limited. A study conducted in Canada reported the association
31 between short-term O₃ and ED visits for cardiac disease by quartiles of
32 neighborhood-level education and income. No effect measure modification was apparent
33 for either measure of SES ([Cakmak et al., 2006a](#)). However, this may be due to the lack
34 of association present between O₃ and ED visits for cardiac disease regardless of SES.

35 Several studies were conducted that examined the modification of the relationship
36 between short-term O₃ concentrations and mortality by SES. A U.S. multicity study

1 reported that communities with a higher proportion of the population unemployed had
2 higher O₃-related mortality effect estimates ([Bell and Dominici, 2008](#)). A study in seven
3 urban centers in Chile reported on modification of the association between O₃ exposure
4 and mortality using multiple SES markers ([Cakmak et al., 2011](#)). Increased risk was
5 observed among the categories of low SES for all measures (personal educational
6 attainment, personal occupation, community income level). Additionally, the APHENA
7 study, which examined the association between O₃ and mortality by percentage
8 unemployed, reported a higher percent change in mortality with increased percent
9 unemployed but this varied across the regions included in the study (U.S., Canada,
10 Europe) ([Katsouyanni et al., 2009](#)). A Chinese study reported that the greatest effects
11 between O₃ concentrations and mortality at lag day 0 were among individuals living in
12 areas of high social deprivation (i.e., low SES), but this association was not consistent
13 across lag days (at other lag times, the middle social deprivation index category had the
14 greatest association) ([Wong et al., 2008](#)). However, another study in Asia comparing low
15 to high educational attainment populations reported no evidence of greater mortality
16 effects (total, CVD, or respiratory) ([Kan et al., 2008](#)). Additionally, a study in Italy
17 reported no difference in risk of mortality among census-block level derived income
18 levels ([Stafoggia et al., 2010](#)). A study of infant mortality in Mexico reported no
19 association between O₃ concentrations and infant mortality among any of the three levels
20 of SES determined using a socioeconomic index based on residential areas ([Romieu et
21 al., 2004a](#)). Another study in Mexico reported a positive association between O₃ levels at
22 lag 0 and respiratory-related infant mortality in only the low SES group (determined
23 based on education, income, and household conditions across residential areas), but no
24 association was observed in any of the SES groups with other lags ([Carbajal-Arroyo et
25 al., 2011](#)).

26 Studies of O₃ concentrations and reproductive outcomes have also examined associations
27 by SES levels. A study in California reported greater decreases in birth weight associated
28 with full pregnancy O₃ concentration for those with neighborhood poverty levels of at
29 least 7% compared with those in neighborhoods with less than 7% poverty (the authors
30 do not provide information on how categories of the SES variable were determined)
31 ([Morello-Frosch et al., 2010](#)). No dose response was apparent and those with
32 neighborhood poverty levels of 7-21% had greater decreases observed for the association
33 than those living in areas with poverty rates of at least 22%. An Australian study reported
34 an inverse association between O₃ exposure during days 31-60 of gestation and
35 abdominal circumference during gestation ([Hansen et al., 2008](#)). The interaction with
36 SES (area-level measured socioeconomic disadvantage) was examined and although the
37 inverse association remained statistically significant in only the highest SES quartile,
38 there were large confidence interval overlaps among estimates for each quartile so no
39 difference in the association for the quartiles was apparent.

1 Evidence from a controlled human exposure study that examined O₃ effects on lung
2 function does not provide support for greater O₃-related health effects in individuals of
3 lower SES. In a follow-up study ([Seal et al., 1993](#)) on modification by race, [Seal et al.](#)
4 ([1996](#)) reported that, of three SES categories, individuals in the middle SES category
5 showed greater concentration-dependent decline in percent-predicted FEV₁ (4-5% at
6 400 ppb O₃) than in low and high SES groups. The authors did not have an “immediately
7 clear” explanation for this finding and controlled human exposure studies are typically
8 not designed to answer questions about SES.

9 Overall, most studies of individuals have reported that individuals with low SES and
10 those living in neighborhoods with low SES are more at risk for O₃-related health effects,
11 resulting in increased risk of respiratory hospital admissions and ED visits. Inconsistent
12 results have been observed in the few studies examining effect modification of
13 associations between O₃ exposure and mortality and reproductive outcomes. Also, a
14 controlled human exposure study does not support evidence of increased risk of
15 respiratory morbidity among individuals with lower SES. Overall, evidence is suggestive
16 of SES as a factor affecting risk of O₃-related health outcomes based on collective
17 evidence from epidemiologic studies of respiratory hospital admissions but inconsistency
18 among epidemiologic studies of mortality and reproductive outcomes. Further studies are
19 needed to confirm this relationship, especially in populations within the U.S.

8.3.4 Race/Ethnicity

20 Based on the 2000 Census, 69.1% of the U.S. population identified as non-Hispanic
21 whites. Approximately 12.1% of people reported their race/ethnicity as non-Hispanic
22 black and 12.6% reported being Hispanic ([SSDAN CensusScope, 2010b](#)).

23 Only a few studies examined the associations between short-term O₃ concentrations and
24 mortality and reported higher effect estimates among blacks ([Medina-Ramón and](#)
25 [Schwartz, 2008](#)) and among communities with larger proportions of blacks ([Bell and](#)
26 [Dominici, 2008](#)). Another study examined long-term exposure to O₃ concentrations and
27 asthma hospital admissions among children in New York State. These authors reported
28 no statistically significant difference in the odds of asthma hospital admissions for blacks
29 compared to other races but did detect higher odds for Hispanics compared to
30 non-Hispanics ([Lin et al., 2008b](#)).

31 Additionally, recent epidemiologic studies have stratified by race when examining the
32 association between O₃ concentration and birth outcomes. A study conducted in Atlanta,
33 GA reported decreases in birth weight with increased third trimester O₃ concentrations
34 among Hispanics but not among non-Hispanic whites ([Darrow et al., 2011b](#)). An inverse

1 association was also present for non-Hispanic blacks but was not statistically significant.
2 A California study reported that the greatest decrease in birth weight associated with full
3 pregnancy O₃ concentration was among non-Hispanic whites ([Morello-Frosch et al.,
4 2010](#)). This inverse association was also apparent, although not as strong, for Hispanics
5 and non-Hispanic blacks. Increased birth weight was associated with higher O₃ exposure
6 among non-Hispanic Asians and Pacific Islanders but these results were not statistically
7 significant.

8 Similar to the epidemiologic studies, a controlled human exposure study suggested
9 differences in lung function responses by race ([Seal et al., 1993](#)). The independent effects
10 of sex-race group and O₃ concentration on lung function were positive, but the interaction
11 between sex-race group and O₃ concentration was not statistically significant. The
12 findings indicated some overall difference between the sex-race groups that was
13 independent of O₃ concentration (the concentration-response curves for the four sex-race
14 groups are parallel). In a multiple comparison procedure on data collapsed across all O₃
15 concentrations for each sex-race group, both black men and black women had larger
16 decrements in FEV₁ than did white men. The authors noted that the O₃ dose per unit of
17 lung tissue would be greater in blacks and females than whites and males, respectively.
18 That this difference in tissue dose might have affected responses to O₃ cannot be ruled
19 out. The college students recruited for the [Seal et al. \(1993\)](#) study were probably from
20 better educated and more SES advantaged families, thus reducing potential for these
21 variables to be confounding factors. [Que et al. \(2011\)](#) also examined pulmonary
22 responses to O₃ exposure in blacks of African American ancestry and in whites. On
23 average, the black males experienced the greatest decrements in FEV₁ following O₃
24 exposure. This decrease was larger than the decrement observed among black females,
25 white males, and white females.

26 Overall, the results of recent studies indicate that there may be race-related increase in
27 risk of O₃-related health effects for some outcomes, although the overall understanding of
28 potential effect measure modification by race is limited by the small number of studies.
29 Additionally, these results may be confounded by other factors, such as SES. Overall,
30 evidence is inadequate to determine if O₃-related health effects vary by race because of
31 the insufficient quantity of studies and lack of consistency within disciplines.

8.4 Behavioral and Other Factors

8.4.1 Diet

1 Diet was not examined as a factor potentially affecting risk in previous O₃ AQCDs, but
2 recent studies have examined modification of the association between O₃ and health
3 effects by dietary factors. Because O₃ mediates some of its toxic effects through oxidative
4 stress, the antioxidant status of an individual is an important factor that may contribute to
5 increased risk of O₃-related health effects. Supplementation with Vitamins C and E has
6 been investigated in a number of studies as a means of inhibiting O₃-mediated damage.

7 Epidemiologic studies have examined effect measure modification by diet and found
8 evidence that certain dietary components are related to the effect O₃ has on respiratory
9 outcomes. In a recent study the effects of fruit/vegetable intake and Mediterranean diet
10 was examined ([Romieu et al., 2009](#)). Increases in these food patterns, which have been
11 noted for their high Vitamins C and E and omega-3 fatty acid content, protected against
12 O₃-related decreases in lung function among children living in Mexico City. Another
13 study examined supplementation of the diets of asthmatic children in Mexico with
14 Vitamins C and E ([Sienra-Monge et al., 2004](#)). Associations were detected between
15 short-term O₃ exposure and nasal airway inflammation among children in the placebo
16 group but not in those receiving the supplementation. The authors concluded that
17 “Vitamin C and E supplementation above the minimum dietary requirement in asthmatic
18 children with a low intake of Vitamin E might provide some protection against the nasal
19 acute inflammatory response to ozone.”

20 The epidemiologic evidence is supported by controlled human exposure studies, which
21 have shown that the first line of defense against oxidative stress is antioxidants-rich
22 extracellular lining fluid (ELF) which scavenge free radicals and limit lipid peroxidation.
23 Exposure to O₃ depletes the antioxidant level in nasal ELF probably due to scrubbing of
24 O₃ ([Mudway et al., 1999a](#)); however, the concentration and the activity of antioxidant
25 enzymes either in ELF or plasma do not appear to be related to O₃ responsiveness
26 (e.g., pulmonary function and inflammation) ([Samet et al., 2001](#); [Avissar et al., 2000](#);
27 [Blomberg et al., 1999](#)). Carefully controlled studies of dietary antioxidant
28 supplementation have demonstrated some protective effects of α -tocopherol (a form of
29 Vitamin E) and ascorbate (Vitamin C) on spirometric measures of lung function after O₃
30 exposure but not on the intensity of subjective symptoms and inflammatory response
31 including cell recruitment, activation and a release of mediators ([Samet et al., 2001](#);
32 [Trenga et al., 2001](#)). Dietary antioxidants have also afforded partial protection to

1 asthmatics by attenuating postexposure bronchial hyperresponsiveness ([Trenga et al.,](#)
2 [2001](#)).

3 Toxicological studies provide evidence of biological plausibility to the epidemiologic and
4 controlled human exposure studies. [Wagner et al. \(2009\)](#); ([2007](#)) found reductions in
5 O₃-exacerbated nasal allergy responses in rats with γ -tocopherol treatment (a form of
6 Vitamin E). O₃-induced inflammation and mucus production were also inhibited by
7 γ -tocopherol. Supplementation with Vitamins C and E partially ameliorated
8 inflammation, oxidative stress, and airway hyperresponsiveness in guinea pigs exposed
9 subchronically to 0.12 ppm O₃ ppm ([Chhabra et al., 2010](#)). Inconsistent results were
10 observed in other toxicological studies of Vitamin C deficiency and O₃-induced
11 responses. Guinea pigs deficient in Vitamin C displayed only minimal injury and
12 inflammation after exposure to O₃ ([Kodavanti et al., 1995](#)). A recent study in mice
13 demonstrated a protective effect of β -carotene in the skin, where it limited the production
14 of proinflammatory markers and indicators of oxidative stress induced by O₃ exposure
15 ([Valacchi et al., 2009](#)). Deficiency of Vitamin A, which has a role in regulating the
16 maintenance and repair of the epithelial layer, particularly in the lung, appears to enhance
17 the risk of O₃-induced lung injury ([Paquette et al., 1996](#)). Differentially susceptible
18 mouse strains that were fed a Vitamin A sufficient diet were observed to have different
19 tissue concentrations of the vitamin, potentially contributing to their respective
20 differences in O₃-related outcomes. In addition to the studies of antioxidants, one
21 toxicological study examined protein deficiency. Protein deficiency alters the levels of
22 enzymes and chemicals in the brain of rats involved with redox status; exposure to
23 0.75 ppm O₃ has been shown to differentially affect Na⁺/K⁺ ATPase, glutathione, and
24 lipid peroxidation, depending on the nutritional status of the animal, but the significance
25 of these changes is unclear ([Calderón Guzmán et al., 2006](#)). There may be a protective
26 effect of overall dietary restriction with respect to lung injury, possibly related to
27 increased Vitamin C in the lung surface fluid ([Kari et al., 1997](#)).

28 There is adequate evidence that individuals with reduced intake of Vitamins E and C are
29 potentially at risk for O₃-related health effects based on substantial, consistent evidence
30 both within and among disciplines. The evidence from epidemiologic studies is supported
31 by controlled human exposure and toxicological studies.

8.4.2 Obesity

32 Obesity, defined as a BMI of 30 kg/m² or greater, is an issue of increasing importance in
33 the U.S., with self-reported rates of obesity of 26.7% in 2009, up from 19.8% in 2000

1 [\(Sherry et al., 2010\)](#). BMI may affect O₃-related health effects through multiple avenues,
2 such as, inflammation in the body, increased preexisting disease, and poor diet.

3 A few studies have been performed examining the association between BMI and
4 O₃-related changes in lung function. An epidemiologic study reported decreased lung
5 function with increased short-term O₃ exposure for both obese and non-obese subjects;
6 however, the magnitude of the reduction in lung function was greater for those subjects
7 who were obese ([Alexeeff et al., 2007](#)). Further decrements in lung function were noted
8 for obese individuals with AHR. Controlled human exposure studies have also detected
9 differential effects of O₃ exposure on lung function for individuals with varying BMIs. In
10 a retrospective analysis of data from 541 healthy, nonsmoking, white males between the
11 ages of 18-35 years from 15 studies conducted at the U.S. EPA Human Studies Facility in
12 Chapel Hill, North Carolina, [McDonnell et al. \(2010\)](#) found that increased body mass
13 index (BMI) was found to be associated with enhanced FEV₁ responses. The BMI effect
14 was of the same order of magnitude but in the opposite direction of the age effect
15 whereby FEV₁ responses diminish with increasing age. In a similar analysis, [Bennett et
16 al. \(2007\)](#) found enhanced FEV₁ decrements following O₃ exposure with increasing BMI
17 in a group of healthy, nonsmoking, women (BMI range 15.7 to 33.4), but not among
18 healthy, nonsmoking men (BMI range 19.1 to 32.9). In the women, greater O₃-induced
19 FEV₁ decrements were seen in individuals that were overweight/obese (BMI >25)
20 compared to normal weight (BMI from 18.5 to 25), and in normal weight compared to
21 underweight (BMI <18.5). Even disregarding the five underweight women, a greater O₃
22 response in the overweight/obese category (BMI >25) was observed compared with the
23 normal weight group (BMI from 18.5 to 24.9).

24 Studies in genetically and dietarily obese mice have shown enhanced pulmonary
25 inflammation and injury with acute O₃ exposure, but responses to longer exposures at a
26 lower concentration appear to differ. A recent study found that obese mice are actually
27 resistant to O₃-induced pulmonary injury and inflammation and reduced lung compliance
28 following exposure to 0.3 ppm O₃ for 72 hours, regardless of whether obesity was
29 genetic- or diet-induced ([Shore et al., 2009](#)).

30 Multiple epidemiologic, human clinical, and toxicological studies have reported
31 suggestive evidence for increased O₃-related respiratory health effects among obese
32 individuals. Future research of the effect modification of the relationship between O₃ and
33 other health-related outcomes besides respiratory health effects by BMI and studies
34 examining the role of physical conditioning will advance understanding of obesity as a
35 factor potentially increasing an individual's risk.

8.4.3 Smoking

1 Previous O₃ AQCDs have concluded that smoking does not increase the risk of O₃-related
2 health effects; in fact, in controlled human exposure studies, smokers have been found to
3 be less responsive to O₃ than non-smokers. Data from recent interviews conducted as part
4 of the 2008 National Health Interview Survey (NHIS) ([Pleis et al., 2009](#)) have shown the
5 rate of smoking among adults ≥ 18 years old to be approximately 20% in the U.S.
6 Approximately 21% of individuals surveyed were identified as former smokers.

7 [Baccarelli et al. \(2007\)](#) performed a study of O₃ concentrations and plasma homocysteine
8 levels (a risk factor for vascular disease). They found no interaction of smoking (smokers
9 versus non-smokers) for the associations between O₃ concentrations and plasma
10 homocysteine levels. Another study examined the association between O₃ and resting
11 heart rate and also reported no interaction with smoking status (current smokers versus
12 current non-smokers) ([Ruidavets et al., 2005a](#)).

13 A study examining correlations between O₃ levels and oxidative DNA damage examined
14 results stratified by current versus never and former smokers ([Palli et al., 2009](#)). Ozone
15 was positively associated with DNA damage for short-term and long-term exposures
16 among never/former smokers. For current smokers, short-term O₃ concentrations were
17 inversely associated with DNA damage; however, the number of current smokers in the
18 study was small (n = 12).

19 The findings of [Palli et al. \(2009\)](#) were consistent with those from controlled human
20 exposure studies that have confirmed that smokers are less responsive to O₃ exposure
21 than non-smokers. Spirometric and plethysmographic pulmonary function decline,
22 nonspecific AHR, and inflammatory responses of smokers to O₃ exposure were all
23 weaker than those reported for non-smokers. Similarly, the time course of development
24 and recovery from these effects, as well as their reproducibility, was not different from
25 non-smokers. Chronic airway inflammation with desensitization of bronchial nerve
26 endings and an increased production of mucus may plausibly explain the
27 pseudo-protective effect of smoking ([Frampton et al., 1997a](#); [Torres et al., 1997](#)).

28 These findings for smoking are consistent with the conclusions from previous AQCDs.
29 An epidemiologic study of O₃-associated DNA damage reported smokers to be less at
30 risk for O₃-related health effects. In addition, both epidemiologic studies of short-term
31 exposure and CVD outcomes found no evidence of effect measure modification by
32 smoking. No toxicological studies provide biological support for O₃-related effects.
33 Overall, evidence of potential differences in O₃-related health effects by smoking status is
34 inadequate due to insufficient coherence and a limited number of studies.

8.4.4 Outdoor Workers

1 Studies included in the 2006 O₃ AQCD reported that individuals who participate in
2 outdoor activities or work outside to be a population at increased risk based on
3 consistently reported associations between O₃ exposure and respiratory health outcomes
4 in these groups ([U.S. EPA, 2006b](#)). Outdoor workers are exposed to ambient O₃
5 concentrations for a greater period of time than individuals who spend their days indoors.
6 As discussed in Section [4.3.3](#) of this ISA, outdoor workers sampled during the work shift
7 had a higher ratio of personal exposure to fixed-site monitor concentrations than health
8 clinic workers who spent most of their time indoors. Additionally, an increase in dose to
9 the lower airways is possible during outdoor exercise due to both increases in the amount
10 of air breathed (i.e., minute ventilation) and a shift from nasal to oronasal breathing
11 ([Sawyer et al., 2007](#); [Nodelman and Ultman, 1999](#); [Hu et al., 1994](#)). For further
12 discussion of the association between FEV₁ responses to O₃ exposure and minute
13 ventilation, refer to Section [6.2.3.1](#) of the 2006 O₃ AQCD. A recent study has explored
14 the potential effect measure modification of O₃ exposure and DNA damage by
15 indoor/outdoor workplace ([Tovalin et al., 2006](#)). In a study of indoor and outdoor
16 workers in Mexico, individuals who worked outdoors in Mexico City had a slight
17 association between O₃ exposure and DNA damage (measured by comet tail length
18 assay), whereas no association was observed for indoor workers. However, workers in
19 another Mexican city, Puebla, demonstrated no association between O₃ levels and DNA
20 damage, regardless of whether they worked indoors or outdoors.

21 Previous studies have shown that increased exposure to O₃ due to outdoor work leads to
22 increased risk of O₃-related health effects, specifically decrements in lung function ([U.S.](#)
23 [EPA, 2006b](#)). Recent evidence from a stratified analysis does not indicate that increased
24 O₃ exposure due to outdoor work leads to DNA damage. However, the strong evidence
25 from the 2006 O₃ AQCD which demonstrated increased exposure, dose, and ultimately
26 risk of O₃-related health effects in this population supports that there is adequate evidence
27 available to indicate that increased exposure to O₃ through outdoor work potentially
28 increases the risk of O₃-related health effects.

8.4.5 Air Conditioning Use

29 Air conditioning use is an important component of O₃ exposure, as use of central air
30 conditioning will limit exposure to O₃ by blocking the penetration of O₃ into the indoor
31 environment (see Section [4.3.2](#)). Air conditioning use is a difficult effect measure
32 modifier to examine in epidemiologic studies because it is often estimated using regional
33 prevalence data and may not reflect individual-level use. More generally, air conditioning

1 prevalence is associated with temperature of a region; those areas with higher
2 temperatures have a greater prevalence of households with air conditioning. Despite these
3 limitations, a few studies have examined effect measure modification by prevalence of air
4 conditioning use in an area. Studies examining multiple cities across the U.S. have
5 assessed whether associations between O₃ concentrations and hospital admissions and
6 mortality varied among areas with high and low prevalence of air conditioning. [Medina-
7 Ramon et al. \(2006\)](#) conducted a study during the warm season and observed a greater
8 association between O₃ levels and pneumonia-hospital admissions among areas with a
9 lower proportion of households having central air conditioning compared to areas with a
10 larger proportion of households with air conditioning. However, a similar observation
11 was not observed when examining COPD hospital admissions complicating the
12 interpretation of the results from this study. [Bell and Dominici \(2008\)](#) found evidence of
13 increased risk of O₃-related mortality in areas with a lower prevalence of central air
14 conditioning in a study of 98 U.S. communities. Conversely, [Medina-Ramón and
15 Schwartz \(2008\)](#) found that among individuals with atrial fibrillation, a lower risk of
16 mortality was observed for areas with a lower prevalence of central air conditioning.

17 The limited number of studies that examined whether air conditioning use modifies the
18 association between O₃ exposure and health has not provided consistent evidence across
19 health endpoints. Therefore, the limited and inconsistent results across epidemiologic
20 studies has provided inadequate evidence to determine whether a lower prevalence of air
21 conditioning use leads to a potential increased risk of O₃-related health effects.

8.5 Summary

22 In this section, epidemiologic, controlled human exposure, and toxicological studies have
23 been evaluated and indicate that various factors may lead to increased risk of O₃-related
24 health effects ([Table 8-5](#)).

25 The populations and lifestages identified in this section that have “adequate” evidence for
26 potentially increased O₃-related health effects are individuals with asthma, younger and
27 older age groups, individuals with reduced intake of certain nutrients, and outdoor
28 workers, based on consistency in findings across studies and evidence of coherence in
29 results from different scientific disciplines. Asthma as a factor potentially affecting risk
30 was supported by controlled human exposure and toxicological studies, as well as some
31 evidence from epidemiologic studies. Generally, studies of age groups reported positive
32 associations for respiratory hospital admissions and ED visits among children. Biological
33 plausibility for this increased risk is supported by toxicological and clinical research.
34 Also, children have higher exposure and dose due to increased time spent outdoors and

1 ventilation rate. Most studies comparing age groups reported greater effects of short-term
 2 O₃ exposure on mortality among older adults, although studies of other health outcomes
 3 had inconsistent findings regarding whether older adults were at increased risk. Older
 4 adults may also withstand greater O₃ exposure and not seek relief as quickly as younger
 5 adults. Multiple epidemiologic, controlled human exposure, and toxicological studies
 6 reported that reduced Vitamins E and C intake are associated with risk of O₃-related
 7 health effects. Previous studies have shown that increased exposure to O₃ due to outdoor
 8 work leads to a potentially increased risk of O₃-related health effects and it is clear that
 9 outdoor workers have higher exposures, and possibly greater internal doses, of O₃, which
 10 may lead to increased risk of O₃-related health effects.

Table 8-5 Summary of evidence for potential increased risk of ozone-related health effects.

| Evidence Classification | Potential At Risk Factor |
|-------------------------|--|
| Adequate evidence | Asthma (Section 8.2.2) Children (Section 8.3.1.1) Older adults (Section 8.3.1.2) Diet (Section 8.4.1) Outdoor workers (Section 8.4.4) |
| Suggestive evidence | Genetic factors (Section 8.1) Sex (Section 8.3.2) SES (Section 8.3.3) Obesity (Section 8.4.2) |
| Inadequate evidence | Influenza/Infection (Section 8.2.1) COPD (Section 8.2.3) CVD (Section 8.2.4) Diabetes (Section 8.2.5) Hyperthyroidism (Section 8.2.6) Race/ethnicity (Section 8.3.4) Smoking (Section 8.4.3) Air conditioning use (Section 8.4.5) |
| Evidence of no effect | -- |

11 In some cases, it is difficult to determine a factor that results in potentially increased risk
 12 of effects. For example, previous assessments have included controlled human exposure
 13 studies in which some healthy individuals demonstrate greater O₃-related health effects
 14 compared to other healthy individuals. Intersubject variability has been observed for lung
 15 function decrements, symptomatic responses, pulmonary inflammation, AHR, and altered
 16 epithelial permeability in healthy adults exposed to O₃ ([Que et al., 2011](#); [Holz et al., 2005](#);
 17 [McDonnell, 1996](#)). These responses to O₃ exposure in healthy individuals tend to
 18 be reproducible within a given individual over a period of several months indicating
 19 differences in the intrinsic responsiveness ([Holz et al., 2005](#); [Hazucha et al., 2003](#); [Holz](#)
 20 [et al., 1999](#); [McDonnell et al., 1985b](#)).

1 Limitations include the challenge of evaluating effect measure modification in
2 epidemiologic studies with widespread populations with variation in numerous factors.
3 For a number of the factors described below, there are few available studies. Many
4 toxicological and controlled human exposure studies are the only ones that have
5 examined certain factors and therefore have not been replicated. In considering
6 epidemiologic studies conducted in other countries, it is possible that those populations
7 may differ in SES or other demographic indicators, thus limiting generalizability to a
8 U.S. population. Additionally, many epidemiologic studies that stratify by factors of
9 interest have small sample sizes, which can decrease precision of effect estimates.

10 These challenges and limitations in evaluating the factors that can increase risk for
11 experiencing O₃-related health effects may contribute to conclusions that evidence for
12 some factors, such as genetic factors, sex, SES, and obesity provided “suggestive”
13 evidence of potentially increased risk. In addition, for a number of factors listed in
14 [Table 8-5](#) the evidence was inadequate to draw conclusions about potential increase in
15 risk of effects. Overall, the factors most strongly supported as contributing to potentially
16 increased risk of O₃-related effects among various populations and lifestages were related
17 to asthma, age group (children and older adults), dietary factors, and working outdoors.

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9 ENVIRONMENTAL EFFECTS: OZONE EFFECTS ON VEGETATION AND ECOSYSTEMS

9.1 Introduction

1 This chapter synthesizes and evaluates the relevant science to help form the scientific
2 foundation for the review of a vegetation- and ecologically-based secondary NAAQS for
3 O₃. The secondary NAAQS are based on welfare effects. The Clean Air Act (CAA)
4 definition of welfare effects includes, but is not limited to, effects on soils, water,
5 wildlife, vegetation, visibility, weather, and climate, as well as effects on materials,
6 economic values, and personal comfort and well-being. The effects of O₃ as a greenhouse
7 gas and its direct effects on climate are discussed in Chapter [10](#) of this document.

8 The intent of the ISA, according to the CAA, is to “accurately reflect the latest scientific
9 knowledge expected from the presence of [a] pollutant in ambient air” (42 U.S.C.7408
10 and 42 U.S.C.7409. This chapter of the ISA includes scientific research from
11 biogeochemistry, soil science, plant physiology, and ecology conducted at multiple levels
12 of biological organization (e.g., organ, organism, population, community, ecosystem).
13 Key information and judgments formerly found in the AQCDs regarding O₃ effects on
14 vegetation and ecosystems are found in this chapter. This chapter of the O₃ ISA serves to
15 update and revise Chapter 9 and AX9 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)).

16 Numerous studies of the effects of O₃ on vegetation and ecosystems were reviewed in the
17 2006 O₃ AQCD. That document concluded that the effects of ambient O₃ on vegetation
18 and ecosystems appear to be widespread across the U.S., and experimental studies
19 demonstrated plausible mechanisms for these effects. Ozone effect studies published
20 from 2005 to July 2011 are reviewed in this document in the context of the previous O₃
21 AQCDs. From 2005 to 2011, some areas have had very little new research published and
22 the reader is referred back to sections of the 2006 O₃ AQCD for a more comprehensive
23 discussion of those subjects. This chapter is focused on studies of vegetation and
24 ecosystems that occur in the U.S. and that provide information on endpoints or processes
25 most relevant to the review of the secondary standard. Many studies have been published
26 about vegetation and ecosystems outside of the U.S. and North America, largely in
27 Europe and Asia. This document includes discussion of studies of vegetation and
28 ecosystems outside of North America only if those studies contribute to the general
29 understanding of O₃ effects across species and ecosystems. For example, studies outside
30 North America are discussed that consider physiological and biochemical processes that
31 contribute to the understanding of effects of O₃ across species. Also, ecosystem studies

1 outside of North America that contribute to the understanding of O₃ effects on general
2 ecosystem processes are discussed in the chapter.

3 Sections of this chapter first discuss exposure methods, followed by effects on vegetation
4 and ecosystems at various levels of biological organization and ends with policy-relevant
5 discussions of exposure indices and exposure-response. [Figure 9-1](#) is a simplified
6 illustrative diagram of the major pathway through which O₃ enters plants and the major
7 endpoints O₃ may affect. First, Section [9.2](#) presents a brief overview of various
8 methodologies that have been, and continue to be, central to quantifying O₃ effects on
9 vegetation (see AX9.1 of the 2006 O₃ AQCD for more detailed discussion) ([U.S. EPA,](#)
10 [2006b](#)). Section [9.3](#) through Section [9.4](#) begin with a discussion of effects at the cellular
11 and subcellular level followed by consideration of the O₃ effects on plant and ecosystem
12 processes ([Figure 9-1](#)). In Section [9.3](#), research is reviewed from the molecular to the
13 biochemical and physiological levels in impacted plants, offering insight into the mode of
14 action of O₃. Section [9.4](#) provides a review of the effects of O₃ exposure on major
15 endpoints at the whole plant scale including growth, reproduction, visible foliar injury
16 and leaf gas exchange in woody and herbaceous plants in the U.S., as well as a brief
17 discussion of O₃ effects on agricultural crop yield and quality. Section [9.4](#) also integrates
18 the effects of O₃ on individual plants in a discussion of available research for assessing
19 the effect of O₃ on ecosystems, along with available studies that could inform
20 assessments of various ecosystem services (See Section [9.4.1.2](#)). The development of
21 indices of O₃ exposure and dose modeling is discussed in Section [9.5](#). Finally, exposure-
22 response relationships for a number of tree species, native vegetation, and crop species
23 and cultivars are reviewed, tabulated, and compared in Section [9.6](#) to form the basis for
24 an assessment of the potential risk to vegetation from current ambient levels of O₃.

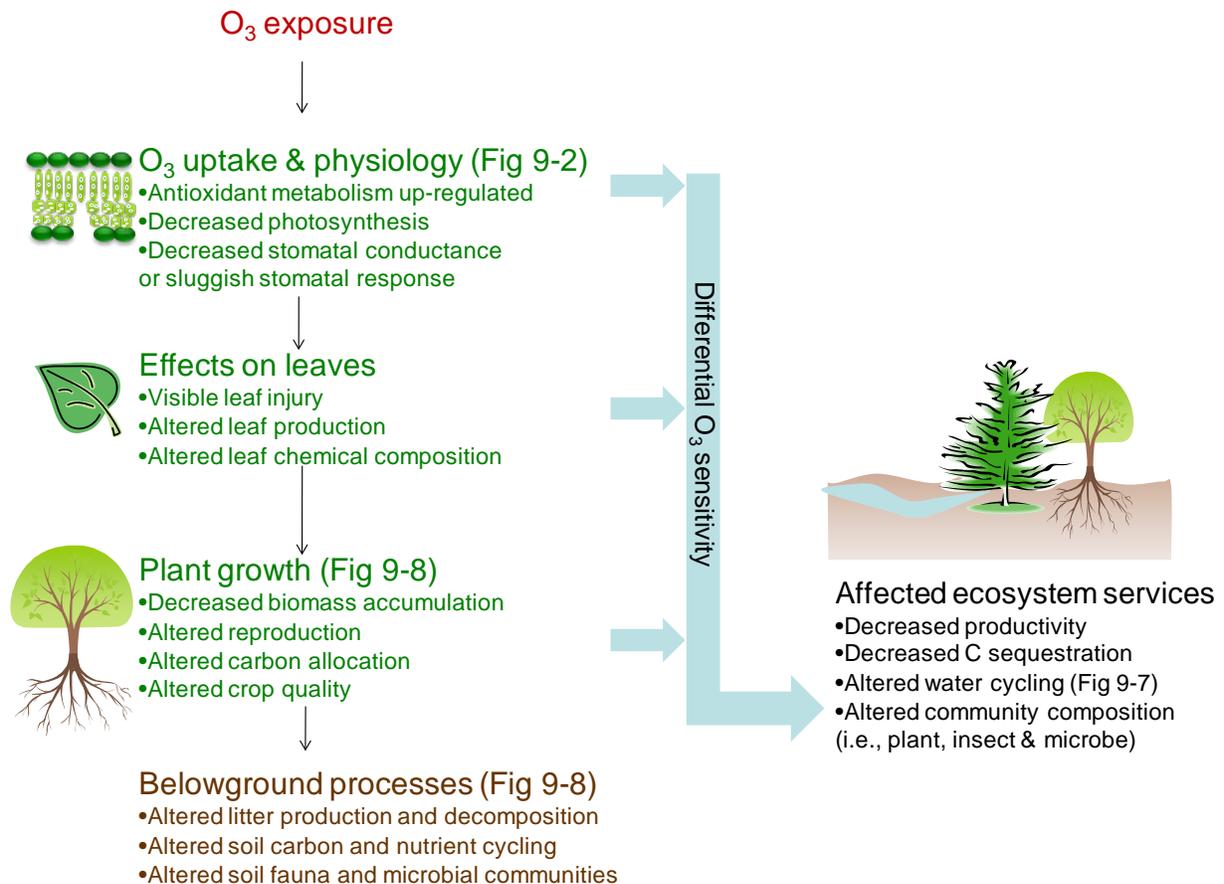


Figure 9-1 An illustrative diagram of the major pathway through which ozone enters plants and the major endpoints that ozone may affect in plants and ecosystems.

9.2 Experimental Exposure Methodologies

9.2.1 Introduction

1 A variety of methods for studying plant response to O₃ exposures have been developed
 2 over the last several decades. The majority of methodologies currently used have been
 3 discussed in detail in the 1996 O₃ AQCD and 2006 O₃ AQCD. This section will serve as
 4 a short overview of the methodologies and the reader is referred to the previous O₃
 5 AQCDs for more in-depth discussion.

9.2.2 “Indoor,” Controlled Environment, and Greenhouse Chambers

1 The earliest experimental investigations of the effects of O₃ on plants utilized simple
2 glass or plastic-covered chambers, often located within greenhouses, into which a flow of
3 O₃-enriched air or oxygen could be passed to provide the exposure. The types, shapes,
4 styles, materials of construction, and locations of these chambers have been numerous.
5 [Hogsett et al. \(1987a\)](#) have summarized the construction and performance of more
6 elaborate and better instrumented chambers since the 1960s, including those installed in
7 greenhouses (with or without some control of temperature and light intensity).

8 One greenhouse chamber approach that continues to yield useful information on the
9 relationships of O₃ uptake to both physiological and growth effects employs continuous
10 stirred tank reactors (CSTRs) first described by [Heck et al. \(1978\)](#). Although originally
11 developed to permit mass-balance studies of O₃ flux to plants, their use has more recently
12 widened to include short-term physiological and growth studies of O₃ × CO₂ interactions
13 ([Loats and Rebbeck, 1999](#); [Reinert et al., 1997](#); [Rao et al., 1995](#); [Reinert and Ho, 1995](#);
14 [Heagle et al., 1994a](#)), and validation of visible foliar injury on a variety of plant species
15 ([Kline et al., 2009](#); [Orendovici et al., 2003](#)). In many cases, supplementary lighting and
16 temperature control of the surrounding structure have been used to control or modify the
17 environmental conditions ([Heagle et al., 1994a](#)).

18 Many investigations have utilized commercially available controlled environment
19 chambers and walk-in rooms adapted to permit the introduction of a flow of O₃ into the
20 controlled air-volume. Such chambers continue to find use in genetic screening and in
21 physiological and biochemical studies aimed primarily at improving the understanding of
22 modes of action. For example, some of the studies of the O₃ responses of common
23 plantain (*Plantago major*) populations have been conducted in controlled environment
24 chambers ([Whitfield et al., 1996](#); [Reiling and Davison, 1994](#)).

25 More recently, some researchers have been interested in attempting to investigate direct
26 O₃ effects on reproductive processes, separate from the effects on vegetative processes
27 ([Black et al., 2010](#)). For this purpose, controlled exposure systems have been employed
28 to expose the reproductive structures of annual plants to gaseous pollutants independently
29 of the vegetative component ([Black et al., 2010](#); [Stewart et al., 1996](#)).

9.2.3 Field Chambers

30 In general, field chamber studies are dominated by the use of various versions of the open
31 top chamber (OTC) design, first described by [Heagle et al. \(1973\)](#) and [Mandl et al.](#)
32 [\(1973\)](#). The OTC method continues to be a widely used technique in the U.S. and Europe

1 for exposing plants to varying levels of O₃. Most of the new information confirms earlier
2 conclusions and provides additional support for OTC use in assessing plant species and in
3 developing exposure-response relationships. Chambers are generally ~3 meters in
4 diameter with 2.5 meter-high walls. [Hogsett et al. \(1987b\)](#) described in detail many of the
5 various modifications to the original OTC designs that appeared subsequently, e.g., the
6 use of larger chambers for exposing small trees ([Kats et al., 1985](#)) or grapevines ([Mandl
7 et al., 1989](#)), the addition of a conical baffle at the top to improve ventilation ([Kats et al.,
8 1976](#)), a frustum at the top to reduce ambient air incursions, and a plastic rain-cap to
9 exclude precipitation ([Hogsett et al., 1985](#)). All versions of OTCs included the discharge
10 of air via ports in annular ducting or interiorly perforated double-layered walls at the base
11 of the chambers to provide turbulent mixing and the upward mass flow of air.

12 Chambered systems, including OTCs, have several advantages. For instance, they can
13 provide a range of treatment levels including charcoal-filtered (CF), clean-air control, and
14 several above ambient concentrations for O₃ experiments. Depending on experimental
15 intent, a replicated, clean-air control treatment is an essential component in many
16 experimental designs. The OTC can provide a consistent, definable exposure because of
17 the constant wind speed and delivery systems. Statistically robust concentration-response
18 (C-R) functions can be developed using such systems for evaluating the implications of
19 various alternative air quality scenarios on vegetation response. Nonetheless, there are
20 several characteristics of the OTC design and operation that can lead to exposures that
21 might differ from those experienced by plants in the field. First, the OTC plants are
22 subjected to constant air flow turbulence, which, by lowering the boundary layer
23 resistance to diffusion, may result in increased uptake. This may lead to an
24 overestimation of effects relative to areas with less turbulence ([Krupa et al., 1995](#); [Legge
25 et al., 1995](#)). However, other research has found that OTC's may slightly change vapor
26 pressure deficit (VPD) in a way that may decrease the uptake of O₃ into leaves ([Piikki et
27 al., 2008a](#)). As with all methods that expose vegetation to modified O₃ concentrations in
28 chambers, OTCs create internal environments that differ from ambient air. This so-called
29 "chamber effect" refers to the modification of microclimatic variables, including reduced
30 and uneven light intensity, uneven rainfall, constant wind speed, reduced dew formation,
31 and increased air temperatures ([Fuhrer, 1994](#); [Manning and Krupa, 1992](#)). However, in at
32 least one case where canopy resistance was quantified in OTCs and in the field, it was
33 determined that gaseous pollutant exposure to crops in OTCs was similar to that which
34 would have occurred at the same concentration in the field ([Unsworth et al., 1984a, b](#)).
35 Because of the standardized methodology and protocols used in National Crop Loss
36 Assessment Network (NCLAN) and other programs, the database can be assumed to be
37 internally consistent.

1 While it is clear that OTCs can alter some aspects of the microenvironment and plant
2 growth, it is important to establish whether or not these differences affect the relative
3 response of a plant to O₃. As noted in the 1996 O₃ AQCD, evidence from a number of
4 comparative studies of OTCs and other exposure systems suggested that responses were
5 essentially the same regardless of exposure system used and chamber effects did not
6 significantly affect response. In studies that included exposure to ambient concentrations
7 of O₃ in both OTCs, and open-air, chamberless control plots, responses in the OTCs were
8 the same as in open-air plots. Examples include studies of tolerant and sensitive white
9 clover clones (*Trifolium repens*) to ambient O₃ in greenhouse, open top, and ambient
10 plots ([Heagle et al., 1996](#)), Black Cherry (*Prunus serotina*) ([Neufeld et al., 1995](#)), and
11 three species of conifers ([Neufeld et al., 2000](#)). Experimental comparisons between
12 exposure methodologies are reviewed in Section [9.2.6](#).

13 Another type of field chamber called a “terracosm” has been developed and used in
14 recent studies ([Lee et al., 2009a](#)). Concern over the need to establish realistic plant-litter-
15 soil relationships as a prerequisite to studies of the effects of O₃ and CO₂ enrichment on
16 ponderosa pine (*Pinus ponderosa*) seedlings led [Tingey et al. \(1996\)](#) to develop closed,
17 partially environmentally controlled, sun-lit chambers (“terracosms”) incorporating
18 lysimeters (1 meter deep) containing forest soil in which the appropriate horizon structure
19 was retained.

20 Other researchers have recently published studies using another type of out-door chamber
21 called recirculating Outdoor Plant Environment Chambers (OPECs) ([Flowers et al.,](#)
22 [2007](#)). These closed chambers are approximately 2.44 meters × 1.52 meters with a growth
23 volume of approximately 3.7 m³ in each chamber. These chambers admit 90% of full
24 sunlight and control temperature, humidity and vapor pressure ([Fiscus et al., 1999](#)).

9.2.4 Plume and FACE-Type Systems

25 Plume systems are chamberless exposure facilities in which the atmosphere surrounding
26 plants in the field is modified by the injection of pollutant gas into the air above or
27 around them from multiple orifices spaced to permit diffusion and turbulence, so as to
28 establish relatively homogeneous conditions as the individual plumes disperse and mix
29 with the ambient air. They can only be used to increase the O₃ levels in the ambient air.

30 The most common plume system used in the U.S. is a modification of the free-air carbon
31 dioxide/ozone enrichment (FACE) system ([Hendrey et al., 1999](#); [Hendrey and Kimball,](#)
32 [1994](#)). Although originally designed to provide chamberless field facilities for studying
33 the CO₂ effects of climate change, FACE systems have been adapted to include the
34 dispensing of O₃ ([Karnosky et al., 1999](#)). This method has been employed in Illinois

1 (SoyFACE) to study soybeans ([Morgan et al., 2004](#); [Rogers et al., 2004](#)) and in
2 Wisconsin (Aspen FACE) to study trembling aspen (*Populus tremuloides*), birch (*Betula*
3 *papyrifera*) and maple (*Acer saccharum*) ([Karnosky et al., 1999](#)). [Volk et al. \(2003\)](#)
4 described a similar system for exposing grasslands that uses 7-m diameter plots. Another
5 similar FACE system has been used in Finland ([Saviranta et al., 2010](#); [Oksanen, 2003](#)).

6 The FACE systems in the U.S. discharge the pollutant gas (O₃ and/or CO₂) through
7 orifices spaced along an annular ring (or torus) or at different heights on a ring of vertical
8 pipes. Computer-controlled feedback from the monitoring of gas concentration regulates
9 the feed rate of enriched air to the dispersion pipes. Feedback of wind speed and
10 directional information ensures that the discharges only occur upwind of the treatment
11 plots, and that discharge is restricted or closed down during periods of low wind speed or
12 calm conditions. The diameter of the arrays and their height (25-30 m) in some FACE
13 systems requires large throughputs of enriched air per plot, particularly in forest tree
14 systems. The cost of the throughputs tends to limit the number of enrichment treatments,
15 although [Hendrey et al. \(1999\)](#) argued that the cost on an enriched volume basis is
16 comparable to that of chamber systems.

17 A different FACE-type facility has been developed for the Kranzberg Ozone Fumigation
18 Experiment (KROFEX) in Germany beginning in 2000 ([Nunn et al., 2002](#); [Werner and](#)
19 [Fabian, 2002](#)). The experiment aims to study the effects of O₃ on mature stands of beech
20 (*Fagus sylvatica*) and spruce (*Picea abies*) trees in a system that functions independently
21 of wind direction. The enrichment of a large volume of the ambient air immediately
22 above the canopy takes place via orifices in vertical tubes suspended from a horizontal
23 grid supported above the canopy.

24 Although plume systems make virtually none of the modifications to the physical
25 environment that are inevitable with chambers, their successful use depends on selecting
26 the appropriate numbers, sizes, and orientations of the discharge orifices to avoid
27 “hot-spots” resulting from the direct impingement of jets of pollutant-enriched air on
28 plant foliage ([Werner and Fabian, 2002](#)). Because mixing is unassisted and completely
29 dependent on wind turbulence and diffusion, local gradients are inevitable especially in
30 large-scale systems. FACE systems have provisions for shutting down under low wind
31 speed or calm conditions and for an experimental area that is usually defined within a
32 generous border in order to strive for homogeneity of the exposure concentrations within
33 the treatment area. They are also dependent upon continuous computer-controlled
34 feedback of the O₃ concentrations in the mixed treated air and of the meteorological
35 conditions. Plume and FACE systems also are unable to reduce O₃ levels below ambient
36 in areas where O₃ concentrations are phytotoxic.

9.2.5 Ambient Gradients

1 Ambient O₃ gradients that occur in the U.S. hold potential for the examination of plant
2 responses over multiple levels of exposure. However, few such gradients can be found
3 that meet the rigorous statistical requirements for comparable site characteristics such as
4 soil type, temperature, rainfall, radiation, and aspect ([Manning and Krupa, 1992](#));
5 although with small plants, soil variability can be avoided by the use of plants in large
6 pots. The use of soil monoliths transported to various locations along natural O₃ gradients
7 is another possible approach to overcome differences in soils; however, this approach is
8 also limited to small plants.

9 Studies in the 1970s used the natural gradients occurring in southern California to assess
10 yield losses of alfalfa and tomato ([Oshima et al., 1977](#); [Oshima et al., 1976](#)). A transect
11 study of the impact of O₃ on the growth of white clover and barley in the U.K. was
12 confounded by differences in the concurrent gradients of SO₂ and NO₂ pollution
13 ([Ashmore et al., 1988](#)). Studies of forest tree species in national parks in the eastern U.S.
14 ([Winner et al., 1989](#)) revealed increasing gradients of O₃ and visible foliar injury with
15 increased elevation.

16 Several studies have used the San Bernardino Mountains Gradient Study in southern
17 California to study the effects of O₃ and N deposition on forests dominated by ponderosa
18 and Jeffrey pine ([Jones and Paine, 2006](#); [Arbaugh et al., 2003](#); [Grulke, 1999](#); [U.S. EPA,
19 1977](#)). However, it is difficult to separate the effects of N and O₃ in some instances in
20 these studies ([Arbaugh et al., 2003](#)). An O₃ gradient in Wisconsin has been used to study
21 foliar injury in a series of trembling aspen clones (*Populus tremuloides*) differing in O₃
22 sensitivity ([Maňková et al., 2005](#); [Karnosky et al., 1999](#)). Also in the Midwest, an
23 east-west O₃ gradient around southern Lake Michigan was used to look at growth and
24 visible foliar injury in (*P. serotina*) and common milkweed (*Asclepias syriaca*) ([Bennett
25 et al., 2006](#)).

26 More recently, studies have been published that have used natural gradients to study a
27 variety of endpoints and species. For example, [Gregg et al. \(2003\)](#) studied cottonwood
28 (*Populus deltoides*) saplings grown in an urban to rural gradient of O₃ by using seven
29 locations in the New York City area. The secondary nature of the reactions of O₃
30 formation and NO_x titration reactions within the city center resulted in significantly
31 higher cumulative O₃ exposures in more rural sites. Potential modifying factors such as
32 soil composition, moisture, or temperature were either controlled or accounted for in
33 analysis. As shown in Section [9.6.3.3](#), the response of this species to O₃ exposure was
34 much stronger than most species. The natural gradient exposures were reproduced in
35 parallel using OTCs, and yielded similar results. Also, the U.S. Forest Service Forest
36 Inventory and Analysis (FIA) program uses large-scale O₃ exposure patterns across the

1 continental U.S. to study occurrences of foliar injury due to O₃ exposure ([Smith et al.,](#)
2 [2003](#)) (Section [9.4.2](#)). Finally, [McLaughlin et al. \(2007a\); 2007b](#)) used spatial and
3 temporal O₃ gradients to study forest growth and water use in the southern Appalachians.
4 These studies found varying O₃ exposures between years and between sites.

9.2.6 Comparative Studies

5 All experimental approaches used to expose plants to O₃ have strengths and weaknesses.
6 One potential weakness of laboratory, greenhouse, or field chamber studies is the
7 potential effect of the chamber on micrometeorology. In contrast, plume, FACE and
8 gradient systems are limited by the very small number of possible exposure levels
9 (almost always no more than two), small replication and the inability to reduce O₃ levels
10 below ambient. In general, experiments that aim at characterizing the effect of a single
11 variable, e.g., exposure to O₃, must not only manipulate the levels of that variable, but
12 also control potentially interacting variables and confounders, or else account for them.
13 However, while increasing control of environmental variables makes it easier to discern
14 the effect of the variable of interest, it must be balanced with the ability to extend
15 conclusions to natural, non-experimental settings. More naturalistic exposure systems, on
16 the other hand, let interacting factors vary freely, resulting in greater unexplainable
17 variability. The various exposure methodologies used with O₃ vary in the balance each
18 strikes between control of environmental inputs, closeness to the natural environment,
19 noisiness of the response data, and ability to make general inferences.

20 Studies have examined the comparability of results obtained through the various exposure
21 methodologies. As noted in the 1996 O₃ AQCD, evidence from the comparative studies
22 of OTCs and from closed chamber and O₃-exclusion exposure systems on the growth of
23 alfalfa (*Medicago sativa*) by [Olszyk et al. \(1986\)](#) suggested that, since significant
24 differences were found for fewer than 10% of the growth parameters measured, the
25 responses were, in general, essentially the same regardless of exposure system used, and
26 chamber effects did not significantly affect response. In 1988, [Heagle et al. \(1988\)](#)
27 concluded: “Although chamber effects on yield are common, there are no results showing
28 that this will result in a changed yield response to O₃.” A study of the effects of an
29 enclosure examined the responses of tolerant and sensitive white clover clones (*Trifolium*
30 *repens*) to ambient O₃ in a greenhouse, open-top chamber, and ambient (no chamber)
31 plots ([Heagle et al., 1996](#)). For individual harvests, greenhouse O₃ exposure reduced the
32 forage weight of the sensitive clone 7 to 23% more than in OTCs. However, the response
33 in OTCs was the same as in ambient plots. Several studies have shown very similar
34 response of yield to O₃ for plants grown in pots or in the ground, suggesting that even

1 such a significant change in environment does not alter the proportional response to O₃,
2 providing that the plants are well watered ([Heagle et al., 1983](#); [Heagle, 1979](#)).

3 A few recent studies have compared results of O₃ experiments between OTCs, FACE
4 experiments, and gradient studies. For example, a series of studies undertaken at Aspen
5 FACE ([Isebrands et al., 2001](#); [Isebrands et al., 2000](#)) showed that O₃ symptom expression
6 was generally similar in OTCs, FACE, and ambient O₃ gradient sites, and supported the
7 previously observed variation among trembling aspen clones using OTCs ([Maňkiovská et
8 al., 2005](#); [Karnosky et al., 1999](#)). In the SoyFACE experiment in Illinois, soybean
9 (Pioneer 93B15 cultivar) yield loss data from a two-year study was published ([Morgan et
10 al., 2006](#)). This cultivar is a recent selection and, like most modern cultivars, has been
11 selected under an already high current O₃ exposure. It was found to have average
12 sensitivity to O₃ compared to 22 other cultivars tested at SoyFACE. In this experiment,
13 ambient hourly O₃ concentrations were increased by approximately 20% and measured
14 yields were decreased by 15% in 2002 as a result of the increased O₃ exposure ([Morgan
15 et al., 2006](#)). To compare these results to chamber studies, [Morgan et al. \(2006\)](#)
16 calculated the expected yield loss from a linear relationship constructed from chamber
17 data using seven-hour seasonal averages ([Ashmore, 2002](#)). They calculated an 8%
18 expected yield loss from the 2002 O₃ exposure using that linear relationship. As reported
19 in Section [9.2.5](#), [Gregg et al. \(2006, 2003\)](#) found similar O₃ effects on cottonwood
20 sapling biomass growth along an ambient O₃ gradient in the New York City area and a
21 parallel OTC study.

22 Finally, EPA conducted comparisons of exposure-response model predictions based on
23 OTC studies, and more recent FACE observations. These comparisons include yield of
24 annual crops, and biomass growth of trees. They are presented in Section [9.6.3](#) of this
25 document.

9.3 Mechanisms Governing Vegetation Response to Ozone

9.3.1 Introduction

26 This section focuses on the effects of O₃ stress on plants and their responses to that stress
27 on the molecular, biochemical and physiological levels. First, the pathway of O₃ uptake
28 into the leaf and the initial chemical reactions occurring in the substomatal cavity and
29 apoplast will be described (Section [9.3.2](#)); additionally, direct effects of O₃ on the
30 stomatal apparatus will be discussed. Once O₃ has entered the substomatal cavity and
31 apoplast, it is thought that the cell must be able to detect the presence of O₃ or its

1 breakdown products in order to initiate the rapid changes in signaling pathways and gene
2 expression that have been measured in O₃-treated plants. While it remains unclear exactly
3 how O₃ and/or its breakdown products are detected in the apoplast and how that leads to
4 signaling of oxidative stress in plants, much progress has been made in examining several
5 different mechanisms that may contribute to detecting the presence of O₃ and its
6 breakdown products, and also initiating a signal transduction cascade, which will be
7 described in Section [9.3.3.1](#). The next section focuses on changes in gene and protein
8 expression measured in plants exposed to O₃, with particular emphasis on results from
9 transcriptome (all RNA molecules produced in a cell) and proteome (all proteins
10 produced in a cell) analyses (Section [9.3.3.2](#)). Subsequently, the role of phytohormones
11 such as salicylic acid (SA), ethylene (ET), jasmonic acid (JA), and abscisic acid (ABA)
12 and their interactions in both signal transduction processes and in determining plant
13 response to O₃ is discussed in Section [9.3.3.3](#). After O₃ uptake, some plants can respond
14 to the oxidative stress with detoxification to minimize damage. These mechanisms of
15 detoxification, with particular emphasis on antioxidant enzymes and metabolites, are
16 reviewed in Section [9.3.4](#). The next section focuses on changes in primary and secondary
17 metabolism in plants exposed to O₃, looking at photosynthesis, respiration and several
18 secondary metabolites, some of which may also act as antioxidants and protect the plant
19 from oxidative stress (Section [9.3.5](#)). For many of these topics, information from the
20 2006 O₃ AQCD has been summarized, as this information is still valid and supported by
21 more recent findings. For other topics, such as genomics and proteomics, which have
22 arisen due to the availability of new technologies, the information is based solely on new
23 publications with no reference to the 2006 O₃ AQCD.

24 As Section [9.3](#) focuses on mechanisms underlying effects of O₃ on plants and their
25 response to it, the conditions that are used to study these mechanisms do not always
26 reflect conditions that a plant may be exposed to in an agricultural setting or natural
27 ecosystem. The goal of many of these studies is to generate an O₃ effect in a relatively
28 short period of time and not always to simulate ambient O₃ exposures. Therefore, plants
29 are often exposed to unrealistically high O₃ concentrations for several hours or days
30 (acute exposure), and only in some cases to ambient or slightly elevated O₃
31 concentrations for longer time periods (chronic exposure). Additionally, the plant species
32 utilized in these studies are often not agriculturally important or commonly found as part
33 of natural ecosystems. Model organisms such as *Arabidopsis thaliana* are used frequently
34 as they are easy to work with, and mutants or transgenic plants are easy to develop or
35 have already been developed. Furthermore, the *Arabidopsis* genome has been sequenced,
36 and much is known about the molecular basis of many biochemical and cellular
37 processes.

1 Many of the studies described in this section focus on changes in the expression of genes
2 in O₃-treated plants. Changes in gene expression (i.e., either upregulation or
3 downregulation of gene expression) do not always translate into changes in protein
4 quantity and/or activity, as there are many levels of post-transcriptional and post-
5 translational modifications which impact protein quantity and activity. Many studies do
6 not evaluate whether the observed changes in gene expression lead to changes at the
7 protein level and, therefore, it is not always clear if the changes in gene expression
8 represent a meaningful biological response to O₃ exposure. However, with the advent of
9 proteomics, some very recent studies have evaluated changes in protein expression for
10 large numbers of proteins in O₃ treated plants, and the findings from these studies support
11 the previous results regarding changes in gene expression studies as a result of O₃
12 exposure. The next step in the process is to determine the implications of the measured
13 changes occurring at the cellular level to whole plants and ecosystems, which is an
14 important topic of study which has not been widely addressed.

15 The most noteworthy new body of research since the 2006 O₃ AQCD is on the
16 understanding of molecular mechanisms underlying how plants are affected by O₃; many
17 of the recent studies reviewed here focus on changes in gene expression in plants exposed
18 to elevated O₃. The findings summarized in the 2006 O₃ AQCD included decreases in
19 transcript levels of photosynthesis associated genes, and increases in transcript levels of
20 genes encoding for pathogenesis-related proteins, enzymes needed for ethylene synthesis,
21 antioxidant enzymes and defense genes such as phenylalanine ammonia lyase in plants
22 exposed to O₃. These findings have been supported by the new studies, and the advent of
23 new technologies has allowed for a more comprehensive understanding of the
24 mechanisms governing how plants are affected by O₃.

25 In summary, these new studies have increased knowledge of the molecular, biochemical
26 and cellular mechanisms occurring in plants in response to O₃ by often using artificial
27 exposure conditions and model organisms. This information adds to the understanding of
28 the basic biology of how plants are affected by oxidative stress in the absence of any
29 other potential stressors. The results of these studies provide important insights, even
30 though they may not always directly translate into effects observed in other plants under
31 more realistic exposure conditions.

9.3.2 Ozone Uptake into the Leaf

32 Appendix AX9.2.3 of the 2006 O₃ AQCD clearly described the process by which O₃
33 enters plant leaves through open stomata ([U.S. EPA, 2006b](#)). This information continues
34 to be valid and is only summarized here.

1 Stomata provide the principal pathway for O₃ to enter and affect plants ([Massman and](#)
2 [Grantz, 1995](#); [Fuentes et al., 1992](#); [Reich, 1987](#); [Leuning et al., 1979](#)). Ozone moves into
3 the leaf interior by diffusing through open stomata, and environmental conditions which
4 promote high rates of gas exchange will favor the uptake of the pollutant by the leaf.
5 Factors that may limit uptake include boundary layer resistance and the size of the
6 stomatal aperture ([Figure 9-2](#)) ([U.S. EPA, 2006b](#)). Once inside the substomatal cavity, O₃
7 is thought to rapidly react with the aqueous apoplast to form breakdown products known
8 as reactive oxygen species (ROS), such as hydrogen peroxide (H₂O₂), superoxide (O₂⁻),
9 hydroxyl radicals (HO·) and peroxy radicals (HO₂·) ([Figure 9-3](#)). Hydrogen peroxide is
10 not only a toxic breakdown product of O₃, but has been shown to function as a signaling
11 molecule, which is activated in response to both biotic and abiotic stressors. The role of
12 H₂O₂ in signaling was described in detail in the 2006 O₃ AQCD. Additional organic
13 molecules present in the apoplast or cell wall, such as those containing double bonds or
14 sulfhydryls that are sensitive to oxidation, could also be converted to oxygenated
15 molecules after interacting with O₃ ([Figure 9-4](#)). These reactions are not only pH
16 dependent, but are also influenced by the presence of other molecules in the apoplast
17 ([U.S. EPA, 2006b](#)). The 2006 O₃ AQCD provided a comprehensive summary of these
18 possible interactions of O₃ with other biomolecules ([U.S. EPA, 2006b](#)). It is in the
19 apoplast that initial detoxification reactions by antioxidant metabolites and enzymes take
20 place, and these initial reactions are critical to reduce concentrations of the oxidative
21 breakdown products of O₃; these reactions are described in more detail in Section [9.3.4](#) of
22 this document.

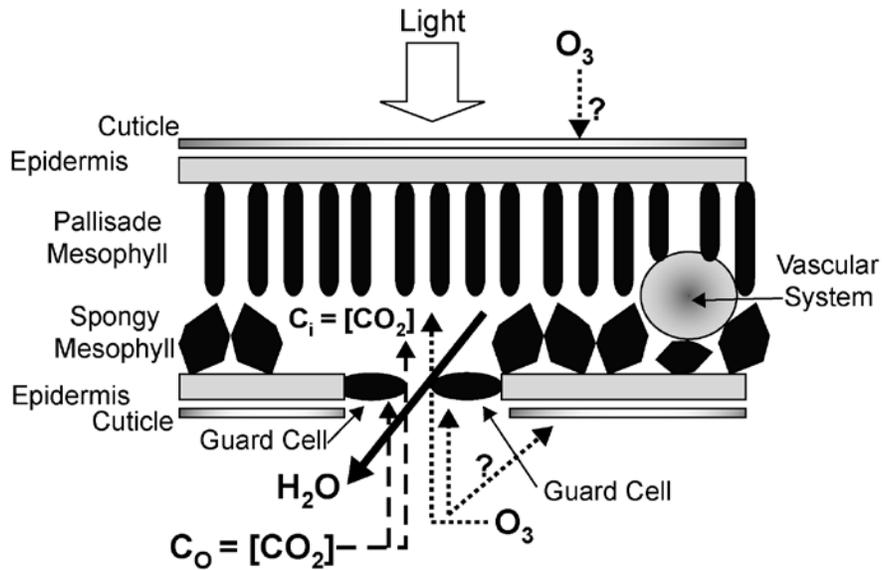
9.3.2.1 Changes in Stomatal Function

23 Ozone-induced changes in stomatal conductance have been reviewed in detail in previous
24 O₃ AQCDs. The findings summarized in these documents demonstrate that stomatal
25 conductance is often reduced in plants exposed to O₃, resulting either from a direct
26 impact of O₃ on the stomatal complex which causes closure, or as a response to
27 increasing CO₂ concentrations in the substomatal cavity as carbon fixation is reduced.
28 Although the nature of these effects depends upon many different factors, including the
29 plant species, concentration and duration of the O₃ exposure, and prevailing
30 meteorological conditions, stomatal conductance is often negatively affected by plant
31 exposure to O₃ ([Wittig et al., 2007](#)). Decreases in conductance have been shown to result
32 from direct as well as indirect effects on stomata ([Wittig et al., 2007](#)). Results from the
33 use of Arabidopsis mutants and new technologies, which allow for analysis of guard cell
34 function in whole plants rather than in isolated guard cells or epidermal peels, suggest
35 that O₃ may also have a direct impact on stomatal guard cells, leading to alterations in

1 stomatal conductance. The use of a new simultaneous O₃ exposure/gas exchange device
2 has demonstrated that exposure of Arabidopsis ecotypes Col-0 and Ler to 150 ppb O₃
3 resulted in a 60-70% decline in stomatal conductance within 9-12 minutes of beginning
4 the exposure. Twenty to thirty minutes later, stomatal conductance had returned to its
5 initial value, even with continuing exposure to O₃, indicating a rapid direct effect of O₃
6 on stomatal function ([Kollist et al., 2007](#)). This transient decrease in stomatal
7 conductance was not observed in the abscisic acid insensitive (ABI2) Arabidopsis
8 mutant. As the ABI2 protein is thought to regulate the signal transduction process
9 involved in stomatal response downstream of ROS production, the authors suggest that
10 the transient decrease in stomatal conductance in the Col-0 and Ler ecotypes results from
11 the biological action of ROS in transducing signals, rather than direct physical damage to
12 guard cells by ROS ([Kollist et al., 2007](#)). This rapid transient decrease in stomatal
13 conductance was also not observed when exposing the Arabidopsis mutant slac1 (slow
14 anion channel-associated 1) to 200 ppb O₃ ([Vahisalu et al., 2008](#)). The SLAC1 protein
15 was shown to be essential for guard cell slow anion channel functioning and for stomatal
16 closure in response to O₃. Based on additional studies using a variety of Arabidopsis
17 mutants impaired in various aspects of stomatal function, [Vahisalu et al. \(2008\)](#) suggest
18 that the presence of ROS in the guard cell apoplast (formed either by O₃ breakdown or
19 through ROS production from NADPH oxidase activity) leads to the activation of a
20 signaling pathway in the guard cells, which includes SLAC1, and results in stomatal
21 closure.

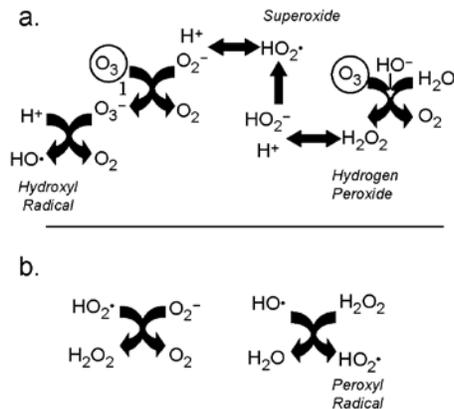
22 A review by [McAinsh et al. \(2002\)](#) discusses the role of calcium as a part of the signal
23 transduction pathway involved in regulating stomatal responses to pollutant stress. A
24 number of studies in this review provide some evidence that exposure to O₃ increases the
25 cytosolic free calcium concentration ([Ca²⁺]_{cyt}) in guard cells, which may result in an
26 inhibition of the plasma membrane inward-rectifying K⁺ channels in guard cells, which
27 allow for the K⁺ uptake needed for stomatal opening ([McAinsh et al., 2002](#); [Torsethaugen
28 et al., 1999](#)). This would compromise the ability of the stomata to respond to various
29 stimuli, including light, CO₂ concentration and drought. [Pei et al. \(2000\)](#) reported that the
30 presence of H₂O₂ activated Ca²⁺-permeable channels, which mediate increases in
31 [Ca²⁺]_{cyt} in guard cell plasma membranes of Arabidopsis. They also determined that
32 abscisic acid (ABA) induced H₂O₂ production in guard cells, leading to ABA-induced
33 stomatal closure via activation of the membrane Ca²⁺ channels. Therefore, it is possible
34 that H₂O₂, a byproduct of O₃ breakdown in the apoplast, could disrupt the Ca²⁺-ABA
35 signaling pathway that is involved in regulating stomatal responses ([McAinsh et al.,
36 2002](#)). The studies described here provide some evidence to suggest that O₃ and its
37 breakdown products can directly affect stomatal functioning by impacting the signal
38 transduction pathways which regulate guard cells. Stomatal sluggishness has been
39 described as a delay in stomatal response to changing environmental conditions in

1 sensitive species exposed to higher concentrations and/or longer-term O₃ exposures
2 ([Paoletti and Grulke, 2010, 2005](#); [McAinsh et al., 2002](#)). It is possible that the signaling
3 pathways described above could be involved in mediating this stomatal sluggishness in
4 some plant species under certain O₃ exposure conditions ([Paoletti and Grulke, 2005](#);
5 [McAinsh et al., 2002](#)).



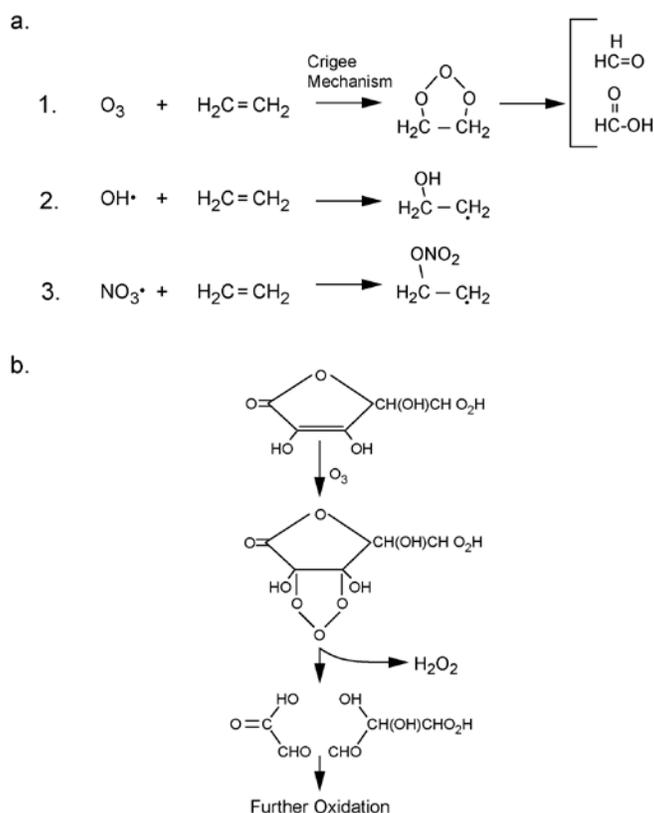
Note: While details among species vary, the general overview remains the same. Light that drives photosynthesis generally falls upon the upper (adaxial) leaf surface. Carbon dioxide and ozone enter through the stomata on the lower (abaxial) leaf surface, while water vapor exits through the stomata (transpiration).

Figure 9-2 The microarchitecture of a dicot leaf.



Note: (a) Ozone reacts at the double bonds to form carbonyl groups. (b) Under certain circumstances, peroxides are generated.

Figure 9-3 Possible reactions of ozone within water.



Note: (a) The typical Crige mechanism is shown in which several reaction paths from the initial product are shown. (b) Typical reaction of ascorbic acid with ozone.

Source: Adapted from [Mudd \(1996\)](#).

Figure 9-4 The Crige mechanism of ozone attack of a double bond.

9.3.3 Cellular to Systemic Responses

9.3.3.1 Ozone Detection and Signal Transduction

1 New technologies allowing for large-scale analysis of oxidative stress-induced changes in
2 gene expression have facilitated the study of signal transduction processes associated
3 with the perception and integration of responses to the stress. Many of these studies have
4 been conducted using *Arabidopsis* or tobacco plants, for which a variety of mutants are
5 available and/or which can be easily genetically modified to generate either loss-of-
6 function or over-expressing genotypes. Several comprehensive review articles provide an
7 overview of what is known of O₃-induced signal transduction processes and how they
8 may help to explain differential sensitivity of plants to the pollutant ([Ludwikow and](#)
9 [Sadowski, 2008](#); [Baier et al., 2005](#); [Kangasjarvi et al., 2005](#)). Additionally, analysis of
10 several studies of transcriptome changes has also allowed for the compilation of these
11 data to determine an initial time-course for O₃-induced activation of various signaling
12 compounds ([Kangasjarvi et al., 2005](#)).

13 A number of different mechanisms for detection of O₃ by plants have been proposed;
14 however, there is still much that is not known about this process. Some of the earliest
15 events that occur in plants exposed to O₃ have been described in the guard cells of
16 stomata. Reactive oxygen species were observed in the chloroplasts of guard cells in the
17 O₃ tolerant Col-0 *Arabidopsis thaliana* ecotype plants within 5 minutes of plant exposure
18 to 350 ppb O₃ ([Joo et al., 2005](#)). Reactive oxygen species from the breakdown of O₃ in
19 the apoplast are believed to activate GTPases (G-proteins), which, in turn, activate
20 several intracellular sources of ROS, including ROS derived from the chloroplasts.
21 G-proteins are also believed to play a role in activating membrane-bound NADPH
22 oxidases to produce ROS and, as a result, propagate the oxidative burst to neighboring
23 cells ([Joo et al., 2005](#)). Therefore, G-proteins are recognized as important molecules
24 involved in plant responses to O₃ and may play a role in detecting the presence of ROS
25 from the breakdown of O₃ in the apoplast ([Kangasjarvi et al., 2005](#); [Booker et al., 2004a](#)).

26 A change in the redox state of the plant and the oxidation of sensitive molecules in itself
27 may represent a means of perception and signaling of oxidative stress in plants.
28 Disulfide-thiol conversions in proteins and the redox state of the glutathione pool may be
29 important components of redox detection and signal transduction ([Foyer and Noctor,](#)
30 [2005a, b](#)).

31 Calcium (Ca²⁺) has also been implicated in the transduction of signals to the nucleus in
32 response to oxidative stress. The influx of Ca²⁺ from the apoplast into the cell occurs
33 early during plant exposure to O₃, and it is thought to play a role in regulating the activity

1 of protein kinases, which are discussed below ([Baier et al., 2005](#); [Hamel et al., 2005](#)).
2 Calcium channel blockers inhibited O₃-induced activation of protein kinases in tobacco
3 suspension cells exposed to 500 ppb O₃ for 10 minutes, indicating that the opening of
4 Ca²⁺ channels is an important upstream signaling event or that the (as yet unknown)
5 upstream process has a requirement for Ca²⁺ ([Samuel et al., 2000](#)).

6 Further transmission of information regarding the presence of ROS to the nucleus
7 involves mitogen-activated protein kinases (MAPK), which phosphorylate proteins and
8 activate various cellular responses ([Hamel et al., 2005](#)). Mitogen-activated protein
9 kinases are induced in several different plant species in response to O₃ exposure,
10 including tobacco ([Samuel et al., 2005](#)), Arabidopsis ([Ludwikow et al., 2004](#)), the shrub
11 *Phillyrea latifolia* ([Paolacci et al., 2007](#)) and poplar ([Hamel et al., 2005](#)). Disruption of
12 these signal transduction pathways by over-expressing or suppressing MAPK activity in
13 different Arabidopsis and tobacco lines resulted in increased plant sensitivity to O₃ ([Miles](#)
14 [et al., 2005](#); [Samuel and Ellis, 2002](#)). Additionally, greater O₃ tolerance of several
15 Arabidopsis ecotypes was correlated with greater upregulation of MAPK signaling
16 pathways upon O₃ exposure than in more sensitive Arabidopsis ecotypes ([Li et al.,](#)
17 [2006b](#); [Mahalingam et al., 2006](#); [Overmyer et al., 2005](#)), indicating that determination of
18 plant sensitivity and plant response to O₃ may, in part, be determined not only by whether
19 these pathways are turned on, but also by the magnitude of the signals moving through
20 these communication channels.

21 In conclusion, experimental evidence suggests that there are likely several different
22 mechanisms by which the plant detects the presence of O₃ or its breakdown products.
23 These mechanisms may vary by species or developmental stage of the plant, or may
24 co-exist and be activated by different exposure conditions. Calcium and protein kinases
25 are likely involved in relaying information about the presence of the stressor to the
26 nucleus and other cellular compartments as a first step in determining whether and how
27 the plant will respond to the stress.

9.3.3.2 Gene and Protein Expression Changes in Response to Ozone

28 The advent of DNA microarray technology has allowed for the study of gene expression
29 in cells on a large scale. Rather than assessing changes in gene expression of individual
30 genes, DNA microarrays facilitate the evaluation of entire transcriptomes, providing a
31 comprehensive picture of simultaneous alterations in gene expression. In addition, these
32 studies have provided more insight into the complex interactions between molecules, how
33 those interactions lead to the communication of information in the cell (or between

1 neighboring cells), and which role these interactions play in determining tolerance or
2 sensitivity and how a plant may respond to stresses such as O₃ ([Ludwikow and Sadowski,](#)
3 [2008](#)). Transcriptome analysis of O₃-treated plants has been performed in several species,
4 including *Arabidopsis thaliana* ([Li et al., 2006b](#); [Tosti et al., 2006](#); [Heidenreich et al.,](#)
5 [2005](#); [Mahalingam et al., 2005](#); [Tamaoki et al., 2003](#)), pepper (*Capsicum annuum*) ([Lee](#)
6 [and Yun, 2006](#)), clover (*Medicago truncatula*) ([Puckette et al., 2008](#)), *Phillyrea latifolia*
7 ([Paolacci et al., 2007](#)), poplar ([Street et al., 2011](#)), and European beech (*Fagus sylvatica*)
8 ([Olbrich et al., 2010](#); [Olbrich et al., 2009](#); [Olbrich et al., 2005](#)). In some cases,
9 researchers compared transcriptomes of two or more cultivars, ecotypes or mutants that
10 differed in their sensitivity to O₃ ([Puckette et al., 2008](#); [Rizzo et al., 2007](#); [Lee and Yun,](#)
11 [2006](#); [Li et al., 2006b](#); [Tamaoki et al., 2003](#)). Species, O₃ exposure conditions
12 (concentration, duration of exposure) and sampling times varied considerably in these
13 studies. However, functional classification of the genes that were either upregulated or
14 downregulated by plant exposure to O₃ exhibited common trends. Genes involved in
15 plant defense, signaling and those associated with the synthesis of plant hormones and
16 secondary metabolism were generally upregulated, while those related to photosynthesis
17 and general metabolism were typically downregulated in O₃-treated plants ([Puckette et](#)
18 [al., 2008](#); [Lee and Yun, 2006](#); [Li et al., 2006b](#); [Tosti et al., 2006](#); [Olbrich et al., 2005](#);
19 [Tamaoki et al., 2003](#)).

20 Analysis of the transcriptome has been used to evaluate differences in gene expression
21 between sensitive and tolerant plants in response to O₃ exposure. In pepper, 67% of the
22 180 genes studied that were affected by O₃ were differentially regulated in the sensitive
23 and tolerant cultivars. At both 0 hours and 48 hours after a 3-day exposure at 150 ppb, O₃
24 responsive genes were either upregulated or downregulated more markedly in the
25 sensitive than in the tolerant cultivar ([Lee and Yun, 2006](#)). Transcriptome analysis also
26 revealed differences in timing and magnitude of changes in gene expression between
27 sensitive and tolerant clovers. Acute exposure (300 ppb O₃ for 6 hours) led to the
28 production of an oxidative burst in both clovers ([Puckette et al., 2008](#)). However, the
29 sensitive-Jemalong cultivar exhibited a sustained ROS burst and a concomitant
30 downregulation of defense response genes at 12 hours after the onset of exposure, while
31 the tolerant JE 154 accession showed much more rapid and large-scale transcriptome
32 changes than the Jemalong cultivar ([Puckette et al., 2008](#)).

33 *Arabidopsis* ecotypes WS and Col-0 were exposed to 1.2 × ambient O₃ concentrations for
34 8-12 days at the SoyFACE site ([Li et al., 2006b](#)). The sensitive WS ecotype showed a far
35 greater number of changes in gene expression in response to this low-level O₃ exposure
36 than the tolerant Col-0 ecotype. In a different study, exposure of the WS ecotype to
37 300 ppb O₃ for 6 hours showed a rapid induction of genes leading to cell death, such as

1 proteases, and downregulation or inactivation of cell signaling genes, demonstrating an
2 ineffective defense response in this O₃ sensitive ecotype ([Mahalingam et al., 2006](#)).

3 The temporal response of plants to O₃ exposure was evaluated in the Arabidopsis Col-0
4 ecotype during a 6-hour exposure at 350 ppb O₃ and for 6 hours after the exposure was
5 completed. Results of this study, shown in [Figure 9-5](#), indicate that genes associated with
6 signal transduction and regulation of transcription were in the class of early upregulated
7 genes, while genes associated with redox homeostasis and defense/stress response were
8 in the class of late upregulated genes ([Mahalingam et al., 2005](#)).

9 A few studies have been conducted to evaluate transcriptome changes in response to
10 longer term chronic O₃ exposures in woody plant species. Longer term exposures resulted
11 in the upregulation of genes associated with secondary metabolites, including
12 isoprenoids, polyamines and phenylpropanoids in 2-year-old seedlings of the
13 Mediterranean shrub *Phillyrea latifolia* exposed to 110 ppb O₃ for 90 days ([Paolacci et](#)
14 [al., 2007](#)). In 3-year-old European beech saplings exposed to O₃ for 20 months (with
15 monthly average twice ambient O₃ concentrations ranging from 11 to 80 ppb),
16 O₃-induced changes in gene transcription were similar to those observed for herbaceous
17 species ([Olbrich et al., 2009](#)). Genes encoding proteins associated with plant stress
18 response, including ethylene biosynthesis, pathogenesis-related proteins and enzymes
19 detoxifying ROS, were upregulated. Some genes associated with primary metabolism, cell
20 structure, cell division and cell growth were reduced ([Olbrich et al., 2009](#)). In a similar
21 study using adult European beech trees, it was determined that the magnitude of the
22 transcriptional changes described above was far greater in the saplings than in the adult
23 trees exposed to the same O₃ concentrations for the same time period ([Olbrich et al.,](#)
24 [2010](#)).

25 The results from transcriptome studies described above have been substantiated by results
26 from proteome analysis in rice, poplar, European beech, wheat, and soybean. Exposure of
27 soybean to 120 ppb O₃ for 12 h/day for 3 days in growth chambers resulted in decreases
28 in the quantity of proteins associated with photosynthesis, while proteins involved with
29 antioxidant defense and carbon metabolism increased ([Ahsan et al., 2010](#)). Young poplar
30 plants exposed to 120 ppb O₃ in a growth chamber for 35 days also showed significant
31 changes in proteins involved in carbon metabolism ([Bohler et al., 2007](#)). Declines in
32 enzymes associated with carbon fixation, the Calvin cycle and photosystem II were
33 measured, while ascorbate peroxidase and enzymes associated with glucose catabolism
34 increased in abundance. In another study to determine the impacts of O₃ on both
35 developing and fully expanded poplar leaves, young poplars were exposed to 120 ppb O₃
36 for 13-h/day for up to 28 days ([Bohler et al., 2010](#)). Impacts on protein quantity only
37 occurred after the plants had been exposed to O₃ for 14 days, and at this point in time,

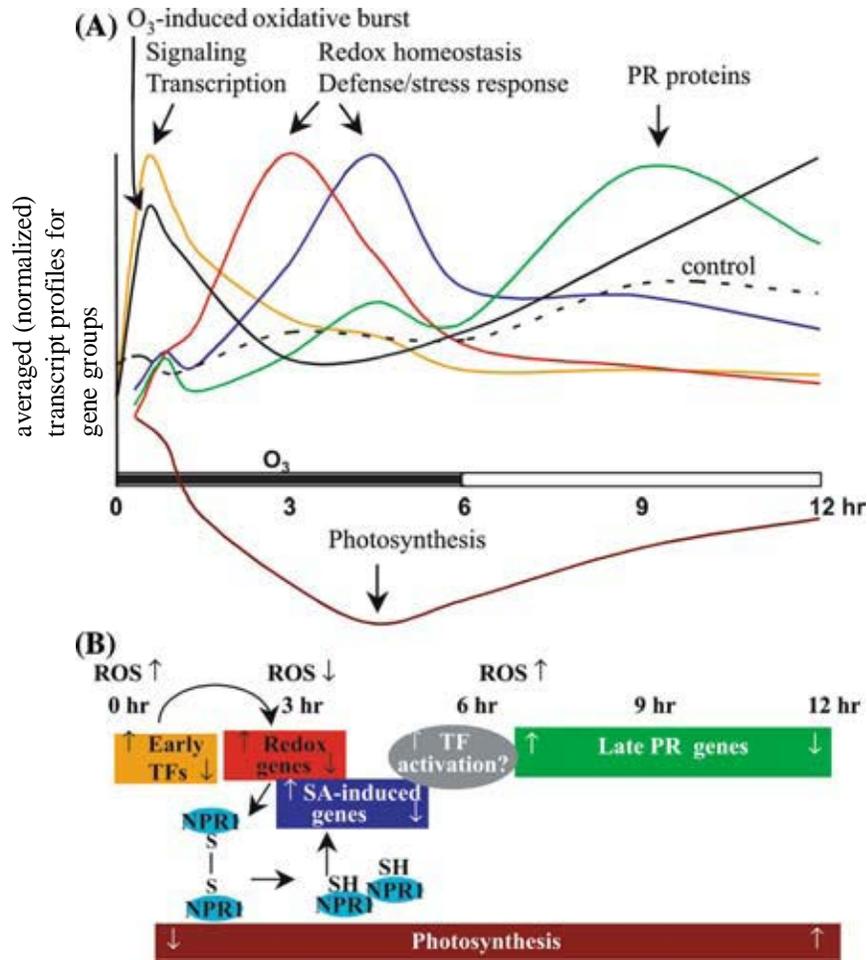
1 several Calvin cycle enzymes were reduced in quantity, while the effects on the light
2 reactions appeared later, at 21 days after beginning treatment. Some of the antioxidant
3 enzymes increased in abundance with O₃ treatment, while others (ascorbate peroxidase)
4 did not. In relationship to leaf expansion, it was shown that O₃ did not affect protein
5 quantity until leaves had reached full expansion, after about 7 days ([Bohler et al., 2010](#)).

6 Two-week-old rice seedlings exposed to varying levels of O₃ (4, 40, 80, 120 ppb) in a
7 growth chamber for 9 days showed reductions in quantities of proteins associated with
8 photosynthesis and energy metabolism, and increases in some antioxidant and defense
9 related proteins ([Feng et al., 2008a](#)). A subsequent study of O₃-treated rice seedlings
10 (exposed to 200 ppb O₃ for 24 hours) focusing on the integration of transcriptomics and
11 proteomics, supported and further enhanced these results ([Cho et al., 2008](#)). The authors
12 found that of the 22,000 genes analyzed from the rice genome, 1,535 were differentially
13 regulated by O₃. Those differentially regulated genes were functionally categorized as
14 transcription factors, MAPK cascades, those encoding for enzymes involved in the
15 synthesis of jasmonic acid (JA), ethylene (ET), shikimate, tryptophan and lignin, and
16 those involved in glycolysis, the citric acid cycle, oxidative respiration and
17 photosynthesis. The authors determined that the proteome and metabolome (all small
18 molecule metabolites in a cell) analysis supported the results of the transcriptome
19 changes described above ([Cho et al., 2008](#)). This type of study, which ties together results
20 from changes in gene expression, protein quantity and activity, and metabolite levels,
21 provides the most complete picture of the molecular and biochemical changes occurring
22 in plants exposed to a stressor such as O₃.

23 [Sarkar et al. \(2010\)](#) compared proteomes of two cultivars of wheat grown in OTCs at
24 several O₃ concentrations, including filtered air, ambient O₃ (mean concentration 47 ppb),
25 ambient + 10 ppb and ambient + 20 ppb for 5 h/day for 50 days. Declines in the rate of
26 photosynthesis and stomatal conductance were related to decreases in proteins involved
27 in carbon fixation and electron transport and increased proteolysis of photosynthetic
28 proteins such as the large subunit of ribulose-1,6-bisphosphate carboxylase/oxygenase
29 (Rubisco). Enzymes that take part in energy metabolism, such as ATP synthesis, were
30 also downregulated, while defense/stress related proteins were upregulated in O₃-treated
31 plants. In comparing the two wheat cultivars, [Sarkar et al. \(2010\)](#) found that while the
32 qualitative changes in protein expression between the two cultivars were similar, the
33 magnitude of these changes differed between the sensitive and tolerant wheat cultivars.
34 Greater foliar injury and a smaller decline in stomatal conductance was observed in the
35 sensitive cultivar as compared to the more tolerant cultivar, along with greater losses in
36 photosynthetic enzymes and higher quantities of antioxidant enzymes. Results from a
37 three-year exposure of European beech saplings to elevated O₃ (AOT40 value was
38 52.6 μL/L•h for 2006 when trees were sampled) supported the results from the short-term

1 exposure studies described above ([Kerner et al., 2011](#)). The O₃ treatment of the saplings
2 resulted in reductions in enzymes associated with the Calvin cycle, which could lead to
3 reduced carbon fixation. Enzymes associated with carbon metabolism/catabolism were
4 increased, and quantities of starch and sucrose were reduced in response to the O₃
5 treatment in these trees, indicating a potential impact of O₃ on overall carbon metabolism
6 in long-term exposure conditions ([Kerner et al., 2011](#)).

7 Transcriptome and proteome studies have provided valuable information about O₃ effects
8 on plants. These studies allow for simultaneous analysis of changes in the expression
9 patterns of many different genes and proteins, and also provide information on how these
10 molecules might interact with one another as a result of plant exposure to oxidative
11 stress. Gene and protein expression patterns generally differ between O₃-sensitive and
12 tolerant plants, which could result from differential uptake or detoxification of O₃ or from
13 differential regulation of the transcriptome and proteome.



Note: (A) Temporal profile of the oxidative stress response to ozone. The biphasic ozone-induced oxidative burst is represented in black, with the ROS control measurements shown as a broken line. Average transcript profiles are shown for early upregulated genes (yellow, peaks at 0.5-1 hours), and the 3 hours (blue), 4.5 hours (red) and 9-12 hours (green) late upregulated genes and for the downregulated genes coding for photosynthesis proteins (brown). (B) Diagrammatic representation of redox regulation of the oxidative stress response.

Source: Reprinted with permission of Springer ([Mahalingam et al., 2005](http://www.springer.com)).

Figure 9-5 Composite diagram of major themes in the temporal evolution of the genetic response to ozone stress.

- 1 All of these studies describe common trends for changes in gene and protein expression
- 2 which occur in a variety of plant species exposed to O₃. While genes associated with
- 3 carbon assimilation and general metabolism are typically downregulated, genes
- 4 associated with signaling, catabolism, and defense are upregulated. The magnitude of
- 5 these changes in gene and protein expression appears to be related to plant species, age
- 6 and their sensitivity or tolerance to O₃.

9.3.3.3 Role of Phytohormones in Plant Response to Ozone

1 Many studies of O₃ effects on plants have analyzed the importance of plant hormones
2 such as SA, ET and JA in determining plant response to O₃. The 2006 O₃ AQCD
3 documents the O₃-induced production of ET and its role in promoting the formation of
4 leaf lesions. Transcriptome analysis and the use of a variety of mutants have allowed for
5 further elucidation of the complex interactions between SA, ET, JA and the role of
6 abscisic acid (ABA) in mediating plant response to O₃ ([Ludwikow and Sadowski, 2008](#)).
7 In addition to their roles in signaling pathways, phytohormones also appear to regulate,
8 and be regulated by, the MAPK signaling cascades described previously. Most evidence
9 suggests that while ET and SA are needed to develop O₃-induced leaf lesions, JA acts
10 antagonistically to SA and ET to limit the lesions ([Figure 9-6](#)) ([Kangasjarvi et al., 2005](#)).

11 The rapid production of ET in O₃ treated plants has been described in many plant species
12 and has been further characterized through the use of a variety of mutants that either
13 over-produce or are insensitive to ET. Production of stress ET in O₃-treated plants, which
14 is thought to be part of a wounding response, was found to be correlated to the degree of
15 injury development in leaves ([U.S. EPA, 2006b](#)). More recent studies have supported
16 these conclusions and have also focused on the interactions occurring between several
17 oxidative-stress induced phytohormones. [Yoshida et al. \(2009\)](#) determined that ET likely
18 amplifies the oxidative signal generated by ROS, thereby promoting lesion formation. By
19 analyzing the O₃-induced transcriptome of several Arabidopsis mutants of the Col-0
20 ecotype, [Tamaoki et al. \(2003\)](#) determined that at 12 hours after initiating the O₃
21 exposure (200 ppb for 12 hours), the ET and JA signaling pathways were the main
22 pathways used to activate plant defense responses, with a lesser role for SA. The authors
23 also demonstrated that low levels of ET production could stimulate the expression of
24 defense genes, rather than promoting cell death which occurs when ET production is
25 high. [Tosti et al. \(2006\)](#) supported these findings by showing that plant exposure to O₃
26 not only results in activation of the biosynthetic pathways of ET, JA and SA, but also
27 increases the expression of genes related to the signal transduction pathways of these
28 phytohormones in O₃-treated Arabidopsis plants (300 ppb O₃ for 6 hours). Conversely, in
29 the O₃ sensitive Ws ecotype, its sensitivity may, in part, be due to intrinsically high ET
30 levels leading to SA accumulation, and the high ET and SA may act to repress
31 JA-associated genes, which would serve to inhibit the spread of lesions ([Mahalingam et](#)
32 [al., 2006](#)). [Ogawa et al. \(2005\)](#) found that increases in SA in O₃-treated plants leads to the
33 formation of leaf lesions in tobacco plants exposed to 200 ppb O₃ for 6 hours.
34 Furthermore, in transgenic tobacco plants with reduced levels of ET production in
35 response to O₃ exposure, several genes encoding for enzymes in the biosynthetic pathway
36 of SA were suppressed, suggesting that SA levels are, in part, controlled by ET in the
37 presence of O₃.

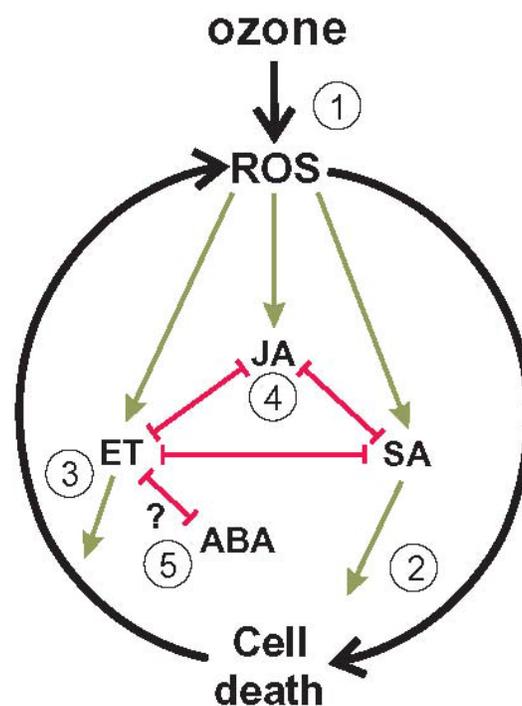
1 Exposure of the Arabidopsis mutant *rcd1* to acute doses of O₃ (250 ppb O₃ for 8-h/day for
2 3 days) resulted in programmed cell death (PCD) and the formation of leaf lesions
3 ([Overmyer et al., 2000](#)). They determined that the observed induction of ET synthesis
4 promotes cell death, and that ET perception and signaling are required for the
5 accumulation of superoxide, which leads to cell death and propagation of lesions.
6 Jasmonic acid, conversely, contains the spread of leaf lesions ([Overmyer et al., 2000](#)).
7 Transcriptome analysis of several Arabidopsis mutants, which are insensitive to SA, ET
8 and JA, exposed to 12-h of 200 ppb O₃ showed that approximately 78 of the upregulated
9 genes measured in this study were controlled by ET and JA signaling pathways, while SA
10 signaling pathways were suggested to antagonize ET and JA pathways ([Tamaoki et al.,
11 2003](#)). In a subsequent transcriptome study on the Col-0 ecotype exposed to 150 ppb O₃
12 for 48-h, JA and ET synthesis were downregulated, while SA was upregulated in O₃-
13 treated plants. In cotton plants exposed to a range of O₃ concentrations (0-120 ppb) and
14 methyl jasmonate (MeJA), [Grantz et al. \(2010b\)](#) determined that exogenous applications
15 of MeJA did not protect plants from chronic O₃ exposure.

16 Abscisic acid has been investigated for its role in regulating stomatal aperture and also
17 for its contribution to signaling pathways in the plant. The role of ABA and the
18 interaction between ABA and H₂O₂ in O₃-induced stomatal closure was described in the
19 2006 O₃ AQCD. It was determined that the presence of H₂O₂, which is formed from O₃
20 degradation, increases the sensitivity of guard cells to ABA and, therefore, more readily
21 results in stomatal closure. More recently, it was determined that synthesis of ABA was
22 induced in O₃-treated Arabidopsis plants (250-350 ppb O₃ for 6 hours), with a more
23 pronounced induction in the O₃ sensitive *rcd3* mutant as compared to the wildtype Col-0
24 ([Overmyer et al., 2008](#)). The *rcd3* mutant also exhibited a lack of O₃-induced stomatal
25 closure, and the RCD3 protein has been shown to be required for slow anion channels
26 ([Overmyer et al., 2008](#)). [Ludwikow et al. \(2009\)](#) used Arabidopsis ABI1td mutants, in
27 which a key negative regulator of ABA action (abscisic acid insensitive1 protein
28 phosphatase 2C) has been knocked out, to examine O₃ responsive genes in this mutant
29 compared to the Arabidopsis Col-0. Results of this study indicate a role for ABI1 in
30 negatively regulating the synthesis of both ABA and ET in O₃-treated plants (350 ppb O₃
31 for 9 hours). Additionally, ABI1 may stimulate JA-related gene expression, providing
32 evidence for an antagonistic interaction between ABA and JA signaling pathways
33 ([Ludwikow et al., 2009](#)).

34 Nitric oxide (NO) has also been shown to play a role in regulating gene expression in
35 plants in response to O₃ exposure. However, little is known to date about NO and its role
36 in the complex interactions of molecules in response to O₃. Exposure of tobacco to O₃
37 (150 ppb for 5 hours) stimulated NO and NO-dependent ET production, while NO
38 production itself did not depend on the presence of ET ([Ederli et al., 2006](#)). Analysis of

1 O₃-treated Arabidopsis indicated the possibility of a dual role for NO in the initiation of
2 cell death and later lesion containment ([Ahlfors et al., 2009](#)).

3 While much work remains to be done to better elucidate how plants detect O₃, what
4 determines their sensitivity to the pollutant and how they might respond to it, it is clear
5 that the mechanism for O₃ detection and signal transduction is very complex. Many of the
6 phytohormones and other signaling molecules thought to be involved in these processes
7 are interactive and depend upon a variety of other factors, which could be either internal
8 or external to the plant. This results in a highly dynamic and complex system, capable of
9 resulting in a spectrum of plant sensitivity to oxidative stress and generating a variety of
10 plant responses to that stress.



Note: Ozone-derived radicals induce endogenous ROS production (1) which results in salicylic acid (SA) accumulation and programmed cell death; (2) Cell death triggers ethylene (ET) production, which is required for the continuing ROS production responsible for the propagation of cell death; (3) Jasmonates counteract the progression of the cycle by antagonizing the cell death promoting function of SA and ET; (4) Abscisic acid (ABA) antagonizes ET function in many situations and might also have this role in ozone-induced cell death; (5) Mutually antagonistic interactions between ET, SA and jasmonic acid (JA) are indicated with red bars.

Source: Reprinted with permission of Blackwell Publishing Ltd. ([Kangasjarvi et al., 2005](#)).

Figure 9-6 The oxidative cell death cycle.

9.3.4 Detoxification

9.3.4.1 Overview of Ozone-induced Defense Mechanisms

1 Plants are exposed to an oxidizing environment on a continual basis, and many reactions
2 that are part of the basic metabolic processes, such as photosynthesis and respiration,
3 generate ROS. As a result, there is an extensive and complex mechanism in place to
4 detoxify these oxidizing radicals, including both enzymes and metabolites, which are
5 located in several locations in the cell and also in the apoplast of the cell. As O₃ enters the
6 leaf through open stomata, the first point of contact of O₃ with the plant is likely in the
7 apoplast, where it breaks down to form oxidizing radicals such as H₂O₂, O₂⁻, HO· and
8 HO₂. Another source of oxidizing radicals is an oxidative burst, generated by a
9 membrane-bound NADPH oxidase enzyme, which is recognized as an integral
10 component of the plant's defense system against pathogens ([Schraudner et al., 1998](#)).
11 Antioxidant metabolites and enzymes located in the apoplast are thought to form a first
12 line of defense by detoxifying O₃ and/or the ROS that are formed as breakdown products
13 of O₃ (Section [9.3.2](#)). However, even with the presence of several antioxidants, including
14 ascorbate, the redox buffering capacity of the apoplast is far less than that of the
15 cytoplasm, as it lacks the regeneration systems necessary to retain a reduced pool of
16 antioxidants ([Foyer and Noctor, 2005b](#)).

17 Redox homeostasis is regulated by the presence of a pool of antioxidants, which are
18 typically found in a reduced state and detoxify ROS produced by oxidases or electron
19 transport components. As ROS increase due to environmental stress such as O₃, it is
20 unclear whether the antioxidant pool can maintain its reduced state ([Foyer and Noctor,
21 2005b](#)). As such, not only the quantity and types of antioxidant enzymes and metabolites
22 present, but also the cellular ability to regenerate those antioxidants are important
23 considerations in mechanisms of plant tolerance to oxidative stress ([Dizengremel et al.,
24 2008](#)). Molecules such as glutathione (GSH), thioredoxins and NADPH play very
25 important roles in this regeneration process; additionally, it has been hypothesized that
26 alterations in carbon metabolism would be necessary to supply the needed reducing
27 power for antioxidant regeneration ([Dizengremel et al., 2008](#)).

9.3.4.2 Role of Antioxidants in Plant Defense Responses

28 Ascorbate has been the focus of many different studies as an antioxidant metabolite that
29 protects plants from exposure to O₃. It is found in several cellular locations, including the
30 chloroplast, the cytosol and the apoplast ([Noctor and Foyer, 1998](#)). Ascorbate is

1 synthesized in the cell and transported to the apoplast. Apoplastic ascorbate can be
2 oxidized to dehydroascorbate (DHA) with exposure to O₃ and is then transported back to
3 the cytoplasm. Here, DHA is reduced to ascorbate by the enzyme dehydroascorbate
4 reductase (DHAR) and reduced GSH, which is part of the ascorbate-glutathione cycle
5 ([Noctor and Foyer, 1998](#)). Many studies have focused on evaluating whether ascorbate is
6 the primary determining factor in differential sensitivity of plants to O₃. An evaluation of
7 several species of wildflowers in Great Smoky Mountains National Park showed a
8 correlation between higher quantities of reduced apoplastic ascorbate and lower levels of
9 foliar injury from O₃ exposure in a field study on tall milkweed plants (*Asclepias*
10 *exaltata* L.) ([Burkey et al., 2006](#); [Souza et al., 2006](#)). [Cheng et al. \(2007\)](#) exposed two
11 soybean cultivars to elevated O₃ (77 ppb) and filtered air for 7-h/day for 6 days. The
12 differences in sensitivity between the two cultivars could not be explained by differential
13 O₃ uptake or by the fraction of reduced ascorbate present in the apoplast. However, total
14 antioxidant capacity of the apoplast was 2-fold higher in the tolerant Essex cultivar as
15 compared to the sensitive Forrest cultivar, indicating that there may be other compounds
16 in the leaf apoplast that scavenge ROS. [D'Haese et al. \(2005\)](#) exposed the NC-S
17 (sensitive) and NC-R (resistant) clones of white clover (*Trifolium repens*) to 60 ppb O₃
18 for 7-h/day for 5 days in environmental chambers. Surprisingly, the NC-S clone had a
19 higher constitutive concentration of apoplastic ascorbate with a higher redox status than
20 the NC-R clone. However, the redox status of symplastic GSH was higher in NC-R, even
21 though the concentration of GSH was not higher than in NC-S. In addition, total
22 symplastic antioxidative capacity was not a determining factor in differential sensitivity
23 between these two clones. [Severino et al. \(2007\)](#) also examined the role of antioxidants in
24 the differential sensitivity of the two white clover clones by growing them in the field for
25 a growing season and then exposing them to elevated O₃ (100 ppb for 8-h/day for
26 10 days) in OTC at the end of the field season. The NC-R clone had greater quantities of
27 total ascorbate and total antioxidants than the NC-S clone at the end of the experiment. In
28 snap bean, plants of the O₃ tolerant Provider cultivar had greater total ascorbate and more
29 ascorbate in the apoplast than the sensitive S156 cultivar after exposure to 71 ppb O₃ for
30 10 days in OTC ([Burkey et al., 2003](#)). While most of the apoplastic ascorbate was in the
31 oxidized form, the ratio of reduced ascorbate to total ascorbate was higher in Provider
32 than S156, indicating that Provider is better able to maintain this ratio to maximize plant
33 protection from oxidative stress. Exposure of two wheat varieties to ambient (7-h average
34 44 ppb O₃) and elevated (7-h average 56 ppb O₃) O₃ for 60 days in open-air field
35 conditions showed higher concentrations of reduced ascorbate in the apoplast in the
36 tolerant Y16 variety than the more sensitive Y2 variety, however no varietal differences
37 were seen in the decrease in reduced ascorbate quantity in response to O₃ exposure ([Feng](#)
38 [et al., 2010](#)). There is much evidence that supports an important role for ascorbate,
39 particularly apoplastic ascorbate, in protecting plants from oxidative stressors such as O₃;

1 however, it is also clear that there is much variation in the importance of ascorbate for
2 different plant species and differing exposure conditions. Additionally, the work of
3 several authors suggests that there may be other compounds in the apoplast which have
4 the capacity to act as antioxidants.

5 While the quantities of antioxidant metabolites such as ascorbate are an important
6 indicator of plant tolerance to O₃, the ability of the plant to recycle oxidized ascorbate
7 efficiently also plays a large role in determining the plant's ability to effectively protect
8 itself from sustained exposure to oxidative stress. Tobacco plants over-expressing DHAR
9 were better protected from exposure to either chronic (100 ppb O₃ 4-h/day for 30 days) or
10 acute (200 ppb O₃ for 2 hours) O₃ conditions than control plants and those with reduced
11 expression of DHAR ([Chen and Gallie, 2005](#)). The DHAR over-expressing plants
12 exhibited an increase in guard cell ascorbic acid, leading to a decrease in stomatal
13 responsiveness to O₃ and an increase in stomatal conductance and O₃ uptake. Despite
14 this, the presence of higher levels of ascorbic acid led to a lower oxidative load and a
15 higher level of photosynthetic activity in the DHAR over-expressing plants ([Chen and
16 Gallie, 2005](#)). A subsequent study with tobacco plants over-expressing DHAR confirmed
17 some of these results. Levels of ascorbic acid were higher in the transgenic tobacco
18 plants, and they exhibited greater tolerance to O₃ exposure (200 ppb O₃) as demonstrated
19 by higher photosynthetic rates in the transgenic plants as compared to the control plants
20 ([Eltayeb et al., 2006](#)). Over-expression of monodehydroascorbate reductase (MDAR) in
21 tobacco plants also showed enhanced stress tolerance in response to O₃ exposure
22 (200 ppb O₃), with higher rates of photosynthesis and higher levels of reduced ascorbic
23 acid as compared to controls ([Eltayeb et al., 2007](#)). Results of these studies demonstrate
24 the importance of ascorbic acid as a detoxification mechanism in some plant species, and
25 also emphasize that the recycling of oxidized ascorbate to maintain a reduced pool of
26 ascorbate is a factor in determining plant tolerance to oxidative stress.

27 The roles of other antioxidant metabolites and enzymes, including GSH, catalase (CAT),
28 peroxidase (POD) and superoxide dismutase (SOD), were comprehensively reviewed in
29 the 2006 O₃ AQCD. Based on the review of the literature, no conclusive and consistent
30 effects of O₃ on the quantity of GSH and CAT could be identified. Both apoplastic and
31 cytosolic POD activity increased in response to O₃ exposure, while various isoforms of
32 SOD showed inconsistent changes in quantity in response to O₃. Additional studies have
33 been conducted to further elucidate the roles of these antioxidant enzymes and
34 metabolites in protecting plants from oxidative stress. Superoxide dismutase and POD
35 activities were measured in both the tolerant Bel B and sensitive Bel W3 tobacco
36 cultivars exposed to ambient O₃ concentrations for 2 weeks 3 times throughout a growing
37 season ([Borowiak et al., 2009](#)). In this study, SOD and POD activity, including that of
38 several different isoforms, increased in both the sensitive and tolerant tobacco cultivars

1 with exposure to O₃, however the isoenzyme composition for POD differed between the
2 sensitive and tolerant tobacco cultivars ([Borowiak et al., 2009](#)) Tulip poplar
3 (*Liriodendron tulipifera*) trees exposed to increasing O₃ concentrations (from 100 to
4 300 ppb O₃ during a 2-week period) showed increases in activities of SOD, ascorbate
5 peroxidase (APX), glutathione reductase (GR), MDAR, DHAR, CAT and POD in the
6 2-week period, although individual enzyme activities increased at different times during
7 the 2-week period ([Ryang et al., 2009](#)).

8 Longer, chronic O₃ exposures in trees revealed increases in SOD and APX activity in
9 *Quercus mongolica* after 45 days of plant exposure to 80 ppb O₃, which were followed by
10 declines in the activities and quantities of these enzymes after 75 days of exposure ([Yan](#)
11 [et al., 2010](#)). Similarly, activities of SOD, APX, DHAR, MDAR, and GR increased in
12 *Ginkgo biloba* trees during the first 50 days of exposure to 80 ppb O₃, followed by
13 decreases in activity below control values after 50 days of exposure ([He et al., 2006](#)).
14 Soybean plants exposed to 70 or 100 ppb O₃ for 4-h/day over the course of a growing
15 season showed elevated POD activity and a decrease in CAT activity at 40 and 60 days
16 after germination ([Singh et al., 2010a](#)).

17 Antioxidant enzymes and metabolites have been shown to play an important role in
18 determining plant tolerance to O₃ and mediating plant responses to O₃. However, there is
19 also some evidence to suggest that the direct reaction of ascorbate with O₃ could lead to
20 the formation of secondary toxicants, such as peroxy compounds, which may act upon
21 signal transduction pathways and modulate plant response to O₃ ([Sandermann, 2008](#)).
22 Therefore, the role of ascorbate and other antioxidants and their interaction with other
23 plant responses to O₃, such as the activation of signal transduction pathways, is likely far
24 more complex than is currently understood.

9.3.5 Effects on Primary and Secondary Metabolism

9.3.5.1 Light and Dark Reactions of Photosynthesis

25 Declines in the rate of photosynthesis and stomatal conductance in O₃-treated plants have
26 been documented for many different plant species ([Booker et al., 2009](#); [Wittig et al.,](#)
27 [2007](#); [U.S. EPA, 2006b](#)). The 2006 O₃ AQCD described the mechanism by which plant
28 exposure to O₃ reduces the quantity of Rubisco, and the more recent scientific literature
29 confirms these findings. While several measures of the light reactions of photosynthesis
30 are sensitive to exposure to O₃ (see below), photosynthetic carbon assimilation is
31 generally considered to be more affected by pollutant exposure, resulting in an overall
32 decline in photosynthesis ([Guidi and Degl'Innocenti, 2008](#); [Heath, 2008](#); [Fiscus et al.,](#)

1 [2005](#)). Loss of carbon assimilation capacity has been shown to result primarily from
2 declines in the quantity of Rubisco ([Singh et al., 2009](#); [Calatayud et al., 2007a](#)).
3 Experimental evidence suggests that both decreases in Rubisco synthesis and enhanced
4 degradation of the protein contribute to the measured reduction in its quantity ([U.S. EPA,](#)
5 [2006b](#)). Reduced carbon assimilation has been linked to reductions in biomass and yield
6 ([Wang et al., 2009b](#); [He et al., 2007](#); [Novak et al., 2007](#); [Gregg et al., 2006](#); [Keutgen et](#)
7 [al., 2005](#)). Recent studies evaluating O₃ induced changes in the transcriptome and
8 proteome of several different species confirm these findings. Levels of mRNA for the
9 small subunit of Rubisco (rbcS) declined in European beech saplings exposed to 300 ppb
10 O₃ for 8-h/day for up to 26 days ([Olbrich et al., 2005](#)). Similar declines in rbcS mRNA
11 were also measured in the beech saplings in a free air exposure system over a course of
12 two growing seasons ([Olbrich et al., 2009](#)). Proteomics studies have also confirmed the
13 effects of O₃ on proteins involved in carbon assimilation. Reductions in quantities of the
14 small and large subunit (rbcL) of Rubisco and Rubisco activase were measured in
15 soybean plants exposed to 120 ppb O₃ for 3 days in growth chambers ([Ahsan et al.,](#)
16 [2010](#)). Exposure of young poplar trees to 120 ppb O₃ for 35 days in exposure chambers
17 resulted in reductions of Rubisco, Rubisco activase, and up to 24 isoforms of Calvin
18 cycle enzymes, most of which play a role in regenerating the CO₂ acceptor molecule,
19 ribulose-1.5-bisphosphate ([Bohler et al., 2007](#)). Reductions in protein quantity of both the
20 small and large subunit of Rubisco were seen in wheat plants exposed to ambient
21 (average concentration 47.3 ppb O₃) and elevated O₃ (ambient + 10 or 20 ppb O₃) in
22 open-top chambers for 5-h/day for 50 days ([Sarkar et al., 2010](#)). Lettuce plants exposed
23 to 100 ppb O₃ in growth chambers for 8-h/day for 3 weeks also showed reductions in
24 transcript and protein levels of the small and large subunits of Rubisco and Rubisco
25 activase ([Goumenaki et al., 2010](#)). The reductions in carbon assimilation have been
26 associated with declines in both the mRNA of the small and large subunits of Rubisco,
27 and with reductions in Rubisco activase mRNA and protein. Additionally, the reduction
28 in Rubisco quantity has also been associated with the O₃-induced oxidative modification
29 of the enzyme, which is evidenced by the increases in carbonyl groups on the protein
30 after plant exposure to O₃.

31 In addition to impacts on carbon assimilation, the deleterious effects of O₃ on the
32 photosynthetic light reactions have received more attention in recent years. Chlorophyll
33 fluorescence provides a useful measure of changes to the photosynthetic process from
34 exposure to oxidative stress. Decreases in the Fv/Fm ratio (a measure of the maximum
35 efficiency of Photosystem II) in dark adapted leaves indicate a decline in the efficiency of
36 the PSII photosystems and a concomitant increase in non-photochemical quenching
37 ([Guidi and Degl'Innocenti, 2008](#); [Scabba et al., 2006](#)). Changes in these parameters have
38 been correlated to differential sensitivity of plants to the pollutant. In a study to evaluate
39 the response of 4 maple species to O₃ (exposed to an 8-h avg of 51 ppb for ambient and

1 79 ppb for elevated treatment in OTC), the 2 species which were most sensitive based on
2 visible injury and declines in CO₂ assimilation also showed the greatest decreases in
3 Fv/Fm in symptomatic leaves. In asymptomatic leaves, CO₂ assimilation decreased
4 significantly but there was no significant decline in Fv/Fm ([Calatayud et al., 2007a](#)).
5 [Degl'Innocenti et al. \(2007\)](#) measured significant decreases in Fv/Fm in young and
6 symptomatic leaves of a resistant tomato genotype (line 93.1033/1) in response to O₃
7 exposure (150 ppb O₃ for 3 hours in a growth chamber), but only minor decreases in
8 asymptomatic leaves with no associated changes in net photosynthetic rate. In the O₃
9 sensitive tomato cultivar Cuor Di Bue, the Fv/Fm ratio did not change, while the
10 photosynthetic rate declined significantly in asymptomatic leaves ([Degl'Innocenti et al.,](#)
11 [2007](#)). In two soybean cultivars, Fv/Fm also declined significantly with plant exposure to
12 O₃ ([Singh et al., 2009](#)). It appears that in asymptomatic leaves, photoinhibition, as
13 indicated by a decrease in Fv/Fm, is not the main reason for a decline in photosynthesis.

14 An evaluation of photosynthetic parameters of two white clover (*Trifolium repens* cv.
15 Regal) clones that differ in their O₃ sensitivity revealed that O₃ (40-110 ppb O₃ for 7-
16 h/day for 5 days) increased the coefficient of non-photochemical quenching (q_{NP}) in both
17 the resistant (NC-R) and sensitive (NC-S) clones, however q_{NP} was significantly lower
18 for the sensitive clone ([Crous et al., 2006](#)). Sensitive *Acer* clones had a lower coefficient
19 of non-photochemical quenching, while exposure to O₃ increased q_{NP} in both sensitive
20 and tolerant clones ([Calatayud et al., 2007a](#)). While exposure to O₃ also increased q_{NP} in
21 tomato, there were no differences in the coefficient of photochemical quenching between
22 cultivars thought to be differentially sensitive to O₃ ([Degl'Innocenti et al., 2007](#)). Higher
23 q_{NP} as a result of exposure to O₃ indicates a reduction in the proportion of absorbed light
24 energy being used to drive photochemistry. A lower coefficient of non-photochemical
25 quenching in O₃ sensitive plants could indicate increased vulnerability to ROS generated
26 during exposure to oxidative stress ([Crous et al., 2006](#)).

27 Most of the research on O₃ effects on photosynthesis has focused on C3 (Calvin cycle)
28 plants because C4 (Hatch-Slack) plants have lower stomatal conductance and are,
29 therefore, thought to be less sensitive to O₃ stress. However, some studies have been
30 conducted to evaluate the effects of O₃ on C4 photosynthesis. In older maize leaves,
31 [Leitao et al. \(2007c\)](#); [Leitao et al. \(2007a\)](#) found that the activity, quantity and transcript
32 levels of both Rubisco and phosphoenolpyruvate carboxylase (PEPc) decreased as a
33 function of rising O₃ concentration. In younger maize leaves, the quantity, activity, and
34 transcript levels of the carboxylases were either increased or unaffected in plants exposed
35 to 40 ppb O₃ for 7- h/day for 28-33 days, but decreased at 80 ppb ([Leitao et al., 2007b](#);
36 [Leitao et al., 2007c](#)). In another study, [Grantz and Vu \(2009\)](#) reported that O₃ exposures
37 (4, 58, and 114 ppb, 12-hour mean) decreased sugarcane biomass production by more
38 than one third and allocation to roots by more than two thirds.

9.3.5.2 Respiration and Dark Respiration

1 While much research emphasis regarding O₃ effects on plants has focused on the negative
2 impacts on carbon assimilation, other studies have measured impacts on catabolic
3 pathways such as shoot respiration and photorespiration. Generally, shoot respiration has
4 been found to increase in plants exposed to O₃. Bean plants exposed to ambient (average
5 12-h mean 43 ppb) and twice ambient (average 12-h mean 80 ppb) O₃ showed increases
6 in respiration. When mathematically partitioned, the maintenance coefficient of
7 respiration was significantly increased in O₃ treated plants, while the growth coefficient
8 of respiration was not affected ([Amthor, 1988](#)). Loblolly pines were exposed to ambient
9 (12-h daily mean was 45 ppb) and twice ambient (12 hours daily mean was 86 ppb) O₃
10 for 12-h/day for approximately seven months per year for 3 and 4 years. While
11 photosynthetic activity declined with the age of the needles and increasing O₃
12 concentration, enzymes associated with respiration showed higher levels of activity with
13 increasing O₃ concentration ([Dizengremel et al., 1994](#)). In their review on the role of
14 metabolic changes in plant redox status after O₃ exposure, [Dizengremel et al. \(2009\)](#)
15 summarized multiple studies in which several different tree species were exposed to O₃
16 concentrations ranging from ambient to 200 ppb O₃ for at least several weeks. In all
17 cases, the activity of enzymes, including phosphofructokinase, pyruvate kinase and
18 fumarase, which are part of several catabolic pathways, were increased in O₃ treated
19 plants.

20 Photorespiration is a light-stimulated process which consumes O₂ and releases CO₂.
21 While it has been regarded as a wasteful process, more recent evidence suggests that it
22 may play a role in photoprotection during photosynthesis ([Bagard et al., 2008](#)). The few
23 studies that have been conducted on O₃ effects on photorespiration suggest that rates of
24 photorespiration decline concomitantly with rates of photosynthesis. Soybean plants were
25 exposed to ambient (daily averages 43-58 ppb) and 1.5 ambient O₃ (daily averages 63-
26 83 ppb) O₃ in OTCs for 12-h/day for 4 months. Rates of photosynthesis and
27 photorespiration and photorespiratory enzyme activity declined only at the end of the
28 growing season and did not appear to be very sensitive to O₃ exposure ([Booker et al.,
29 1997](#)). Young hybrid poplars exposed to 120 ppb O₃ for 13-h/day for 35 days in
30 phytotron chambers showed that effects on photorespiration and photosynthesis were
31 dependent upon the developmental stage of the leaf. While young leaves were not
32 impacted, reductions in photosynthesis and photorespiration were measured in fully
33 expanded leaves ([Bagard et al., 2008](#)).

9.3.5.3 Secondary Metabolism

1 Transcriptome analysis of Arabidopsis plants has revealed modulation of several genes
2 involved in plant secondary metabolism ([Ludwikow and Sadowski, 2008](#)). Phenylalanine
3 ammonia lyase (PAL) has been the focus of many studies involving plant exposure to O₃
4 due to its importance in linking the phenylpropanoid pathway of plant secondary
5 metabolism to primary metabolism in the form of the shikimate pathway. Genes encoding
6 several enzymes of the phenylpropanoid pathway and lignin biosynthesis were
7 upregulated in transcriptome analysis of Arabidopsis plants (Col-0) exposed to 350 ppb
8 O₃ for 6 hours, while 2 genes involved in flavonoid biosynthesis were downregulated
9 ([Ludwikow et al., 2004](#)). Exposure of Arabidopsis (Col-0) to lower O₃ concentrations
10 (150 ppb for 8-h/day for 2 days) resulted in the induction of 11 transcripts involved in
11 flavonoid synthesis. In their exposure of 2-year-old Mediterranean shrub *Phillyrea*
12 *latifolia* to 110 ppb O₃ for 90 days, [Paolacci et al. \(2007\)](#) identified four clones that were
13 upregulated and corresponded to genes involved in the synthesis of secondary
14 metabolites, such as isoprenoids, polyamines and phenylpropanoids. Upregulation of
15 genes involved in isoprene synthesis was also observed in *Medicago trunculata* exposed
16 to 300 ppb O₃ for 6 hours, while genes encoding enzymes of the flavonoid synthesis
17 pathway were either upregulated or downregulated ([Puckette et al., 2008](#)). Exposure of
18 red clover to 1.5 × ambient O₃ (average concentrations of 32.4 ppb) for up to 9 weeks in
19 an open field exposure system resulted in increases in leaf total phenolic content.
20 However, the types of phenolics that were increased in response to O₃ exposure differed
21 depending upon the developmental stage of the plant. While almost all of the 31 different
22 phenolic compounds measured increased in quantity initially during the exposure, after
23 3 weeks the quantity of isoflavones decreased while other phenolics increased ([Saviranta](#)
24 [et al., 2010](#)). Exposure of beech saplings to ambient and 2 × ambient O₃ concentrations
25 over 2 growing seasons resulted in the induction of several enzymes which contribute to
26 lignin formation, while enzymes involved in flavonoid biosynthesis were downregulated
27 ([Olbrich et al., 2009](#)). Exposure of tobacco Bel W3 to 160 ppb O₃ for 5 hours showed
28 upregulation of almost all genes encoding for enzymes which are part of the
29 prechorismate pathway ([Janzik et al., 2005](#)). Isoprenoids can serve as antioxidant
30 compounds in plants exposed to oxidative stress ([Paolacci et al., 2007](#)).

31 The prechorismate pathway is the pathway leading to the formation of chorismate, a
32 precursor to the formation of the aromatic amino acids tryptophan, tyrosine and
33 phenylalanine. These amino acids are precursors for the formation of many secondary
34 aromatic compounds, and, therefore, the prechorismate pathway represents a branch-
35 point in the regulation of metabolites into either primary or secondary metabolism ([Janzik](#)
36 [et al., 2005](#)). Exposure of the O₃ sensitive Bel W3 tobacco cultivar at 160 ppb for 5 hours
37 showed an increase in transcript levels of most of the genes encoding enzymes of the

1 prechorismate pathway. However, shikimate kinase (SK) did not show any change in
2 transcript levels and only one of three isoforms of DAHPS (3-deoxy-D-arabino-
3 heptulosonate-7-phosphate synthase), the first enzyme in this pathway, was induced by O₃
4 exposure ([Janzik et al., 2005](#)). Differential induction of DAHPS isoforms was also
5 observed in European beech after 40 days of exposure to 150-190 ppb O₃. At this time
6 point in the beech experiment, transcript levels of shikimate pathway enzymes, including
7 SK, were generally strongly induced after an only weak initial induction after the first
8 40 days of exposure. Both soluble and cell-wall bound phenolic metabolites showed only
9 minimal increases in response to O₃ for the duration of the exposure period ([Alonso et al.,
10 2007](#)). Total leaf phenolics decreased with leaf age in *Populus nigra* exposed to 80 ppb
11 O₃ for 12-h/day for 14 days. Ozone increased the concentration of total leaf phenolics in
12 newly expanded leaves, with the greatest increases occurring in compounds such as
13 quercetin glycoside, which has a high antioxidant capacity ([Fares et al., 2010b](#)). While
14 several phenylpropanoid pathway enzymes were induced in two poplar clones exposed to
15 60 ppb O₃ for 5-h/day for 15 days, the degree of induction differed between the two
16 clones. In the tolerant I-214 clone, PAL activity increased 9-fold in O₃-treated plants as
17 compared to controls, while there was no significant difference in PAL activity in the
18 sensitive Eridano clone ([DiBaccio et al., 2008](#)).

19 Polyamines such as putrescine, spermidine and spermine play a variety of roles in plants
20 and have been implicated in plant defense responses to both abiotic and biotic stresses.
21 They exist in both a free form and conjugated to hydroxycinnamic acids. Investigations
22 on the role of polyamines have found that levels of putrescine increase in response to
23 oxidative stress. This increase stems largely from the increase in the activity of arginine
24 decarboxylase (ADC), a key enzyme in the synthesis of putrescine ([Groppa and
25 Benavides, 2008](#)). [Langebartels et al. \(1991\)](#) described differences in putrescine
26 accumulation in O₃-treated tobacco plants exposed to several O₃ concentrations, ranging
27 from 0-400 ppb for 5-7 hours. A large and rapid increase in putrescine occurred in the
28 tolerant Bel B cultivar and only a small increase in the sensitive Bel W3 cultivar, which
29 occurred only after the formation of necrotic leaf lesions. [Van Buuren et al. \(2002\)](#)
30 further examined the role of polyamines in these two tobacco cultivars during an acute
31 (130 ppb O₃ for 7-h in a growth chamber) exposure. They found that while free
32 putrescine accumulated in undamaged tissue of both cultivars, conjugated putrescine
33 predominantly accumulated in tissues undergoing cell death after plant exposure to O₃
34 ([Van Buuren et al., 2002](#)). The authors suggest that while free putrescine may not play a
35 role in conferring tolerance in the Bel B cultivar, conjugated putrescine may play a role in
36 O₃-induced programmed cell death in Bel W3 plants.

37 Isoprene is emitted by some plant species and represents the predominant biogenic source
38 of hydrocarbon emissions in the atmosphere ([Guenther et al., 2006](#)). In the atmosphere,

1 the oxidation of isoprene by hydroxyl radicals can enhance O₃ formation in the presence
2 of NO_x, thereby impacting the O₃ concentration that plants are exposed to. While
3 isoprene emission varies widely between species, it has been proposed to stabilize
4 membranes and provide those plant species that produce it with a mechanism of
5 thermotolerance ([Sharkey et al., 2008](#)). It has also been suggested that isoprene may act
6 as an antioxidant compound to scavenge O₃ ([Loreto and Velikova, 2001](#)). Recent studies
7 using a variety of plant species have shown conflicting results in trying to understand the
8 effects of O₃ on isoprene emission. Exposure to acute doses of O₃ (300 ppb for 3-h) in
9 detached leaves of *Phragmites australis* resulted in stimulation of isoprene emissions
10 ([Velikova et al., 2005](#)). Similar increases in isoprene emissions were measured in
11 *Populus nigra* after exposure to 100 ppb O₃ for 5 days continuously ([Fares et al., 2008](#)).
12 Isoprene emission in attached leaves of *Populus alba*, which were exposed to 150 ppb O₃
13 for 11-h/day for 30 days inside cuvettes, was inhibited, while isoprene emission and
14 transcript levels of isoprene synthase mRNA were increased in the leaves exposed to
15 ambient O₃ (40 ppb), which were located above the leaves enclosed in the exposure
16 cuvettes ([Fares et al., 2006](#)). Exposure of 2 genotypes of hybrid poplar to 120 ppb O₃ for
17 6-h/day for 8 days resulted in a significant reduction in isoprene emission in the O₃-
18 sensitive but not the tolerant genotype ([Ryan et al., 2009](#)). Similarly, O₃ treatment
19 (80 ppb 12-h/day for 14 days) of *Populus nigra* showed that isoprene emission was
20 reduced in the treated plants relative to the control plants ([Fares et al., 2010b](#)). Based on
21 results of this and other studies, [Fares et al. \(2010b\)](#) concluded that the isoprenoid
22 pathway may be induced in plants exposed to acute O₃ doses, while at lower doses
23 isoprene emission may be inhibited. [Vickers et al. \(2009\)](#) developed transgenic tobacco
24 plants with the isoprene synthase gene from *Populus alba* and exposed them to 120 ppb
25 O₃ for 6-h/day for 2 days. They determined that the wildtype plants showed significantly
26 more O₃ damage, including the development of leaf lesions and a decline in
27 photosynthetic rates, than the transgenic, isoprene-emitting plants. Transgenic plants also
28 accumulated less H₂O₂ and had lower levels of lipid peroxidation following exposure to
29 O₃ than the wildtype plants ([Vickers et al., 2009](#)). These results indicate that isoprene
30 may have a protective role for plants exposed to oxidative stress.

9.3.6 Summary

31 The results of recent studies on the effects of O₃ stress on plants support and strengthen
32 those reported in the 2006 O₃ AQCD. The most significant new body of evidence since
33 the 2006 O₃ AQCD comes from research on molecular mechanisms of the biochemical
34 and physiological changes observed in many plant species in response to O₃ exposure.
35 Recent studies have employed new techniques, such as those used in evaluating

1 transcriptomes and proteomes to perform very comprehensive analyses of changes in
2 gene transcription and protein expression in plants exposed to O₃. These newer molecular
3 studies not only provide very important information regarding the many mechanisms of
4 plant responses to O₃, they also allow for the analysis of interactions between various
5 biochemical pathways which are induced in response to O₃. However, many of these
6 studies have been conducted in artificial conditions with model plants, which are
7 typically exposed to very high, short doses of O₃. Therefore, additional work remains to
8 elucidate whether these plant responses are transferable to other plant species exposed to
9 more realistic ambient conditions.

10 Ozone is taken up into leaves through open stomata. Once inside the substomatal cavity,
11 O₃ is thought to rapidly react with the aqueous layer surrounding the cell (apoplast) to
12 form breakdown products such as hydrogen peroxide (H₂O₂), superoxide (O₂⁻), hydroxyl
13 radicals (HO[·]) and peroxy radicals (HO₂[·]). Plants could be detecting the presence of O₃
14 and/or its breakdown products in a variety different ways, depending upon the plant
15 species and the exposure parameters. Experimental evidence suggests that mitogen-
16 activated protein kinases and calcium are important components of the signal
17 transduction pathways, which communicate signals to the nucleus and lead to changes in
18 gene expression in response to O₃. It is probable that there are multiple detection
19 mechanisms and signal transduction pathways, and their activation may depend upon the
20 plant species, its developmental stage and/or O₃ exposure conditions. Initiation of signal
21 transduction pathways in O₃ treated plants has also been observed in stomatal guard cells.
22 Reductions in stomatal conductance have been described for many plant species exposed
23 to O₃, and new experimental evidence suggests that this reduction may be due not only to
24 a decrease in carboxylation efficiency, but also to a direct impact of O₃ on stomatal guard
25 cell function, leading to a changes in stomatal conductance.

26 Alterations in gene transcription that have been observed in O₃-treated plants are now
27 evaluated more comprehensively using DNA microarray studies, which measure changes
28 in the entire transcriptome rather than measuring the transcript levels of individual genes.
29 These studies have demonstrated very consistent trends, even though O₃ exposure
30 conditions (concentration, duration of exposure), plant species and sampling times vary
31 significantly. Genes involved in plant defense, signaling, and those associated with the
32 synthesis of plant hormones and secondary metabolism are generally upregulated in
33 plants exposed to O₃, while those related to photosynthesis and general metabolism are
34 typically downregulated. Proteome studies support these results by demonstrating
35 concomitant increases or decreases in the proteins encoded by these genes. Transcriptome
36 analysis has also illuminated the complex interactions that exist between several different
37 phytohormones and how they modulate plant sensitivity and response to O₃.
38 Experimental evidence suggests that while ethylene and salicylic acid are needed to

1 develop O₃-induced leaf lesions, jasmonic acid acts antagonistically to ethylene and
2 salicylic acid to limit the spread of the lesions. Abscisic acid, in addition to its role in
3 regulating stomatal aperture, may also act antagonistically to the jasmonic acid signaling
4 pathway. Changes in the quantity and activity of these phytohormones and the
5 interactions between them reveal some of the complexity of plant responses to an
6 oxidative stressor such as O₃.

7 Another critical area of interest is to better understand and quantify the capacity of the
8 plant to detoxify oxygen radicals using antioxidant metabolites, such as ascorbate and
9 glutathione, and the enzymes that regenerate them. Ascorbate remains an important focus
10 of research, and, due to its location in the apoplast in addition to other cellular
11 compartments, it is regarded as a first line of defense against oxygen radicals formed in
12 the apoplast. Most studies demonstrate that antioxidant metabolites and enzymes increase
13 in quantity and activity in plants exposed to O₃, indicating that they play an important
14 role in protecting plants from oxidative stress. However, attempts to quantify the
15 detoxification capacity of plants have remained unsuccessful, as high quantities of
16 antioxidant metabolites and enzymes do not always translate into greater protection of the
17 plant. Considerable variation exists between plant species, different developmental
18 stages, and the environmental and O₃ exposure conditions which plants are exposed to.

19 As indicated earlier, the described alterations in transcript levels of genes correlate with
20 observed changes quantity and activity of the enzymes and metabolites involved in
21 primary and secondary metabolism. In addition to the generalized upregulation of the
22 antioxidant defense system, photosynthesis typically declines in O₃ treated plants.
23 Declines in C fixation due to reductions in quantity and activity of Rubisco were
24 extensively described in the 2006 O₃ AQCD. More recent studies support these results
25 and indicate that declines in Rubisco activity may also result from reductions in Rubisco
26 activase enzyme quantity. Other studies, which have focused on the light reactions of
27 photosynthesis, demonstrate that plant exposure to O₃ results in declines in electron
28 transport efficiency and a decreased capacity to quench oxidizing radicals. Therefore, the
29 overall declines in photosynthesis observed in O₃-treated plants likely result from
30 combined impacts on stomatal conductance, carbon fixation and the light reactions.
31 While photosynthesis generally declines in plants exposed to O₃, catabolic pathways such
32 as respiration have been shown to increase. It has been hypothesized that increased
33 respiration may result from greater energy needs for defense and repair. Secondary
34 metabolism is generally upregulated in a variety of species exposed to O₃ as a part of a
35 generalized plant defense mechanism. Some secondary metabolites, such as flavonoids
36 and polyamines, are of particular interest as they are known to have antioxidant
37 properties. The combination of decreases in C assimilation and increases in catabolism

1 and the production of secondary metabolites would negatively impact plants by
2 decreasing the energy available for growth and reproduction.

9.4 Nature of Effects on Vegetation and Ecosystems

9.4.1 Introduction

3 Ambient O₃ concentrations have long been known to cause visible symptoms, decreases
4 in photosynthetic rates, decreases in growth and yield of plants as well as many other
5 effects on ecosystems ([U.S. EPA, 2006b](#), [1996c](#), [1986](#), [1978a](#)). Numerous studies have
6 related O₃ exposure to plant responses, with most effort focused on the yield of crops and
7 the growth of tree seedlings. Many experiments exposed individual plants grown in pots
8 or soil under controlled conditions to known concentrations of O₃ for a segment of
9 daylight hours for some portion of the plant's life span. Information in this section also
10 goes beyond individual plant-scale responses to consider effects at the broader ecosystem
11 scale, including effects related to ecosystem services.

12 This section will focus mainly on studies published since the release of the 2006 O₃
13 AQCD. However, because much O₃ research was conducted prior to the 2006 O₃ AQCD,
14 the present discussion of vegetation and ecosystem response to O₃ exposure is largely
15 based on the conclusions of the 1978, 1986, 1996, and 2006 O₃ AQCDs.

9.4.1.1 Ecosystem Scale, Function, and Structure

16 Information presented in this section was collected at multiple spatial scales or levels of
17 biological organization, ranging from the physiology of a given species to population,
18 community, and ecosystem investigations. An ecological population is a group of
19 individuals of the same species and a community is an assemblage of populations of
20 different species interacting with one another that inhabit an area. For this assessment,
21 "ecosystem" is defined as the interactive system formed from all living organisms and
22 their abiotic (physical and chemical) environment within a given area ([IPCC, 2007a](#)). The
23 boundaries of what could be called an ecosystem are somewhat arbitrary, depending on
24 the focus of interest or study. Thus, the extent of an ecosystem may range from very
25 small spatial scales or levels of biological organization to, ultimately, the entire Earth
26 ([IPCC, 2007a](#)). All ecosystems, regardless of size or complexity, have interactions and
27 physical exchanges between biota and abiotic factors, this includes both structural

1 (e.g., soil type and food web trophic levels) and functional (e.g., energy flow,
2 decomposition, nitrification) attributes.

3 Ecosystems can be described, in part, by their structure, i.e., the number and type of
4 species present. Structure may refer to a variety of measurements including the species
5 richness, abundance, community composition and biodiversity as well as landscape
6 attributes. Competition among and within species and their tolerance to environmental
7 stressors are key elements of survivorship. When environmental conditions are shifted,
8 for example, by the presence of anthropogenic air pollution, these competitive
9 relationships may change and tolerance to stress may be exceeded. Ecosystems may also
10 be defined on a functional basis. “Function” refers to the suite of processes and
11 interactions among the ecosystem components and their environment that involve
12 nutrient and energy flow as well as other attributes including water dynamics and the flux
13 of trace gases. Plants, via such processes as photosynthesis, respiration, C allocation,
14 nutrient uptake and evaporation, affect energy flow, C, nutrient cycling and water
15 cycling. The energy accumulated and stored by vegetation (via photosynthetic C capture)
16 is available to other organisms. Energy moves from one organism to another through
17 food webs, until it is ultimately released as heat. Nutrients and water can be recycled. Air
18 pollution alters the function of ecosystems when elemental cycles or the energy flow are
19 altered. This alteration can also be manifested in changes in the biotic composition of
20 ecosystems.

21 There are at least three levels of ecosystem response to pollutants: (1) the individual
22 organism and its environment; (2) the population and its environment; and (3) the
23 biological community composed of many species and their environment ([Billings, 1978](#)).
24 Individual organisms within a population vary in their ability to withstand the stress of
25 environmental change. The response of individual organisms within a population is based
26 on their genetic constitution, stage of growth at time of exposure to stress, and the
27 microhabitat in which they are growing ([Levine and Pinto, 1998](#)). The stress range within
28 which organisms can exist and function determines the ability of the population to
29 survive.

9.4.1.2 Ecosystem Services

30 Ecosystem structure and function may be translated into ecosystem services. Ecosystem
31 services are the benefits people obtain from ecosystems ([UNEP, 2003](#)). Ecosystems
32 provide many goods and services that are of vital importance for the functioning of the
33 biosphere and provide the basis for the delivery of tangible benefits to human society.

1 [Hassan et al. \(2005\)](#) define these benefits to include supporting, provisioning, regulating,
2 and cultural services:

- 3 ▪ Supporting services are necessary for the production of all other ecosystem
4 services. Some examples include biomass production, production of
5 atmospheric O₂, soil formation and retention, nutrient cycling, water cycling,
6 and provisioning of habitat. Biodiversity is a supporting service that is
7 increasingly recognized to sustain many of the goods and services that humans
8 enjoy from ecosystems. These provide a basis for three higher-level categories
9 of services.
- 10 ▪ Provisioning services, such as products ([Gitay et al., 2001](#)), i.e., food
11 (including game, roots, seeds, nuts and other fruit, spices, fodder), water, fiber
12 (including wood, textiles), and medicinal and cosmetic products (such as
13 aromatic plants, pigments).
- 14 ▪ Regulating services that are of paramount importance for human society such
15 as (1) C sequestration, (2) climate and water regulation, (3) protection from
16 natural hazards such as floods, avalanches, or rock-fall, (4) water and air
17 purification, and (5) disease and pest regulation.
- 18 ▪ Cultural services that satisfy human spiritual and aesthetic appreciation of
19 ecosystems and their components including recreational and other nonmaterial
20 benefits.

21 In the sections that follow, available information on individual, population and
22 community response to O₃ will be discussed. Effects of O₃ on productivity and
23 C sequestration, water cycling, below-ground processes, competition and biodiversity,
24 and insects and wildlife are considered below and in the context of ecosystem services
25 where appropriate.

9.4.2 Visible Foliar Injury and Biomonitoring

26 Visible foliar injury resulting from exposure to O₃ has been well characterized and
27 documented over several decades on many tree, shrub, herbaceous, and crop species
28 ([U.S. EPA, 2006b, 1996b, 1984, 1978a](#)). Visible foliar injury symptoms are considered
29 diagnostic as they have been verified experimentally in exposure-response studies, using
30 exposure methodologies such as CSTRs, OTCs, and free-air fumigation (see Section [9.2](#)
31 for more detail on exposure methodologies). Several pictorial atlases and guides have
32 been published, providing details on diagnosis and identification of O₃-induced visible
33 foliar injury on many plant species throughout North America ([Flagler, 1998](#); [NAPAP,](#)
34 [1987](#)) and Europe ([Innes et al., 2001](#); [Sánchez et al., 2001](#)). Typical visible injury

1 symptoms on broad-leaved plants include: stippling, flecking, surface bleaching, bifacial
2 necrosis, pigmentation (e.g., bronzing), chlorosis, and/or premature senescence. Typical
3 visible injury symptoms for conifers include: chlorotic banding, tip burn, flecking,
4 chlorotic mottling, and/or premature senescence of needles. Although common patterns
5 of injury develop within a species, these foliar lesions can vary considerably between and
6 within taxonomic groups. Furthermore, the degree and extent of visible foliar injury
7 development varies from year to year and site to site ([Orendovici-Best et al., 2008](#);
8 [Chappelka et al., 2007](#); [Smith et al., 2003](#)), even among co-members of a population
9 exposed to similar O₃ levels, due to the influence of co-occurring environmental and
10 genetic factors ([Souza et al., 2006](#); [Chappelka et al., 2003](#); [Somers et al., 1998](#)).
11 Nevertheless, [Chappelka et al. \(2007\)](#) reported that the average incidence of O₃-induced
12 foliar injury was 73% on milkweed observed in the Great Smoky Mountains National
13 Park in the years 1992-1996.

14 Although the majority of O₃-induced visible foliar injury occurrence has been observed
15 on seedlings and small plants, many studies have reported visible injury of mature
16 coniferous trees, primarily in the western U.S. ([Arbaugh et al., 1998](#)) and to mature
17 deciduous trees in eastern North America ([Schaub et al., 2005](#); [Vollenweider et al., 2003](#);
18 [Chappelka et al., 1999a](#); [Chappelka et al., 1999b](#); [Somers et al., 1998](#); [Hildebrand et al.,](#)
19 [1996](#)).

20 It is important to note that visible foliar injury occurs only when sensitive plants are
21 exposed to elevated O₃ concentrations in a predisposing environment. A major modifying
22 factor for O₃-induced visible foliar injury is the amount of soil moisture available to a
23 plant during the year that the visible foliar injury is being assessed. This is because lack
24 of soil moisture generally decreases stomatal conductance of plants and, therefore, limits
25 the amount of O₃ entering the leaf that can cause injury ([Matyssek et al., 2006](#); [Panek,](#)
26 [2004](#); [Grulke et al., 2003a](#); [Panek and Goldstein, 2001](#); [Temple et al., 1992](#); [Temple et](#)
27 [al., 1988](#)). Consequently, many studies have shown that dry periods in local areas tend to
28 decrease the incidence and severity of O₃-induced visible foliar injury; therefore, the
29 incidence of visible foliar injury is not always higher in years and areas with higher O₃,
30 especially with co-occurring drought ([Smith et al., 2003](#)). Other factors such as leaf age
31 influence the severity of symptom expression with older leaves showing greater injury
32 severity as a result of greater seasonal exposure ([Zhang et al., 2010a](#)).

33 Although visible injury is a valuable indicator of the presence of phytotoxic
34 concentrations of O₃ in ambient air, it is not always a reliable indicator of other negative
35 effects on vegetation. The significance of O₃ injury at the leaf and whole plant levels
36 depends on how much of the total leaf area of the plant has been affected, as well as the
37 plant's age, size, developmental stage, and degree of functional redundancy among the

1 existing leaf area. Previous O₃ AQCDs have noted the difficulty in relating visible foliar
2 injury symptoms to other vegetation effects such as individual plant growth, stand
3 growth, or ecosystem characteristics ([U.S. EPA, 2006b, 1996b](#)). As a result, it is not
4 presently possible to determine, with consistency across species and environments, what
5 degree of injury at the leaf level has significance to the vigor of the whole plant.
6 However, in some cases, visible foliar symptoms have been correlated with decreased
7 vegetative growth ([Somers et al., 1998](#); [Karnosky et al., 1996](#); [Peterson et al., 1987](#);
8 [Benoit et al., 1982](#)) and with impaired reproductive function ([Chappelka, 2002](#); [Black et
9 al., 2000](#)). Conversely, the lack of visible injury does not always indicate a lack of
10 phytotoxic concentrations of O₃ or a lack of non-visible O₃ effects ([Gregg et al., 2006](#),
11 [2003](#)).

9.4.2.1 Biomonitoring

12 The use of biological indicators to detect phytotoxic levels of O₃ is a longstanding and
13 effective methodology ([Chappelka and Samuelson, 1998](#); [Manning and Krupa, 1992](#)). A
14 plant bioindicator can be defined as a vascular or nonvascular plant exhibiting a typical
15 and verifiable response when exposed to a plant stress such as an air pollutant ([Manning,
16 2003](#)). To be considered a good indicator species, plants must (1) exhibit a distinct,
17 verified response; (2) have few or no confounding disease or pest problems; and (3)
18 exhibit genetic stability ([U.S. EPA, 2006b](#)). Such sensitive plants can be used to detect
19 the presence of a specific air pollutant such as O₃ in the ambient air at a specific location
20 or region and, as a result of the magnitude of their response, provide unique information
21 regarding specific ambient air quality. Bioindicators can be either introduced sentinels,
22 such as the widely used tobacco (*Nicotiana tabacum*) variety Bel W3 ([Calatayud et al.,
23 2007b](#); [Laffray et al., 2007](#); [Nali et al., 2007](#); [Gombert et al., 2006](#); [Kostka-Rick and
24 Hahn, 2005](#); [Heggstad, 1991](#)) or detectors, which are sensitive native plant species
25 ([Chappelka et al., 2007](#); [Souza et al., 2006](#)). The approach is especially useful in areas
26 where O₃ monitors are not operated ([Manning, 2003](#)). For example, in remote wilderness
27 areas where instrument monitoring is generally not available, the use of bioindicator
28 surveys in conjunction with the use of passive samplers ([Krupa et al., 2001](#)) may be a
29 useful methodology ([Manning, 2003](#)). However, it requires expertise in recognizing those
30 signs and symptoms uniquely attributable to exposure to O₃ as well as in their
31 quantitative assessment.

32 Since the 2006 O₃ AQCD, new sensitive plant species have been identified from field
33 surveys and verified in controlled exposure studies ([Kline et al., 2009](#); [Kline et al., 2008](#)).
34 Several multiple-year field surveys have also been conducted at National Wildlife

1 Refuges in Maine, Michigan, New Jersey, and South Carolina ([Davis, 2009](#), [2007a](#), [b](#);
2 [Davis and Orendovici, 2006](#)).

3 The USDA Forest Service through the Forest Health Monitoring Program (FHM) (1990 -
4 2001) and currently the Forest Inventory and Analysis (FIA) Program has been collecting
5 data regarding the incidence and severity of visible foliar injury on a variety of O₃
6 sensitive plant species throughout the U.S. ([Coulston et al., 2003](#); [Smith et al., 2003](#)). The
7 plots where these data are taken are known as biosites. These biosites are located
8 throughout the country and analysis of visible foliar injury within these sites follows a set
9 of established protocols. For more details, see <http://www.nrs.fs.fed.us/fia/topics/ozone/>
10 ([USDA, 2011](#)). The network has provided evidence of O₃ concentrations high enough to
11 induce visible symptoms on sensitive vegetation. From repeated observations and
12 measurements made over a number of years, specific patterns of areas experiencing
13 visible O₃ injury symptoms can be identified. ([Coulston et al., 2003](#)) used information
14 gathered over a 6-year period (1994-1999) from the network to identify several species
15 that were sensitive to O₃ over entire regions, including sweetgum (*Liquidambar*
16 *styraciflua*), loblolly pine (*Pinus taeda*), and black cherry (*P. serotina*). In a study of the
17 west coast of the U.S, [Campbell et al. \(2007\)](#) reported O₃ injury in 25-37% of biosites in
18 California forested ecosystems from 2000-2005.

19 A study by [Kohut \(2007\)](#) assessed the estimated risk of O₃-induced visible foliar injury
20 on bioindicator plants ([NPS, 2006](#)) in 244 national parks in support of the National Park
21 Service's Vital Signs Monitoring Network ([NPS, 2007](#)). The risk assessment was based
22 on a simple model relating response to the interaction of species, level of O₃ exposure,
23 and exposure environment. [Kohut \(2007\)](#) concluded that the estimated risk of visible
24 foliar injury was high in 65 parks (27%), moderate in 46 parks (19%), and low in 131
25 parks (54%). Some of the well-known parks with a high risk of O₃-induced visible foliar
26 injury include Gettysburg, Valley Forge, Delaware Water Gap, Cape Cod, Fire Island,
27 Antietam, Harpers Ferry, Manassas, Wolf Trap Farm Park, Mammoth Cave, Shiloh,
28 Sleeping Bear Dunes, Great Smoky Mountains, Joshua Tree, Sequoia and Kings Canyon,
29 and Yosemite.

30 Lichens have also long been used as biomonitors of air pollution effects on forest health
31 ([Nash, 2008](#)). It has been suspected, based on field surveys in the San Bernardino
32 Mountains surrounding the Los Angeles air basin, that declines in lichen diversity and
33 abundance were correlated with measured O₃ gradients ([Gül et al., 2011](#)). Several recent
34 studies in North America ([Geiser and Neitlich, 2007](#); [Gombert et al., 2006](#); [Jovan and](#)
35 [McCune, 2006](#)) and Europe ([Nali et al., 2007](#); [Gombert et al., 2006](#)) have used lichens as
36 biomonitors of atmospheric deposition (e.g., N and S) and O₃ exposure. [Nali et al. \(2007\)](#)
37 found that epiphytic lichen biodiversity was not related to O₃ geographical distribution.

1 In addition, a recent study by [Riddell et al. \(2010\)](#) found that lichen species, *Ramalina*
2 *menziesii*, showed no decline in physiological response to low and moderate
3 concentrations of O₃ and may not be a good indicator for O₃ pollution. Mosses have also
4 been used as biomonitors of air pollution; however, there remains a knowledge gap in the
5 understanding of the effects of ozone on mosses as there has been very little information
6 available on this topic in recent years.

9.4.2.2 Summary

7 Visible foliar injury resulting from exposure to O₃ has been well characterized and
8 documented over several decades of research on many tree, shrub, herbaceous, and crop
9 species ([U.S. EPA, 2006b](#), [1996b](#), [1984](#), [1978a](#)). Ozone-induced visible foliar injury
10 symptoms on certain bioindicator plant species are considered diagnostic as they have
11 been verified experimentally in exposure-response studies, using exposure methodologies
12 such as continuous stirred tank reactors (CSTRs), OTCs, and free-air fumigation.
13 Experimental evidence has clearly established a consistent association of visible injury
14 with O₃ exposure, with greater exposure often resulting in greater and more prevalent
15 injury. Since the 2006 O₃ AQCD, results of several multi-year field surveys of
16 O₃-induced visible foliar injury at National Wildlife Refuges in Maine, Michigan, New
17 Jersey, and South Carolina have been published. New sensitive species showing visible
18 foliar injury continue to be identified from field surveys and verified in controlled
19 exposure studies.

20 The use of biological indicators in field surveys to detect phytotoxic levels of O₃ is a
21 longstanding and effective methodology. The USDA Forest Service through the Forest
22 Health Monitoring (FHM) Program (1990-2001) and currently the Forest Inventory and
23 Analysis (FIA) Program has been collecting data regarding the incidence and severity of
24 visible foliar injury on a variety of O₃ sensitive plant species throughout the U.S. The
25 network has provided evidence that O₃ concentrations were high enough to induce visible
26 symptoms on sensitive vegetation. From repeated observations and measurements made
27 over a number of years, specific patterns of areas experiencing visible O₃ injury
28 symptoms can be identified. As noted in the preceding section, a study of 244 national
29 parks indicated that the estimated risk of visible foliar injury was high in 65 parks (27%),
30 moderate in 46 parks (19%), and low in 131 parks (54%).

31 Evidence is sufficient to conclude that there **is a causal relationship between ambient**
32 **O₃ exposure and the occurrence of O₃-induced visible foliar injury on sensitive**
33 **vegetation across the U.S.**

9.4.3 Growth, Productivity and Carbon Storage in Natural Ecosystems

1 Ambient O₃ concentrations have long been known to cause decreases in photosynthetic
2 rates, decreases in growth, and decreases in yield ([U.S. EPA, 2006b](#), [1996c](#), [1986](#),
3 [1978a](#)). The O₃-induced damages at the plant scale may translate to damages at the stand,
4 then ecosystem scales, and cause changes in productivity and C storage. This section
5 focuses on the responses of C cycling to seasonal or multi-year exposures to O₃ at levels
6 of organization ranging from individual plants to ecosystems. Quantitative responses
7 include changes in plant growth, plant biomass allocation, ecosystem production and
8 ecosystem C sequestration. Most information available on plant-scale responses was
9 obtained from studies that used a single species especially tree seedlings and crops, while
10 some used mixtures of herbaceous species. Ecosystem changes are difficult to evaluate in
11 natural settings, due to the complexity of interactions, the number of potential
12 confounders, and the large spatial and temporal scales. The discussion of ecosystem
13 effects focuses on new studies at the large-scale FACE experiments and on ecological
14 model simulations.

9.4.3.1 Plant Growth and Biomass Allocation

15 The previous O₃ AQCDs concluded that there is strong evidence that exposure to O₃
16 decreases photosynthesis and growth in numerous plant species ([U.S. EPA, 2006b](#),
17 [1996b](#), [1984](#), [1978a](#)). Studies published since the last review support those conclusions
18 and are summarized below.

19 In general, research conducted over several decades has indicated that exposure to O₃
20 alters stomatal conductance and reduces photosynthesis in a wide variety of plant species.
21 In a review of more than 55 studies, [Wittig et al. \(2007\)](#) reported that current O₃
22 concentrations in the northern hemisphere are decreasing stomatal conductance (13%)
23 and photosynthesis (11%) across tree species. It was also found that younger trees (<4
24 years) were affected less by O₃ than older trees. Further, the authors also found that
25 decreases in photosynthesis are consistent with the cumulative uptake of O₃ into the leaf.
26 In contrast, several studies reported that O₃ exposure may result in loss of stomatal
27 control, incomplete stomatal closure at night and a decoupling of photosynthesis and
28 stomatal conductance, which may have implications for whole- plant water use
29 (Section [9.4.5](#)).

30 In a recently published meta-analysis, [Wittig et al. \(2009\)](#) quantitatively compiled peer
31 reviewed studies from the past 40 years on the effect of current and future O₃ exposures
32 on the physiology and growth of forest species. They found that current ambient O₃

1 concentrations as reported in those studies significantly decreased annual total biomass
2 growth (7%) across 263 studies. The authors calculated the ambient O₃ concentrations
3 across these studies to average 40 ppb. This average was calculated across the duration of
4 each study and there were therefore many hourly exposures well above 40 ppb. The
5 decreased growth effect was reported to be greater (11 to 17%) in elevated O₃ exposures
6 (97 ppb) ([Wittig et al., 2009](#)). This meta-analysis demonstrates the coherence of O₃
7 effects across numerous studies and species that used a variety of experimental
8 techniques, and these results support the conclusion of the previous AQCD that exposure
9 to O₃ decreases plant growth.

10 In two companion papers, [McLaughlin et al. \(2007a\)](#); [\(2007b\)](#) investigated the effects of
11 ambient O₃ on tree growth and hydrology at forest sites in the southern Appalachian
12 Mountains. The authors reported that the cumulative effects of ambient levels of O₃
13 decreased seasonal stem growth by 30-50% for most tree species in a high O₃ year in
14 comparison to a low O₃ year ([McLaughlin et al., 2007a](#)). The authors also reported that
15 high ambient O₃ concentrations can disrupt whole-tree water use and in turn reduce late-
16 season streamflow ([McLaughlin et al., 2007b](#)); see Section [9.4.5](#) for more on water
17 cycling.

18 Since the 2006 O₃ AQCD, several recent studies have reported results from the Aspen
19 FACE “free air” O₃ and CO₂ exposure experiment in Wisconsin ([Darbah et al., 2008](#);
20 [Riikonen et al., 2008](#); [Darbah et al., 2007](#); [Kubiske et al., 2007](#); [Kubiske et al., 2006](#);
21 [King et al., 2005](#)). At the Aspen FACE site, single-species and two-species stands of trees
22 were grown in 12, 30-m diameter rings corresponding to three replications of a full
23 factorial arrangement of two levels each of CO₂ and O₃ exposure. Over the first
24 seven years of stand development, [Kubiske et al. \(2006\)](#) observed that elevated O₃
25 decreased tree heights, diameters, and main stem volumes in the aspen community by 11,
26 16, and 20%, respectively. In addition, [Kubiske et al. \(2007\)](#) reported that elevated O₃
27 may change intra- and inter-species competition. For example, O₃ treatments increased
28 the rate of conversion from a mixed aspen-birch community to a birch dominated
29 community. In a comparison presented in Section [9.6.3](#) of this document, EPA found that
30 effects on biomass accumulation in aspen during the first seven years closely agreed with
31 the exposure-response function based on data from earlier OTC experiments.

32 Several studies at the Aspen FACE site also considered other growth-related effects of
33 elevated O₃. [Darbah et al. \(2008\)](#); [Darbah et al. \(2007\)](#) reported that O₃ treatments
34 decreased paper birch seed weight and seed germination and that this would likely lead to
35 a negative impact of regeneration for that species. [Riikonen et al. \(2008\)](#) found that
36 elevated O₃ decreased the amount of starch in birch buds by 16%, and reduced aspen bud
37 size, which may have been related to the observed delay in spring leaf development. The

1 results suggest that elevated O₃ concentrations have the potential to alter C metabolism of
2 overwintering buds, which may have carry-over effects in the subsequent growing season
3 ([Riikonen et al., 2008](#)).

4 Effects on growth of understory vegetation were also investigated at Aspen FACE.
5 [Bandeuff et al. \(2006\)](#) found that the effects of elevated CO₂ and O₃ on understory species
6 composition, total and individual species biomass, N content, and ¹⁵N recovery were a
7 result of overstory community responses to those treatments; however, the lack of
8 apparent direct O₃ treatment effects may have been due to high variability in the data.
9 Total understory biomass increased with increasing light and was greatest under the open
10 canopy of the aspen/maple community, as well as the more open canopy of the elevated
11 O₃ treatments ([Bandeuff et al., 2006](#)). Similarly, data from a study by [Awmack et al.](#)
12 ([2007](#)) suggest that elevated CO₂ and O₃ may have indirect growth effects on red
13 (*Trifolium pratense*) and white (*Trifolium repens*) clover in the understory via overstory
14 community effects; however, no direct effects of elevated O₃ were observed.

15 Overall, the studies at the Aspen FACE experiment are consistent with many of the OTC
16 studies that were evaluated in previous O₃ AQCDs demonstrating that O₃ exposure
17 decreases growth in numerous plant species. These results strengthen the understanding
18 of O₃ effects on forests and demonstrate the relevance of the knowledge gained from
19 trees grown in open-top chamber studies.

20 For some annual species, particularly crops, the relevant measurement for an assessment
21 of the risk of O₃ exposure is yield or growth, e.g., production of grain or biomass. For
22 plants grown in mixtures such as hayfields, and natural or semi-natural grasslands
23 (including native nonagricultural species), affected factors other than production of
24 biomass may be important. Such endpoints include biodiversity or species composition,
25 and effects on those endpoints may be indirect, resulting, for example, from competitive
26 interactions among plants in mixed-species communities. Most of the available data on
27 non-crop herbaceous species are for grasslands, with many of the recent studies
28 conducted in Europe. See Section [9.4.7](#) for a review of the recent literature on O₃ effects
29 on competition and biodiversity in grasslands.

Root growth

30 Although O₃ does not penetrate soil, it could alter root development by decreasing
31 C assimilation via photosynthesis leading to less C allocation to the roots ([Andersen,](#)
32 [2003](#)). The response of root development to O₃ exposure depends on available
33 photosynthate within the plant and could vary over time. Many biotic and abiotic factors,
34 such as community dynamics and drought stress, have been found to alter root

1 development under elevated O₃. Generally, there is clear evidence that O₃ reduces C
2 allocation to roots; however, results of a few recent individual studies have shown
3 negative ([Jones et al., 2010](#)), non-significant ([Andersen et al., 2010](#); [Phillips et al., 2009](#))
4 and positive effects ([Pregitzer et al., 2008](#); [Grebenc and Kraigher, 2007](#)) on root biomass
5 and root: shoot ratio.

6 An earlier study at the Aspen FACE experiment found that elevated O₃ reduced coarse
7 root and fine roots biomass in young stands of paper birch and trembling aspen ([King et
8 al., 2001](#)). However, this reduction disappeared several years later. Ozone significantly
9 increased fine-root (<1.0 mm) in the aspen community ([Pregitzer et al., 2008](#)). This
10 increase in fine root production was due to changes in community composition, such as
11 better survival of the O₃-tolerant aspen genotype, birch, and maple, rather than changes in
12 C allocation at the individual tree level ([Pregitzer et al., 2008](#); [Zak et al., 2007](#)). In an
13 adult European beech/Norway spruce forest in Germany, drought was found to nullify the
14 O₃-driven stimulation of fine root growth. Ozone stimulated fine-root production of
15 beech during the humid year, but had no significant impact on fine root production in the
16 dry year ([Matyssek et al., 2010](#); [Nikolova et al., 2010](#)).

17 Using a non-destructive method, [Vollsnæs et al. \(2010\)](#) studied the in vivo root
18 development of subterranean clover (*Trifolium subterraneum*) before, during and after
19 short-term O₃ exposure. It was found that O₃ reduced root tip formation, root elongation,
20 the total root length, and the ratios between below- and above-ground growth within
21 one week after exposure. Those effects persisted for up to three weeks; however, biomass
22 and biomass ratios were not significantly altered at the harvest five weeks after exposure.

23 Several recent meta-analyses have generally indicated that O₃ reduced C allocated to
24 roots. In one meta-analysis, [Grantz et al. \(2006\)](#) estimated the effect of O₃ on the
25 root:shoot allometric coefficient (k), the ratio between the relative growth rate of the root
26 and shoot. The results showed that O₃ reduced the root:shoot allometric coefficient by
27 5.6%, and the largest decline of the root:shoot allometric coefficient was observed in
28 slow-growing plants. In another meta-analysis including 263 publications, [Wittig et al.
29 \(2009\)](#) found that current O₃ exposure had no significant impacts on root biomass and
30 root:shoot ratio when compared to pre-industrial O₃ exposure. However, if O₃
31 concentrations rose to 81-101 ppb (projected O₃ levels in 2100), both root biomass and
32 root:shoot ratio were found to significantly decrease. Gymnosperms and angiosperms
33 differed in their responses, with gymnosperms being less sensitive to elevated O₃. In two
34 other meta-analyses, [Wang and Taub \(2010\)](#) found elevated O₃ reduced biomass
35 allocation to roots by 8.3% at ambient CO₂ and 6.0% at elevated CO₂, and [Morgan et al.
36 \(2003\)](#) found O₃ reduced root dry weight of soybean.

9.4.3.2 Summary

1 The previous O₃ AQCDs concluded that there is strong and consistent evidence that
2 ambient concentrations of O₃ decrease photosynthesis and growth in numerous plant
3 species across the U.S. Studies published since the last review continue to support that
4 conclusion.

5 The meta-analyses by [Wittig et al. \(2009\)](#); [Wittig et al. \(2007\)](#) demonstrate the coherence
6 of O₃ effects on plant photosynthesis and growth across numerous studies and species
7 using a variety of experimental techniques. Furthermore, recent meta-analyses have
8 generally indicated that O₃ reduced C allocation to roots ([Wittig et al., 2009](#); [Grantz et
9 al., 2006](#)). Since the 2006 O₃ AQCD, several studies were published based on the Aspen
10 FACE experiment using “free air,” O₃, and CO₂ exposures in a planted forest in
11 Wisconsin. Overall, the studies at the Aspen FACE experiment were consistent with
12 many of the open-top chamber (OTC) studies that were the foundation of previous O₃
13 NAAQS reviews. These results strengthen the understanding of O₃ effects on forests and
14 demonstrate the relevance of the knowledge gained from trees grown in open-top
15 chamber studies.

16 Evidence is sufficient to conclude that there **is a causal relationship between ambient**
17 **O₃ exposure and reduced growth of native woody and herbaceous vegetation.**

9.4.3.3 Reproduction

18 Studies during recent decades have demonstrated O₃ effects on various stages of plant
19 reproduction. The impacts of O₃ on reproductive development, as reviewed by [Black et
20 al. \(2000\)](#), can occur by influencing (1) age at which flowering occurs, particularly in
21 long-lived trees that often have long juvenile periods of early growth without flower and
22 seed production; (2) flower bud initiation and development; (3) pollen germination and
23 pollen tube growth; (4) seed, fruit, or cone yields; and (5) seed quality ([Table 9-1](#)) ([U.S.
24 EPA, 2006b](#)). Several recent studies since the 2006 O₃ AQCD further demonstrate the
25 effects of O₃ on reproductive processes in herbaceous and woody plant species. Although
26 there have been documented effects of ozone on reproductive processes, a knowledge gap
27 still exists pertaining to the exact mechanism of these responses.

28 [Ramo et al. \(2007\)](#) exposed several meadow species to elevated O₃ (40-50 ppb) and CO₂
29 (+100 ppm), both individually and combined, over three growing seasons in ground-
30 planted mesocosms, using OTCs. Elevated O₃ delayed flowering of *Campanula*
31 *rotundifolia* and *Vicia cracca*. Ozone also reduced the overall number of produced
32 flowers and decreased fresh weight of individual *Fragaria vesca* berries.

1 [Black et al. \(2007\)](#) exposed *Brassica campestris* to 70 ppb for two days during late
2 vegetative growth or ten days during most of the vegetative phase. The two-day exposure
3 had no effect on growth or reproductive characteristics, while the 10 day exposure
4 reduced vegetative growth and reproductive site number on the terminal raceme,
5 emphasizing the importance of exposure duration and timing. Mature seed number and
6 weight per pod were unaffected due to reduced seed abortion, suggesting that, although
7 O₃ affected reproductive processes, indeterminate species such as *B. campestris* possess
8 enough compensatory flexibility to avoid reduced seed production [Black et al. \(2007\)](#).

9 In the determinate species, *Plantago major*, [Black et al. \(2010\)](#) found that O₃ may have
10 direct effects on reproductive development in populations of differing sensitivity. Only
11 the first flowering spike was exposed to 120 ppb O₃ for 7 hours per day on 9 successive
12 days (corresponding to flower development) while the leaves and second spike were
13 exposed to charcoal-filtered air. Exposure of the first spike to O₃ affected seed number
14 per capsule on both spikes even though spike two was not exposed. The combined seed
15 weight of spikes one and two was increased by 19% in the two resistant populations,
16 suggesting an overcompensation for injury; whereas, a decrease of 21% was observed in
17 the most sensitive population ([Black et al., 2010](#)). The question remains as to whether
18 these effects are true direct ozone-induced effects or compensatory responses.

19 Studies by [Darbah et al. \(2008\)](#); [Darbah et al. \(2007\)](#) of paper birch (*Betula papyrifera*)
20 trees at the Aspen FACE site in Rhineland, WI investigated the effects of elevated O₃
21 and/or CO₂ on reproductive fitness. Elevated O₃ increased flowering, but decreased seed
22 weight and germination success rate of seeds from the exposed trees. These results
23 suggest that O₃ can dramatically affect flowering, seed production, and seed quality of
24 paper birch, ultimately affecting its reproductive fitness ([Darbah et al., 2008](#); [Darbah et](#)
25 [al., 2007](#)).

Table 9-1 Ozone effects on plant reproductive processes

| Species | Condition Measures | References |
|---|------------------------|--|
| <i>Apocynum androsaemifolium</i> (spreading dogbane) | Flowering time | Bergweiler and Manning (1999) |
| <i>Buddleia davidii</i> (butterfly bush) | Flowering time | Findley et al. (1997) |
| <i>Rubus cuneifolius</i> (sand blackberry) | Pollen germination | Chappelka (2002) |
| <i>Plantago major</i> (plantain) | Pollen tube elongation | Stewart (1998) |
| <i>Fragaria x ananassa</i> (cultivated strawberry) | Fruit yield | Drogoudi and Ashmore (2001) ; Drogoudi and Ashmore (2000) |
| <i>Plantago major</i> (plantain) | Seed yield | Lyons and Barnes (1998) ; Pearson et al. (1996) ; Reiling and Davison (1992) ; Whitfield et al. (1997) |
| Understory herbs | Seed yield | Harward and Treshow (1975) |

Source: Derived from Table AX9-22 of the 2006 O₃ AQCD.

9.4.3.4 Ecosystem Productivity and Carbon Sequestration

1 During the previous NAAQS review, there were limited studies that investigated the
2 effect of O₃ exposure on ecosystem productivity and C sequestration. Recent studies from
3 long-term FACE experiments provide more evidence of the association of O₃ exposure
4 and changes in productivity at the ecosystem level of organization. In addition to
5 experimental studies, model studies also assessed the impact of O₃ exposure on
6 productivity and C sequestration from stand to global scales.

7 In this section productivity of ecosystems is expressed in different ways depending on the
8 model or the measurements of a study. The most common metric of productivity is Gross
9 Primary Productivity. Gross Primary Productivity (GPP) is total carbon that enters the
10 ecosystem through photosynthesis by plants. Plants return a larger portion of this carbon
11 back to the atmosphere through respiration from roots and aboveground portions of plants
12 (R_{plant}). Net primary production (NPP) is the difference between total carbon gain (GPP)
13 and carbon loss through R_{plant} . Net ecosystem productivity (NEP) is the difference
14 between NPP and carbon loss through heterotrophic respiration (R_{het}) (mostly
15 decomposition of dead organic matter) ([Lambers et al., 1998](#)). Similarly net ecosystem
16 exchange (NEE) is the net flux of carbon between the land and the atmosphere, typically
17 measured using eddy covariance techniques. Positive values of NEE usually refer to
18 carbon released to the atmosphere (i.e., a source), and negative values refer to carbon
19 uptake (i.e., a sink). Other studies have calculated net carbon exchange (NCE). NCE is
20 defined as NPP minus R_{het} , E_c (the carbon emission during the conversion of natural
21 ecosystems to agriculture) and E_p (the sum of carbon emission from the decomposition of

1 agricultural products). For natural vegetation, E_c and E_p are equal to 0, so NCE is equal
2 NEP ([Felzer et al., 2005](#)). In general, modeling studies take into account the effect of O_3
3 on C fixation of a system and there is generally not an effect on R_{plant} , R_{het} , E_c or E_p .
4 Therefore, decreases in GPP, NPP, NEP, NEE and NCE indicate a general decrease in
5 productivity of an ecosystem.

6 Two types of models are most often used to study the ecological consequences of O_3
7 exposure: (1) single plant growth models such as TREGRO and PnET-II ([Hogsett et al.,](#)
8 [2008](#); [Martin et al., 2001](#); [Ollinger et al., 1997b](#)), and (2) process-based ecosystem
9 models such as PnET-CN, Dynamic Land Ecosystem Model (DLEM), Terrestrial
10 Ecosystem Model (TEM), or Met Office Surface Exchange Scheme - Top-down
11 Representation of Interactive Foliage and Flora Including Dynamics (MOSES-TRIFFID)
12 ([Felzer et al., 2009](#); [Ren et al., 2007b](#); [Sitch et al., 2007](#); [Ollinger et al., 2002](#))
13 ([Table 9-2](#)). In these models, carbon uptake is simulated through photosynthesis
14 (TREGRO, PnET -II, PnET- CN, DLEM and MOSES-TRIFFID) or gross primary
15 production (TEM). Photosynthesis rate at leaf level is modeled by a function of stomatal
16 conductance and other parameters in TREGRO, PnET -II, PnET- CN, DLEM and
17 MOSES-TRIFFID. Photosynthesis at canopy level is calculated by summing either
18 photosynthesis of different leaf types (TREGRO, DLEM, and MOSES-TRIFFID) or
19 photosynthesis of different canopy layers (PnET -II, PnET- CN). The detrimental effect
20 of O_3 on plant growth is often simulated by multiplying photosynthesis rate by a
21 coefficient that is dependent on stomatal conductance and cumulative O_3 uptake
22 ([Table 9-2](#)). Different plant functional groups (PFTs, such as deciduous trees, coniferous
23 trees or crops) show different responses to O_3 exposure. PnET-iI, PnET-CN, TEM,
24 DLEM and MOSES-TRIFFID estimate this difference by modifying net photosynthesis
25 with coefficients that represent the O_3 induced fractional reduction of photosynthesis for
26 each functional group. The coefficients used in PnET-iI, PnET-CN, TEM, DLEM are
27 derived from the functions of O_3 exposure (AOT40) versus photosynthesis reduction
28 from [Reich \(1987\)](#) and [Tjoelker et al. \(1995\)](#). The coefficients used in MOSES-TRIFFID
29 are derived from the O_3 dose-photosynthesis response function from [Pleijel et al. \(2004a\)](#)
30 and [Karlsson et al. \(2004\)](#), where O_3 dose is estimated by a metric named CUOt
31 (cumulative stomatal uptake of O_3). The O_3 threshold of CUOt is $1.6 \text{ nmol/m}^2/\text{sec}$ for
32 woody PFT and $5 \text{ nmol/m}^2/\text{sec}$ for grass PFT, and is different from AOT40, which has an
33 O_3 threshold level of 40 ppb for all PFTs. Experimental and model studies on ecosystem
34 productivity and C sequestration at the forest stand scale as well as regional and global
35 scales are reviewed in the following section.

Table 9-2 Comparison of models used to simulate the ecological consequences of ozone exposure.

| Model | Model feature | Carbon uptake | Ozone effect | Reference |
|------------------------------|---|--|--|--|
| TREGRO | Hourly or daily step, single plant model simulating vegetation growth process | Leaf: leaf photosynthesis is a function of stomatal conductance, mesophyll conductance and the gradient of CO ₂ from atmosphere to the mesophyll cells Canopy: Leaf is divided into different ages. The canopy photosynthesis rate is the sum of the photosynthesis of all foliage groups | The effect of O ₃ on photosynthesis is simulated by reducing mesophyll conductance, and increasing respiration. The degree of O ₃ damage is determined by ambient O ₃ exposure, and the threshold O ₃ concentration below which O ₃ does not affect mesophyll conductance and respiration | Hogsett et al. (2008) ; Weinstein et al. (2005) ; Tingey et al. (2004) |
| PnET-il and PnET - CN | PnET-il: Monthly time-step, single plant model PnET - CN: Monthly time-step, ecosystem model | Leaf: Maximum photosynthesis rate is determined by a function of foliar N concentration, and stomatal conductance is determined by a function of the actual rate of the photosynthesis. Canopy: canopy is divided into multiple, even-mass layers and photosynthesis is simulated by a multilayered canopy submodel | The effect of O ₃ on photosynthesis is simulated by an equation of stomatal conductance and O ₃ dose (AOT40). The model assumes that photosynthesis and stomatal conductance remain coupled under O ₃ exposure, with a reduction in photosynthesis for a given month causing a proportion reduction in stomatal conductance. | Ollinger et al. (2002) ; Ollinger et al. (1997b) ; Pan et al. (2009) |
| TEM | Monthly time-step, ecosystem model | Ecosystem: TEM is run at a 0.5*0.5 degree resolution. Each grid cell is classified by vegetation type and soil texture, and vegetation and detritus are assumed to distribute homogeneously within grid cells. Carbon flows into ecosystem via gross primary production, which is a function of maximum rate of assimilation, photosynthetically active radiation, the leaf area relative to the maximum annual leaf area, mean monthly air temperate, and nitrogen availability. | The direct O ₃ reduction on GPP is simulated by multiplying GPP by f(O ₃) _t , where f(O ₃) _t is determined by evapotranspiration, mean stomatal conductance, ambient AOT40, and empirically O ₃ response coefficient derived from previous publications. | Felzer et al. (2005) ; (2004) |
| DLEM | Daily time-step ecosystem model | Leaf: photosynthesis is a function of 6 parameters: photosynthetic photon flux density, stomatal conductance, daytime temperature, the atmospheric CO ₂ concentration, the leaf N content and the length of daytime. Canopy: Photosynthetic rates for sunlit leaf and shaded leaf scale up to the canopy level by multiplying the estimated leaf area index Ecosystem: GPP is the sum of gross C fixation of different plant function groups | The detrimental effect of O ₃ is simulated by multiplying the rate of photosynthesis by O ₃ eff, where O ₃ eff is a function of stomatal conductance, ambient AOT40, and O ₃ sensitive coefficient. Ozone's indirect effect on stomatal conductance is also simulated, with a reduction in photosynthesis for a given month causing a reduction in stomatal conductance, and therefore canopy conductance. | Ren et al. (2007b) ; (Ren et al., 2007a) ; Zhang et al. (2007a) |
| MOSES-TRIFFID | 30 minute time-step, dynamic global vegetation model | Leaf: photosynthesis is a function of environmental and leaf parameters and stomatal conductance; Stomatal conductance is a function of the concentration of CO ₂ and H ₂ O in air at the leaf surface and the current rate of photosynthesis of the leaf Canopy: Photosynthetic rates scale up to the canopy level by multiplying a function of leaf area index and PAR extinction coefficient Ecosystem: GPP is the sum of gross C fixation of different plant function groups | The effect of O ₃ is simulated by multiplying the rate of photosynthesis by F, where F depends upon stomatal conductance, O ₃ exposure, a critical threshold for O ₃ damage, and O ₃ sensitive coefficient (functional type dependent) | Sitch et al. (2007) |

Local scale

1 Both experimental and modeling studies have provided new information on effects of O₃
2 exposure at the stand or site level, i.e., at the local scale. The above- and below-ground
3 biomass and net primary production (NPP) were measured at the Aspen FACE site after 7
4 years of O₃ exposure. Elevated O₃ caused 23, 13 and 14% reductions in total biomass
5 relative to the control in the aspen, aspen–birch and aspen–maple communities,
6 respectively ([King et al., 2005](#)). At the Kranzberg Forest FACE experiment in Germany,
7 O₃ reduced annual volume growth by 9.5 m³/ha in a mixed mature stand of Norway
8 spruce and European beech ([Pretzsch et al., 2010](#)). At the grassland FACE experiment at
9 Alp Flix, Switzerland, O₃ reduced the seasonal mean rates of ecosystem respiration and
10 GPP by 8%, but had no significant impacts on aboveground dry matter productivity or
11 growing season net ecosystem production (NEP) ([Volk et al., 2011](#)). Ozone also altered
12 C accumulation and turnover in soil, as discussed in Section [9.4.6](#).

13 Changes in forest stand productivity under elevated O₃ were assessed by several model
14 studies. TREGRO ([Table 9-2](#)) has been widely used to simulate the effects of O₃ on the
15 growth of several species in different regions in the U.S. [Hogsett et al. \(2008\)](#) used
16 TREGRO to evaluate the effectiveness of various forms and levels of air quality
17 standards for protecting tree growth in the San Bernardino Mountains of California. They
18 found that O₃ exposures at the Crestline site resulted in a mean 20.9% biomass reduction
19 from 1980 to 1985 and 10.3% biomass reduction from 1995 to 2000, compared to the
20 “background” O₃ concentrations (O₃ concentration in Crook County, Oregon). The level
21 of vegetation protection projected was different depending on the air quality scenarios
22 under consideration. Specifically, when air quality was simulated to just meet the
23 California 8-h average maximum of 70 ppb and the maximum 3 months 12-h SUM06 of
24 25 ppm-h, annual growth reductions were limited to 1% or less, while air quality that just
25 met a previous NAAQS (the second highest 1-h max [125 ppb]) resulted in 6-7% annual
26 reduction in growth, resulting in the least protection relative to background O₃ ([Hogsett et
27 al., 2008](#)).

28 ZELIG is a forest succession gap model, and has been used to evaluate the dynamics of
29 natural stand succession. Combining TREGRO with ZELIG, [Weinstein et al. \(2005\)](#)
30 simulated the effects of different O₃ levels (0.5, 1.5, 1.75, and 2 times [×] ambient) on the
31 growth and competitive interactions of white fir and ponderosa pine at three sites in
32 California: Lassen National Park, Yosemite National Park, and Crestline. Their results
33 suggested that O₃ had little impact on white fir, but greatly reduced the growth of
34 ponderosa pine. If current O₃ concentrations continue over the next century, ambient O₃
35 exposure (SUM06 of 110 ppm-h) at Crestline was predicted to decrease individual tree
36 C budget by 10% and decrease ponderosa pine abundance by 16%. Effects at Lassen

1 National Park and Yosemite National Park sites were found to be smaller because of
2 lower O₃ exposure levels ([Weinstein et al., 2005](#)).

3 To evaluate the influence of interspecies competition on O₃ effects, the linked TREGRO
4 and ZELIG modeling system was used to predict the effects of O₃ over 100 years on the
5 basal area of species in a *Liriodendron tulipifera*-dominated forest in the Great Smoky
6 Mountains National Park ([Weinstein et al., 2001](#)). Ambient O₃ was predicted to decrease
7 individual tree C budget by 28% and reduce the basal area of *L. tulipifera* by 10%,
8 whereas a 1.5×-ambient exposure was predicted to cause a 42% decrease in the individual
9 tree C budget and a 30% reduction in basal area. Individual tree C balance for *Acer*
10 *rubrum* decreased 14% and 23% under ambient and 1.5×-ambient exposure, respectively.
11 *Prunus serotina* was predicted to have less than a 2% decrease in tree C balance in all
12 scenarios, but its basal area was greatly altered by the O₃ effects on the other tree species.
13 Basal area of *A. rubrum* and *P. serotina* was predicted to increase for some years, but
14 then decrease by up to 30%, depending on the scenario. The effects of O₃ on stand
15 productivity and dynamics were also studied by other tree growth or stand models, such
16 as ECOPHYS, INTRASTAND and LINKAGES. ECOPHYS is a functional-structural
17 tree growth model. The model used the linear relationship between the maximum
18 capacity of carboxylation and O₃ dose to predict the relative effect of O₃ on leaf
19 photosynthesis ([Martin et al., 2001](#)). Simulations with ECOPHYS found that O₃
20 decreased stem dry matter production, stem diameter and leaf dry matter production,
21 induced earlier leaf abscission, and inhibited root growth ([Martin et al., 2001](#)).
22 INTRASTAND is an hourly time step model for forest stand carbon and water budgets.
23 LINKAGES is a monthly time step model simulating forest growth and community
24 dynamics. Linking INTRASTAND with LINKAGES, [Hanson et al. \(2005\)](#) found that a
25 simulated increase in O₃ concentration in 2100 (a mean 20-ppb increase over the current
26 O₃ concentration) yields a 35% loss of net ecosystem C exchange (NEE) with respect to
27 the current conditions (174 g C/m²/year).

Regional and global scales

28 Since the publication of the 2006 O₃ AQCD, there is additional evidence suggesting that
29 O₃ exposure alters ecosystem productivity and biogeochemical cycling at the regional
30 scale, i.e., at scales ranging from watershed to subcontinental divisions, and at continental
31 and global scales. Most of those studies were conducted by using process-based
32 ecosystem models ([Table 9-2](#)) and are briefly reviewed in the following sections.

33 [Ollinger et al. \(1997a\)](#) simulated the effect of O₃ on hardwood forest productivity of 64
34 hardwood sites in the northeastern U.S. with PnET-iI ([Table 9-2](#)). Their simulations
35 indicated that O₃ caused a 3-16% reduction in NPP from 1987 to 1992 ([Table 9-3](#)). The

1 interactive effects of O₃, N deposition, elevated CO₂ and land use history on C dynamics
2 were estimated by PnET-CN ([Table 9-2](#)) ([Ollinger et al., 2002](#)). The results indicated that
3 O₃ offset the increase in net C exchange caused by elevated CO₂ and N deposition by
4 13% (25.0 g C/m²/year) under agriculture site history, and 23% (33.6 g C/m²/year) under
5 timber harvest site history. PnET-CN was also used to assess changes in C sequestration
6 of U.S. Mid-Atlantic temperate forest. [Pan et al. \(2009\)](#) designed a factorial modeling
7 experiment to separate the effects of changes in atmospheric composition, historical
8 climatic variability and land-disturbances on the C cycle. They found that O₃ acted as a
9 negative factor, partially offsetting the growth stimulation caused by elevated CO₂ and
10 N deposition in U.S. Mid-Atlantic temperate forest. Ozone decreased NPP of most forest
11 types by 7-8%. Among all the forest types, spruce-fir forest was most resistant to O₃
12 damage, and NPP decreased by only 1% ([Pan et al., 2009](#)).

13 [Felzer et al. \(2004\)](#) developed TEM 4.3 ([Table 9-2](#)) to simulate the effects of O₃ on plant
14 growth and estimated effects of O₃ on NPP and C sequestration of deciduous trees,
15 conifers and crops in the conterminous U.S. The results indicated that O₃ reduced NPP
16 and C sequestration in the U.S. ([Table 9-3](#)) with the largest decreases (over 13% in some
17 locations) in NPP occurring in the Midwest agricultural lands during the mid-summer.
18 TEM was also used to evaluate the magnitude of O₃ damage at the global scale
19 ([Table 9-3](#)) ([Felzer et al., 2005](#)). Simulations for the period 1860 to 1995 show that the
20 largest reductions in NPP and net C exchange occurred in the mid western U.S., eastern
21 Europe, and eastern China ([Felzer et al., 2005](#)). DLEM ([Table 9-2](#)) was developed to
22 simulate the detrimental effect of O₃ on ecosystems, and has been used to examine the O₃
23 damage on NPP and C sequestration in Great Smoky Mountains National Park ([Zhang et](#)
24 [al., 2007a](#)), grassland ecosystems and terrestrial ecosystems in China ([Ren et al., 2007b](#);
25 [Ren et al., 2007a](#)). Results of those simulations are listed in [Table 9-3](#).

26 Instead of using AOT40 as their O₃ exposure metric as PnET, TEM and DLEM did, [Sitch](#)
27 [et al. \(2007\)](#) incorporated a different O₃ metric named CUOt (cumulative stomatal uptake
28 of O₃), derived from [Pleijel et al. \(2004a\)](#), into the MOSES-TRIFFID coupled model
29 ([Table 9-2](#)). In the CUOt metric, the fractional reduction of plant production is dependent
30 on O₃ uptake by stomata over a critical threshold for damage with this threshold level
31 varying by plant functional type. Consistent with previous studies, their model simulation
32 indicated that O₃ reduced global gross primary production (GPP), C-exchange rate and
33 C sequestration ([Table 9-3](#)). The largest reductions in GPP and land-C storage were
34 projected over North America, Europe, China and India. In the model, reduced ecosystem
35 C uptake due to O₃ damage results in additional CO₂ accumulation in the atmosphere and
36 an indirect radiative forcing of climate change. Their simulations indicated that the
37 indirect radiative forcing caused by O₃ (0.62-1.09 W/m²) could have even greater impact
38 on global warming than the direct radiative forcing of O₃ (0.89 W/m²) ([Sitch et al., 2007](#)).

1 Results from the various model studies presented in [Table 9-3](#) are difficult to compare
2 because of the various spatial and temporal scales used. However, all the studies showed
3 that O₃ exposure decreased ecosystem productivity and C sequestration. These results are
4 consistent and coherent with experimental results obtained from studies at the leaf, plant
5 and ecosystem scales ([Sitch et al., 2007](#); [Felzer et al., 2005](#)). Many of the models use the
6 same underlying function to simulate the effect of O₃ exposure to C uptake. For example
7 the functions of O₃ exposure (AOT40) versus photosynthesis reduction for PnET-iL,
8 PnET-CN, TEM, DLEM were all from [Reich \(1987\)](#) and [Tjoelker et al. \(1995\)](#).
9 Therefore, it is not surprising that the results are similar. While these models can be
10 improved and more evaluation with experimental data can be done, these models
11 represent the state of the science for estimating the effect of O₃ exposure on productivity
12 and C sequestration.

9.4.3.5 Summary

13 During the previous NAAQS reviews, there were very few studies that investigated the
14 effect of O₃ exposure on ecosystem productivity and C sequestration. Recent studies from
15 long-term FACE experiments, such as Aspen FACE, SoyFACE and the Kranzberg Forest
16 (Germany), provide evidence of the association of O₃ exposure and reduced productivity
17 at the ecosystem level of organization. Studies at the leaf and plant scales show that O₃
18 decreased photosynthesis and plant growth, which provides coherence and biological
19 plausibility for the decrease in ecosystem productivity. Results across different ecosystem
20 models, such as TREGRO, PnET, TEM and DLEM, are consistent with the FACE
21 experimental evidence, which show that O₃ reduced productivity of various ecosystems.
22 Productivity is measured by various metrics such as GPP, NPP, NEP, NCE, NEE and
23 individual tree biomass gain. All these metrics indicate a decrease in CO₂ fixation by the
24 systems that were studied.

25 Although O₃ generally causes negative effects on plant growth, the magnitude of the
26 response varies among plant communities. For example, O₃ had little impact on white fir,
27 but greatly reduced growth of ponderosa pine in southern California ([Weinstein et al.,
28 2005](#)). Ozone decreased net primary production (NPP) of most forest types in the Mid-
29 Atlantic region, but had small impacts on spruce-fir forest ([Pan et al., 2009](#)).

30 In addition to plant growth, other indicators that are typically estimated by model studies
31 include net ecosystem CO₂ exchange (NEE), C sequestration, and crop yield. Model
32 simulations consistently found that O₃ exposure caused negative impacts on these
33 indicators, but the severity of these impacts was influenced by multiple interactions of
34 biological and environmental factors. The suppression of ecosystem C sinks results in

1 more CO₂ accumulation in the atmosphere. Globally, the indirect radiative forcing caused
2 by O₃ exposure through lowering the ecosystem C sink could have an even greater impact
3 on global warming than the direct radiative forcing of O₃ ([Sitch et al., 2007](#)). Ozone
4 could also affect regional C budgets through interacting with multiple factors, such as
5 N deposition, elevated CO₂ and land use history. Model simulations suggested that O₃
6 partially offset the growth stimulation caused by elevated CO₂ and N deposition in both
7 Northeast- and Mid-Atlantic-region forest ecosystems of the U.S. ([Pan et al., 2009](#);
8 [Ollinger et al., 2002](#)).

9 The evidence is sufficient to infer that there **is a causal relationship between O₃**
10 **exposure and reduced productivity, and a likely causal relationship between O₃**
11 **exposure and reduced carbon sequestration in terrestrial ecosystems.**

Table 9-3 Modeled effects of ozone on primary production, C exchange, and C sequestration.

| | Scale | Model | Index | O ₃ Impacts | Reference |
|------------------------|-------------------|---------------|-------------------|--|---|
| GPP | Global | MOSES-TRIFFID | CUOt ^a | Decreased by 14-23% over the period 1901-2100 | Sitch et al. (2007) |
| NPP | Global | TEM | AOT40 | Decreased by 0.8% without agricultural management and a decrease of 2.9% with optimal agricultural management | Felzer et al. (2005) |
| | U.S. | TEM | AOT40 | Reduced by 2.3% without optimal N fertilization and 7.2% with optimal N fertilization from 1983-1993 | Felzer et al. (2005) |
| | U.S. | TEM | AOT40 | Reduced by 2.6–6.8% during the late 1980s to early 1990s. | Felzer et al. (2004) |
| | Northeastern U.S. | PnET | AOT40 | A reduction of 3-16% from 1987-1992 | Ollinger et al. (1997a) |
| | U.S. Mid-Atlantic | PnET | AOT40 | Decreased NPP of most forest types by 7-8% | Pan et al. (2009) |
| | China | DLEM | AOT40 | Reduced NPP of grassland in China by 8.5 Tg ^b C from 1960s to 1990s | Ren et al. (2007a) |
| C exchange | Global | TEM | AOT40 | Reduced net C exchange (1950–1995) by 0.1 Pg C/yr without agricultural management and 0.3 Pg C/yr with optimal agricultural management | Felzer et al. (2005) |
| | Global | MOSES-TRIFFID | CUOt | Decreased global mean land–atmosphere C fluxes by 1.3 Pg C/yr and 1.7 Pg C/yr for the ‘high’ and ‘low’ plant O ₃ sensitivity models, respectively | Sitch et al. (2007) |
| C sequestration | Global | MOSES-TRIFFID | CUOt | Reduced land-C storage accumulation by between 143 Pg C/yr and 263 Pg C/yr from 1900–2100 | Sitch et al. (2007) |
| | U.S. | TEM | AOT40 | Reduced C sequestration by 18–38 Tg C/yr from 1950 to 1995 | Felzer et al. (2004) |
| | GSM National Park | DLEM | AOT40 | Decreased the ecosystem C storage of deciduous forests by 2.5% and pine forest by 1.4% from 1971 to 2001 | Zhang et al. (2007a) |
| | China | DLEM | AOT40 | Reduced total C storage by 0.06% in 1960s and 1.6% in 1990s in China’s terrestrial ecosystems | Ren et al. (2007b) |
| | China | DLEM | AOT40 | O ₃ exposure reduced the net C sink of China’s terrestrial ecosystem by 7% from 1961 to 2005 | Tian et al. (2011) |
| | China | DLEM | AOT40 | Ozone induced net carbon exchange reduction ranged from 0.4-43.1% , depending on different forest type | Ren et al. (2011) |

^aCUOt is defined as the cumulative stomatal uptake of O₃, using a constant O₃-uptake rate threshold of t nmol/m²/sec.

^bPg equals 1 × 10¹⁵ grams.

9.4.4 Crop Yield and Quality in Agricultural Systems

1 The detrimental effect of O₃ on crop production has been recognized since the 1960s and
 2 a large body of research has stemmed from that recognition. Previous O₃ AQCDs have
 3 extensively reviewed this body of literature. [Table 9-4](#) summarizes recent experimental
 4 studies of O₃ effects on agricultural crops, exclusive of growth and yield. Growth and
 5 yield results are summarized in [Table 9-17](#).

1 The actual concentration and duration threshold for O₃ damage varies from species to
2 species and sometimes even among genotypes of the same species ([Guidi et al., 2009](#);
3 [Sawada and Kohno, 2009](#); [Biswas et al., 2008](#); [Ariyaphanphitak et al., 2005](#); [Dalstein and](#)
4 [Vas, 2005](#); [Keutgen et al., 2005](#)). A number of comprehensive reviews and meta-analyses
5 have recently been published discussing both the current understanding of the
6 quantitative effects of O₃ concentration on a variety of crop species and the potential
7 focus areas for biotechnological improvement to a future growing environment that will
8 include higher O₃ concentrations ([Bender and Weigel, 2011](#); [Booker et al., 2009](#);
9 [VanDingenen et al., 2009](#); [Ainsworth, 2008](#); [Feng et al., 2008](#); [Hayes et al., 2007](#); [Mills](#)
10 [et al., 2007](#); [Grantz et al., 2006](#); [Morgan et al., 2003](#)). Since the 2006 O₃ AQCD ([U.S.](#)
11 [EPA, 2006b](#)), exposure-response indices for a variety of crops have been suggested
12 ([Mills et al., 2007a](#)) and many reports have investigated the effects of O₃ concentration
13 on seed or fruit quality to extend the knowledge base beyond yield quantity. This section
14 will outline the key findings from these papers as well as highlight some of the recent
15 research addressing the endpoints such as yields and crop quality.

16 This section will also highlight recent literature that focuses on O₃ damage to crops as
17 influenced by other environmental factors. Genetic variability is not the only factor that
18 determines crop response to O₃ damage. Ozone concentration throughout a growing-
19 season is not homogeneous and other environmental conditions such as elevated CO₂
20 concentrations, drought, cold or nutrient availability may alleviate or exacerbate the
21 oxidative stress response to a given O₃ concentration.

9.4.4.1 Yield

22 It is well known that yield is negatively impacted in many crop species in response to
23 high O₃ concentration. However, the concentrations at which damage is observed vary
24 from species to species. Numerous analyses of experiments conducted in OTCs and with
25 naturally occurring gradients demonstrate that the effects of O₃ exposure also vary
26 depending on the growth stage of the plant; plants grown for seed or grain are often most
27 sensitive to exposure during the seed or grain-filling period ([Soja et al., 2000](#); [Pleijel et](#)
28 [al., 1998](#); [Younglove et al., 1994](#); [Lee et al., 1988a](#)). AX9.5.4.1 of the 2006 O₃ AQCD
29 summarized many previous studies on crop yield.

Field studies and meta-analyses

30 The effect of O₃ exposure on U.S. crops remains an important area of research and
31 several studies have been published on this topic since the 2006 O₃ AQCD ([U.S. EPA,](#)
32 [2006b](#)) ([Table 9-4](#) and [Table 9-17](#)). For example, one study with cotton in a crop-weed

1 interaction study ([Grantz and Shrestha, 2006](#)) utilizing OTCs suggests that 12-hour
2 average O₃ concentrations of 79.9 ppb decreased cotton biomass by 25% and 12-hour
3 average O₃ concentration of 122.7 ppb decreased cotton biomass by 75% compared to
4 charcoal filtered control (12-h avg: 12.8 ppb). Further, this study suggests that the weed,
5 yellow nutsedge, was less sensitive to increasing O₃ concentration, which would increase
6 weed competition ([Grantz and Shrestha, 2006](#)). In a study of peanuts in North Carolina,
7 near ambient and elevated exposures of O₃ reduced photosynthesis and yield compared to
8 very low O₃ conditions ([Booker et al., 2007](#); [Burkey et al., 2007](#)). In another study,
9 [Grantz and Vu \(2009\)](#) reported that sugarcane biomass growth significantly declined
10 under O₃ exposure.

11 The average yield loss reported across a number of meta-analytic studies have been
12 published recently for soybean ([Morgan et al., 2003](#)), wheat ([Feng et al., 2008b](#)), rice
13 ([Ainsworth, 2008](#)), semi-natural vegetation ([Hayes et al., 2007](#)), potato, bean and barley
14 ([Feng and Kobayashi, 2009](#)). Meta-analysis allows for the objective development of a
15 quantitative consensus of the effects of a treatment across a wide body of literature.
16 Further, this technique allows for a compilation of data across a range of O₃ fumigation
17 techniques, durations and concentrations in order to assemble the existing literature in a
18 meaningful manner.

19 [Morgan et al. \(2003\)](#) reported an average seed yield loss for soybean of 24% compared to
20 charcoal filtered air across all O₃ concentrations used in the 53 compiled studies. The
21 decrease in seed yield appeared to be the product of nearly equal decreases (7-12%) in
22 seed weight, seed number and pod number. As would be expected, the lowest O₃
23 concentration (30-59 ppb) resulted in the smallest yield losses, approximately 8%, while
24 the highest O₃ concentration (80-120 ppb) resulted in the largest yield losses,
25 approximately 35% ([Morgan et al., 2003](#)). Further, the oil/protein ratio within the
26 soybean seed was altered due to growth at elevated O₃ concentrations, with a decrease in
27 oil content. The studies included in this meta-analysis all used enclosed fumigation
28 systems or growth chambers which may have altered the coupling of the atmosphere to
29 the lower plant canopy ([McLeod and Long, 1999](#)), although the results of [Morgan et al.](#)
30 [\(2006\)](#), [Betzelberger et al. \(2010\)](#), and the comparisons presented in Section [9.6.3](#)
31 strongly suggest that decreases in yield between ambient and elevated exposures are not
32 affected by exposure method. Utilizing the Soybean Free Air gas Concentration
33 Enrichment Facility (SoyFACE; www.soyface.illinois.edu). [Morgan et al. \(2006\)](#)
34 reported a 20% seed yield loss due to a 23% increase in average daytime O₃
35 concentration (56-69 ppb) within a single soybean cultivar across two growing seasons in
36 Illinois, which lies within the range predicted by the meta-analysis. A further breakdown
37 of the effects of current O₃ concentrations (AOT40 of 4.7 ppm-h) on bean seed quality
38 (*Phaseolus vulgaris*) has identified that growth at current O₃ concentrations compared to

1 charcoal-filtered air raised total lipids, total crude protein and dietary fiber content ([Iriti et](#)
2 [al., 2009](#)). An increase in total phenolics was also observed, however the individual
3 phenolic compounds responded differently, with significant decreases in anthocyanin
4 content. The seeds from ambient O₃ exposed plants also displayed increased total
5 antioxidant capacity compared to charcoal-filtered air controls ([Iriti et al., 2009](#)).
6 [Betzelberger et al. \(2010\)](#) has recently utilized the SoyFACE facility to compare the
7 impact of elevated O₃ concentrations across 10 soybean cultivars to investigate
8 intraspecific variability of the O₃ response to find physiological or biochemical markers
9 for eventual O₃ tolerance breeding efforts ([Betzelberger et al., 2010](#)). They report an
10 average 17% decrease in yield across all 10 cultivars across two growing seasons due to a
11 doubling of ambient O₃ concentrations, with the individual cultivar responses ranging
12 from -7% to -36%. The exposure-response functions derived for these 10 current
13 cultivars were similar to the response functions derived from the NCLAN studies
14 conducted in the 1980s ([Heagle, 1989](#)), suggesting there has not been any selection for
15 increased tolerance to O₃ in more recent cultivars. More complete comparisons between
16 yield predictions based on data from cultivars used in NCLAN studies, and yield data for
17 modern cultivars from SoyFACE are reported in Section [9.6.3](#) of this document. They
18 confirm that the response of soybean yield to O₃ exposure has not changed in current
19 cultivars.

20 A meta-analysis has also been performed on studies investigating the effects of O₃
21 concentrations on wheat ([Feng et al., 2008b](#)). Across 23 studies included, elevated O₃
22 concentrations (ranging from a 7-h daily average of 31-200 ppb) decreased grain yield by
23 29%. Winter wheat and spring wheat did not differ in their responses; however the
24 response in both varieties to increasing O₃ concentrations resulted in successively larger
25 decreases in yield, from a 20% decrease in 42 ppb to 60% in 153 ppb O₃. These yield
26 losses were mainly caused by a combination of decreases in individual grain weight
27 (-18%), ear number per plant (-16%), and grain number per ear (-11%). Further, the grain
28 starch concentration decreased by 8% and the grain protein yield decreased by 18% due
29 to growth at elevated O₃ concentrations as well. However, increases in grain calcium and
30 potassium levels were reported ([Feng et al., 2008b](#)).

31 A recent meta-analysis found that growth at elevated O₃ concentrations negatively
32 impacts nearly every aspect of rice performance as well ([Ainsworth, 2008](#)). While rice is
33 not a major crop in the U.S., it provides a staple food for over half of the global
34 population ([IRRI, 2002](#)) and the effects of rising O₃ concentrations on rice yields merit
35 consideration. On average, rice yields decreased 14% in 62 ppb O₃ compared to charcoal-
36 filtered air. This yield loss was largely driven by a 20% decrease in grain number
37 ([Ainsworth, 2008](#)).

1 [Feng and Kobayashi \(2009\)](#) have recently compiled yield data for six major crop species,
2 potato, barley, wheat, rice, bean and soybean and grouped the O₃ treatments used in those
3 studies into three categories: baseline O₃ concentrations (<26 ppb), current ambient 7- or
4 12-h daily O₃ concentrations (31-50 ppb), and future ambient 7- or 12-h daily O₃
5 concentrations (51-75 ppb). Using these categories, they have effectively characterized
6 the effects of current O₃ concentrations and the effects of future O₃ concentrations
7 compared to baseline O₃ concentrations. At current O₃ concentrations, which ranged from
8 41-49 ppb in the studies included, soybean (-7.7%), bean (-19.0%), barley (-8.9%), wheat
9 (-9.7%), rice (-17.5%) and potato (-5.3%) all had yield losses compared to the baseline
10 O₃ concentrations (<26 ppb). At future O₃ concentrations, averaging 63 ppb, soybean
11 (-21.6%), bean (-41.4%), barley (-14%), wheat (-28%), rice (-17.5%) and potato (-11.9%)
12 all had significantly larger yield losses compared to the losses at current O₃
13 concentrations (<26 ppb) ([Feng and Kobayashi, 2009](#)).

14 A review of OTC studies has determined the AOT40 critical level that causes a 5% yield
15 reduction across a variety of agricultural and horticultural species ([Mills et al., 2007a](#)).
16 The authors classify the species studied into three groups: sensitive, moderate and
17 tolerant. The sensitive crops, including watermelon, beans, cotton, wheat, turnip, onion,
18 soybean, lettuce, and tomato, respond with a 5% reduction in yield under a 3-month
19 AOT40 of 6 ppm-h. Watermelon was the most sensitive with a critical level of
20 1.6 ppm-h. The moderately sensitive crops, including sugar beet, oilseed rape, potato,
21 tobacco, rice, maize, grape and broccoli, responded with a 5% reduction in yield between
22 8.6 and 20 ppm-h. The crops classified as tolerant, including strawberry, plum and barley,
23 responded with a 5% yield reduction between 62-83.3 ppm-h ([Mills et al., 2007a](#)).

24 [Feng and Kobayashi \(2009\)](#) compared their exposure-response results to those published
25 by [Mills et al. \(2007a\)](#) and found the ranges of yield loss to be similar for soybean, rice
26 and bean. However, [Feng and Kobayashi \(2009\)](#) reported smaller yield losses for potato
27 and wheat and larger yield losses for barley compared to the dose-response functions
28 published by [Mills et al. \(2007a\)](#), which they attributed to their more lenient criteria for
29 literature inclusion.

30 While the studies investigating the impact of various O₃ concentrations on yield are
31 important and aid in determining the vulnerability of various crops to a variety of O₃
32 concentrations, there is still uncertainty as to how these crops respond under field
33 conditions with interacting environmental factors such as temperature, soil moisture, CO₂
34 concentration, and soil fertility ([Booker et al., 2009](#)). Further, there appears to be a
35 distinct developmental and genotype dependent influence on plant sensitivity to O₃ that
36 has yet to be fully investigated across O₃ concentrations in a field setting. The potentially
37 mitigating effect of breeding selection for O₃ resistance has received very little attention

1 in the published scientific literature. Anecdotal reports suggest that such selection may
2 have occurred in recent decades for some crops in areas of the country with high ambient
3 exposures. However, the only published literature available is on soybean and these
4 studies indicate that sensitivity has not changed in cultivars of soybean between the
5 1980s and the 2000s ([Betzberger et al., 2010](#)). This conclusion for soybeans is
6 confirmed by comparisons presented in Section [9.6.3](#) of this document.

Yield loss at regional and global scales

7 Because O₃ is heterogeneous in both time and space and O₃ monitoring stations are
8 predominantly near urban areas, the impacts of O₃ on current crop yields at large
9 geographical scales are difficult to estimate. [Fishman et al. \(2010\)](#) have used satellite
10 observations to estimate O₃ concentrations in the contiguous tri-state area of Iowa,
11 Illinois and Indiana and have combined that information with other measured
12 environmental variables to model the historical impact of O₃ concentrations on soybean
13 yield across the 2002-2006 growing seasons. When soybean yield across Iowa, Indiana
14 and Illinois was modeled as a function of seasonal temperature, soil moisture and O₃
15 concentrations, O₃ had the largest contribution to the variability in yield for the southern-
16 most latitudes included in the dataset. [Fishman et al. \(2010\)](#) determined that O₃
17 concentrations significantly reduced soybean yield by 0.38 to 1.63% for every
18 additional ppb of exposure across the 5 years. This value is consistent with previous
19 chamber studies ([Heagle, 1989](#)) and results from SoyFACE ([Morgan et al., 2006](#)).
20 Satellite estimates of tropospheric O₃ concentrations exist globally ([Fishman et al., 2008](#)),
21 therefore utilizing this historical modeling approach is feasible across a wider
22 geographical area, longer time-span and perhaps for more crop species.

23 The detrimental effects of O₃ on crop production at regional or global scales were also
24 assessed by several model studies. Two large scale field studies were conducted in the
25 U.S. (NCLAN) and in Europe (European Open Top Chamber Programme, EOTCP) to
26 assess the impact of O₃ on crop production. Ozone exposure-response regression models
27 derived from the two programs have been widely used to estimate crop yield loss
28 ([Avnery et al., 2011a, b](#); [VanDingenen et al., 2009](#); [Tong and Mauzerall, 2008](#); [Wang and
29 Mauzerall, 2004](#)). Those studies found that O₃ generally reduced crop yield and that
30 different crops showed different sensitivity to O₃ pollution (

31 Table 9-5). Ozone was calculated to induce a possible 45-82 million metric tons loss for
32 wheat globally. Production losses for rice, maize and soybean were on the order of
33 17-23 million metric tons globally ([VanDingenen et al., 2009](#)). The largest yield losses
34 occur in high-production areas exposed to high O₃ concentrations, such the Midwest and

1 the Mississippi Valley regions in the U.S., Europe, China and India ([VanDingenen et al.,](#)
2 [2009](#); [Tong et al., 2007](#)).

9.4.4.2 Crop Quality

3 In general, it appears that increasing O₃ concentrations above current ambient
4 concentrations can cause species-dependent biomass losses, decreases in root biomass
5 and nutritive quality, accelerated senescence and shifts in biodiversity. A study conducted
6 with highbush blackberry has demonstrated decreased nutritive quality with increasing O₃
7 concentration despite no change in biomass between charcoal-filtered control, ambient O₃
8 and 2 × ambient O₃ exposures ([Ditchkoff et al., 2009](#)). A study conducted with sedge
9 using control (30 ppb), low (55 ppb), medium (80 ppb) and high (105 ppb) O₃ treatments
10 has demonstrated decreased root biomass and accelerated senescence in the medium and
11 high O₃ treatments ([Jones et al., 2010](#)). Alfalfa showed no biomass changes across
12 two years of double ambient O₃ concentrations (AOT40 of 13.9 ppm-h) using FACE
13 fumigation ([Maggio et al., 2009](#)). However a modeling study has demonstrated that 84%
14 of the variability in the relative feed value in high-yielding alfalfa was due to the
15 variability in mean O₃ concentration from 1998-2002 ([Lin et al., 2007](#)). Further, in a
16 managed grassland FACE system, the reduction in total biomass harvest over five years
17 decreased twice as fast in the elevated treatment (AOT40 of 13-59 ppm-h) compared to
18 ambient (AOT40 of 1-20.7 ppm-h). Compared with the ambient control, loss in annual
19 dry matter yield was 23% after 5 year. Further, functional groups were differentially
20 affected, with legumes showing the strongest negative response ([Volk et al., 2006](#)).
21 However, a later study by [Stampfli and Fuhrer \(2010\)](#) at the same site suggested that
22 [Volk et al. \(2006\)](#) likely overestimated the effects of O₃ on yield reduction because the
23 overlapping effects of species dynamics caused by heterogeneous initial conditions and a
24 change in management were not considered by these authors. An OTC study conducted
25 with *Trifolium subterraneum* exposed to filtered (<15 ppb), ambient, and 40 ppb above
26 ambient O₃ demonstrated decreases in biomass in the highest O₃ treatment as well as 10-
27 20% decreased nutritive quality which was mainly attributed to accelerated senescence
28 ([Sanz et al., 2005](#)). A study conducted with Eastern gamagrass and big bluestem in OTCs
29 suggested that big bluestem was not sensitive to O₃, but gamagrass displayed decreased
30 nutritive quality in the 2 × ambient O₃ treatment, due to higher lignin content and
31 decreased N ([Lewis et al., 2006](#)).

9.4.4.3 Summary

1 The detrimental effect of O₃ on crop production has been recognized since the 1960's and
2 a large body of research has subsequently stemmed from those initial findings. Previous
3 O₃ AQCDs have extensively reviewed this body of literature ([U.S. EPA, 2006b](#)). Current
4 O₃ concentrations across the U.S. are high enough to cause yield loss for a variety of
5 agricultural crops including, but not limited to, soybean, wheat, potato, watermelon,
6 beans, turnip, onion, lettuce, and tomato. Continued increases in O₃ concentration may
7 further decrease yield in these sensitive crops. Despite the well-documented yield losses
8 due to increasing O₃ concentration, there is still a knowledge gap pertaining to the exact
9 mechanisms of O₃-induced yield loss. Research has linked increasing O₃ concentration to
10 decreased photosynthetic rates and accelerated senescence, which are related to yield.

11 New research is beginning to consider the mechanism of damage caused by prolonged,
12 lower O₃ concentration (so-called chronic exposure) compared to short, very high O₃
13 concentration (so-called acute exposure). Both types of O₃ exposure cause damage to
14 agricultural crops, but through very different mechanisms. Historically, most research on
15 the mechanism of O₃ damage used acute exposure studies. During the last decade, it has
16 become clear that the cellular and biochemical processes involved in the response to
17 acute O₃ exposure are not involved in response to chronic O₃ exposure, even though both
18 cause yield loss in agriculturally important crops.

19 In addition, recent research has highlighted the effects of O₃ on crop quality. Increasing
20 O₃ concentration decreases nutritive quality of grasses, decreases macro- and micro-
21 nutrient concentrations in fruits and vegetable crops, and decreases cotton fiber quality.
22 These areas of research require further investigation to determine mechanisms and
23 exposure-response relationships.

24 During the previous NAAQS reviews, there were very few studies that estimated O₃
25 impacts on crop yields at large geographical scales. Recent modeling studies found that
26 O₃ generally reduced crop yield, but the impacts varied across regions and crop species.
27 For example, the largest O₃-induced crop yield losses occurred in high-production areas
28 exposed to high O₃ concentrations, such the Midwest and the Mississippi Valley regions
29 of the U.S. ([VanDingenen et al., 2009](#)). Among crop species, the estimated yield loss for
30 wheat and soybean were higher than for rice and maize ([VanDingenen et al., 2009](#)).

31 Using satellite air-column observations with direct air-sampling O₃ data, [Fishman et al.](#)
32 [\(2010\)](#) modeled the yield-loss due to O₃ over the continuous tri-state area of Illinois,
33 Iowa and Wisconsin. They determined that O₃ concentrations significantly reduced
34 soybean yield, which further reinforces previous results from FACE-type experiments
35 and OTC experiments. Evidence is sufficient to conclude that **there is a causal**

1
2

relationship between O₃ exposure and reduced yield and quality of agricultural crops.

Table 9-4 Summary of recent studies of ozone effects on crops (exclusive of growth and yield).

| Species Facility Location | Exposure Duration | Ozone Exposure ^a (Additional treatment) | Variable(s) measured | Percent (%) change from CF ^b (% change from ambient) | Reference |
|---|--|---|---|--|--|
| Alfalfa (<i>Medicago sativa</i> cv. Beaver) Growth chambers | 1, 2 or 4 days | 3 or 5 h/day 85 ppb (Exposure duration) | Relative feed value | n.s. *high variability among treatment groups (N/A) | Muntifering et al. (2006b) |
| Bean (<i>Phaseolus vulgaris</i> l. cv Borlotto) OTC, ground- planted Curno, Italy | 4 months | Seasonal AOT40: CF = 0.5 ppm-h; Ambient = 4.6 ppm-h (N/A) | Seed lipid, Protein content Fiber content | +28.5 (N/A) +7.88 (N/A) +14.54 (N/A) | Iriti et al. (2009) |
| Big Blue Stem (<i>Andropogon gerardii</i>) OTC Alabama, U.S. | 4 months | 12-h avg: CF = 14 ppb; Ambient = 29 ppb; Elevated = 71 ppb (N/A) | Relative feed value | n.s. (n.s.) | Lewis et al. (2006) |
| <i>Brassica napus</i> Growth chambers Belgium | 4 days | CF & 176 ppb for 4 h/day (N/A) | Glucosinolates | -41 (N/A) | Gielen et al. (2006) |
| <i>Brassica napus</i> cv. Westar Growth chambers Finland | 17-26 days | 8-h avg: CF & 100 ppb (Bt/non-Bt; herbivory) | VOC emissions | -30.7 (N/A); -34 (N/A) | Himanen et al. (2009b) |
| Eastern Gamagrass (<i>Tripsacum dactyloides</i>) OTC Alabama, U.S. | 4 months | 12-h avg: CF = 14 ppb; Ambient = 29 ppb; Elevated = 71 ppb (N/A) | Relative feed value | -17 (-12) | Lewis et al. (2006) |
| Lettuce (<i>Lactuca sativa</i>) OTC Carcaixent Experimental Station, Spain | 30 days | 12-h mean: CF = 10.2 ppb; NF = 30.1 ppb; NF+O ₃ = 62.7 ppb (4 cultivars) | Lipid peroxidation; Root length | +77 (+38) -22 (-14) | Calatayud et al. (2002) |
| Peanut (<i>Arachis hypogaea</i>) OTC Raleigh, NC; U.S. | 3 yr | 12-h avg: CF = 22 ppb; Ambient = 46 ppb; Elevated = 75 ppb (CO ₂ : 375 ppm; 548 ppm; 730 ppm) | Harvest biomass | -40 (-10) | Booker et al. (2007) |
| <i>Poa pratensis</i> OTC Braunschweig, Germany | 3 yr; 4-5 weeks in the spring | 8-h avg: CF+25 = 21.7 ppb; NF+50 = 73.1 ppb (Competition) | Relative feed value | N/A (n.s.; -8) | Bender et al. (2006) |

| Species Facility Location | Exposure Duration | Ozone Exposure ^a (Additional treatment) | Variable(s) measured | Percent (%) change from CF ^b (% change from ambient) | Reference |
|---|----------------------|--|---|--|--|
| Potato (<i>Solanum tuberosum</i> cv. Bintje) OTC Sweden & Finland | 2 yr | CF = 10 ppb; Ambient = 25 ppb; Ambient(+) = (36 ppb); Ambient(++) = (47 ppb) (N/A) | [K], [Ca], [Mg], [P], [N] per dry weight of tubers *dose-response regression, report significant positive or negative slope with increasing [O ₃] | [N] [P] [Ca] n.s.; [K] & [Mg] sig + (N/A) | Piikki et al. (2007) |
| Potato (<i>Solanum tuberosum</i> cv. Indira) Climate chambers Germany | 8 weeks | CF = 10 ppb; Ambient = 50 ppb; 2x Ambient = 100 ppb (CO ₂ : 400 ppm & 700 ppm) | Pathogen infestation using percent necrosis | +52 (n.s.) | Plessl et al. (2007) |
| Soybean OTC Italy | 3 yr | AOT40: CF = 0 ppm-h; Ambient = 3.4 ppm-h; Elevated = 9.0 ppm-h (Well-watered & water-stressed) | Daily evapotranspiration | -28 (-14) | Bou Jaoudé et al. (2008a) |
| Soybean (<i>Glycine max</i> cv. 93B15) SoyFACE Urbana, IL; U.S. | 3 yr May-Oct | AOT40: Ambient = 5-22 ppm-h; Elevated = 20-43 ppm-h (CO ₂ : 550 ppm; environmental variability) | Photosynthesis in new leaves, | N/A (n.s.) | Bernacchi et al. (2006) |
| Soybean (<i>Glycine max</i> cv. 93B15) SoyFACE Urbana, IL; U.S. | 4 months | 8-h avg: Ambient = 38.5 ppb; Elevated = 52 ppb (Herbivory) | Herbivory defense-related genes | N/A (N/A) | Casteel et al. (2008) |
| Soybean (<i>Glycine max</i> cv. Essex) OTC, ground- planted Raleigh, NC; U.S. | 2 yr | 12-h avg: CF = 21 ppb; 1.5x Ambient = 74 ppb (CO ₂ : 370 ppm & 714 ppm) | Post-harvest residue | N/A (-15.46) | Booker et al. (2005) |
| Soybean (<i>Glycine max</i> cv. Essex) OTCs, 21 L pots Raleigh, NC; U.S. | 3 months | 12-h avg: CF = 18 ppb); Elevated = 72 ppb) (CO ₂ : 367 & 718) | Water-use efficiency | n.s. (N/A) | Booker et al. (2004b) |
| Soybean (<i>Glycine max</i>) 10 cultivars) SoyFACE Urbana, IL; U.S. | 2 yr | 8-h avg (ppb): Ambient = 46.3 & 37.9; Elevated = 82.5 & 61.3 (Cultivar comparisons) | Total antioxidant capacity | N/A (+19) | Betzelberger et al. (2010) |
| Spring Wheat (<i>Triticum aestivum</i> cv. Minaret; Satu; Drabant; Dragon) OTCs Belgium, Finland, & Sweden | 7 yr | Seasonal AOT40s ranged from: 0 to16 ppm-h (N/A) | Seed protein content; 1,000-seed weight regressed across all experiments | N/A (Significant negative correlation) N/A (Significant negative correlation) | Piikki et al. (2008b) |

| Species Facility Location | Exposure Duration | Ozone Exposure ^a (Additional treatment) | Variable(s) measured | Percent (%) change from CF ^b (% change from ambient) | Reference |
|--|----------------------|--|--|--|--|
| Strawberry (<i>Fragaria x ananassa</i> Duch. Cv. Korona & Elsanta) Growth chambers Bonn, Germany | 2 months | 8-h avg: CF = 0 ppb; Elevated = 78 ppb (N/A) | Total leaf area | -16 (N/A) | Keutgen et al. (2005) |
| Sweet Potato Growth Chambers Bonn, Germany | 4 weeks | 8-h avg: CF = 0 ppb; Ambient <40 ppb; Elevated = 255 ppb (N/A) | Tuber weight | -14 (-11.5) | Keutgen et al. (2008) |
| Tomato (<i>Lycopersicon esculentum</i>) OTC Valencia, Spain | 133 days | 8- mean: CF = 16.3 ppb; NF = 30.1 ppb; NF(+) = 83.2 ppb (Various cultivars; early & late harvest) | Brix degree | -7.2 (-3.6) | Dalstein and Vas (2005) |
| <i>Trifolium repens</i> & <i>Trifolium pretense</i> Aspen FACE Rhineland, WI; U.S. | 3 months | 3-mo daylight avg: Ambient = 34.8 ppb; 1.2x Ambient = 42.23 ppb (CO ₂ ; 560 ppm) | Lignin; Dry-matter digestibility | N/A (+19.3) N/A (-4.2) | Muntifering et al. (2006a) |

^aOzone exposure in ppb unless otherwise noted.

^bCF = Carbon-filtered air.

NF = Non-filtered air.

Table 9-5 Modeled effects of ozone on crop yield loss at regional and global scales

| Scale | Index | O ₃ Impacts | Reference |
|-----------|------------------|--|--|
| Global | M7a; M12b; AOT40 | Reduced by 7.3% to 12.3% for wheat, 5.4% to 15.6% for soybean, 2.8% to 3.7% for rice, and 2.4% to 4.1% for maize in year 2000. | Van Dingenen et al. (2009) |
| Global | M12b; AOT40 | O ₃ -induced global yield reductions ranged from 8.5-14% for soybean, 3.9-15% for wheat, and 2.2-5.5% for maize in year 2000. Global crop production losses totaled 79-121 million metric tons, worth \$11-18 billion annually (in U.S. Dollars; 2000). | Avnery et al. (2011a) |
| U.S. | M7; M12; AOT40 | Reduced by 4.1% to 4.4% for wheat, 7.1% to 17.7% for soybean, 2.6% to 3.2% for rice, and 2.2% to 3.6% for maize in year 2000. | Van Dingenen et al. (2009) |
| U.S. | SUM06 | Caused a loss of 53.8 million to 438 million bushels in soybean production, which account for 1.7–14.2% of total U.S. soybean production in 2005 | Tong et al. (2007) |
| East Asia | M7; M12 | Reduced the yield of wheat, rice and corn by 1–9% and soybean by 23–27% in China, Japan and South Korea in 1990 | Wang and Mauzerall (2004) |

^aM7 is defined as 7-h mean O₃ concentration (ppb).

^bM12 is defined as 12-h mean O₃ concentration (ppb).

9.4.5 Water Cycling

1 Ozone can affect water use in plants and ecosystems through several mechanisms
 2 including damage to stomatal functioning and loss of leaf area. [Figure 9-7](#) provides a
 3 simple illustration of potential effects of O₃ exposure on water cycling. Section [9.3.2](#)
 4 reviewed possible mechanisms for effects of O₃ exposure on stomatal functioning. This
 5 section on water cycling discusses how this alteration of stomatal functioning may affect
 6 water use in leaves, whole plants, a planted forest and watersheds. .

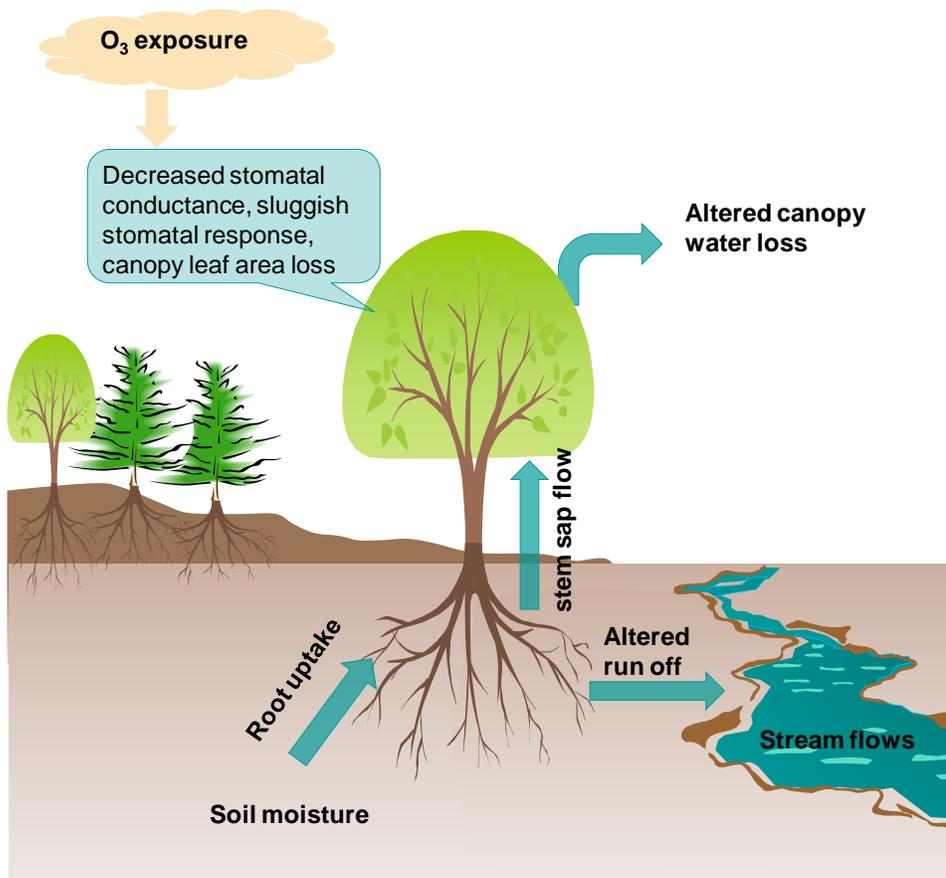


Figure 9-7 The potential effects of ozone exposure on water cycling.

1 In the literature, there is not a clear consensus on the nature of leaf-level stomatal
 2 conductance response to O₃ exposure. At the leaf level, O₃ exposure is known to result in
 3 stomatal patchiness ([Paoletti and Grulke, 2005](#); [Omasa et al., 1987](#); [Ellenson and](#)
 4 [Amundson, 1982](#)), i.e., the heterogeneous aperture widths of stomata on the leaf surface,
 5 and, as a result, the collective response of groups of stomata on leaves and canopies
 6 determines larger-scale responses to O₃. When measured at steady-state high light
 7 conditions, leaf-level stomatal conductance is often found to be reduced when exposed to
 8 O₃. For example, a meta-analysis of 55 studies found that O₃ reduced stomatal
 9 conductance by 11% ([Wittig et al., 2007](#)). However, these steady-state measurements
 10 were generally taken at saturating light conditions and steady-state vapor pressure deficit
 11 (VPD). Saturating light and steady-state VPD conditions are not common in the field
 12 since many parts of the plant canopy are shaded throughout the day. When studied under
 13 varying environmental conditions, many studies have reported incomplete stomatal
 14 closure with elevated O₃ exposure during the day ([Mills et al., 2009](#); [Grulke et al., 2007b](#);
 15 [Matyssek et al., 1995](#); [Wieser and Havranek, 1995](#)) or at night ([Grulke et al., 2004](#)). This

1 may be due to sluggish stomatal response. Sluggish stomatal response, defined as a delay
2 in stomatal response to changing environmental factors relative to controls ([Paoletti and](#)
3 [Grulke, 2010](#)) has also been documented by several researchers ([Grulke et al., 2007c](#);
4 [Matyssek et al., 1995](#); [Pearson and Mansfield, 1993](#); [Wallin and Skärby, 1992](#); [Lee et al.,](#)
5 [1990](#); [Skarby et al., 1987](#); [Keller and Häsler, 1984](#); [Reich and Lassoie, 1984](#)). Sluggish
6 stomatal response associated with O₃ exposure suggests an uncoupling of the normally
7 tight relationship between carbon assimilation and stomatal conductance as measured
8 under steady-state conditions ([Gregg et al., 2006](#); [Paoletti and Grulke, 2005](#)). Several tree
9 and ecosystem models, such as TREGRO, PnET and DLEM, rely on this tight
10 relationship to simulate water and carbon dynamics. The O₃-induced impairment of
11 stomatal control may be more pronounced for plants growing under water stress
12 ([Wilkinson and Davies, 2010](#); [Grulke et al., 2007a](#); [Paoletti and Grulke, 2005](#); [Bonn et](#)
13 [al., 2004](#); [Kellomaki and Wang, 1997](#); [Tjoelker et al., 1995](#); [Reich and Lassoie, 1984](#)).
14 Since leaf-level stomatal regulation is usually assessed in a steady state rather than as a
15 dynamic response to changing environmental conditions, steady state measurements
16 cannot detect sluggish stomatal response. Because of sluggish stomatal responses, water
17 loss from plants could be greater or reduced under dynamic environmental conditions
18 over days and months. In situations where stomata fail to close under low light or water
19 stressed conditions, water loss may be greater over time. In other situations, it is possible
20 that sluggish stomata may fail to completely open in response to environmental stimuli
21 and result in decreased water loss.

22 In addition to the impacts on stomatal performance, O₃-induced physiological changes,
23 such as reduced leaf area index and accelerated leaf senescence could alter water use
24 efficiency. It is well established from chamber and field studies that O₃ exposure is
25 correlated with lower foliar retention ([Karnosky et al., 2003](#); [Topa et al., 2001](#); [Pell et al.,](#)
26 [1999](#); [Grulke and Lee, 1997](#); [Karnosky et al., 1996](#); [Miller et al., 1972](#); [Miller et al.,](#)
27 [1963](#)). However, [Lee et al. \(2009a\)](#) did not find changes in needle area of ponderosa pine
28 and reported that greater canopy conductance followed by water stress under elevated O₃
29 may have been caused by stomatal dysfunction. At the Aspen FACE experiment, stand-
30 level water use, as indicated by sap flux per unit ground area, was not significantly
31 affected by elevated O₃ despite a 22% decrease in leaf area index and 20% decrease in
32 basal area ([Uddling et al., 2008](#)). The lack of negative effect of elevated O₃ on stand
33 water use may be due to the substantially increased leaf area-specific hydraulic
34 conductance ([Uddling et al., 2009](#)). The increased leaf area-specific hydraulic
35 conductance may be caused by the sluggish stomatal response. For example, in the pure
36 aspen stands, the stomatal closure response to increasing vapor pressure deficit was less
37 sensitive and mid-day leaf water potential was more negative under elevated O₃
38 compared to controls. This suggests that O₃ impaired stomatal control over transpiration
39 ([Uddling et al., 2009](#)). Another potential factor contributing to the unchanged stand-level

1 water use included the higher proportion of sun leaves in trees under elevated O₃
2 compared with control trees ([Uddling et al., 2008](#)).

3 Elevated O₃ could also affect evapotranspiration by altering tree crown interception of
4 precipitation. Ozone was shown to change branch architectural parameters, and the
5 effects were species-dependent at the Aspen FACE experiment ([Rhea et al., 2010](#)). The
6 authors found that there was a significant correlation between canopy architecture
7 parameters and stemflow (the flow of intercepted water down the stem of a tree) for birch
8 but not aspen.

9 It is difficult to scale up physiology measurements from leaves to ecosystems. Thus, the
10 current understanding of how stomatal response at the leaf scale is integrated at the scale
11 of whole forest canopies, and therefore how it influences tree and forest stand water use
12 is limited. Field studies by ([McLaughlin et al., 2007a; 2007b](#)) provided valuable insight
13 into the possible consequences of stomatal sluggishness for ecosystem water cycling.
14 [McLaughlin et al. \(2007a\); \(2007b\)](#) indicated that O₃ increased water use in a mixed
15 deciduous forest in eastern Tennessee. [McLaughlin et al. \(2007a\); \(2007b\)](#) found that O₃,
16 with daily maximum levels ranging from 69.2 to 82.9 ppb, reduced stem growth by 30-
17 50% in the high-O₃ year 2002. The decrease in growth rate was caused in part by
18 amplification of diurnal cycles of water loss and recovery. Peak hourly O₃ exposure
19 increased the rate of water loss through transpiration as indicated by the increased stem
20 sap flow. The authors suggested that a potential mechanism for the increased sap flow
21 could be altered stomatal regulation from O₃ exposure, but this was inferred through sap
22 flow measurements and was not directly measured. The increased canopy water loss
23 resulted in higher water uptake by the trees as reflected in the reduced soil moisture in the
24 rooting zone. The change in tree water use led to further impacts on the hydrological
25 cycle at the landscape level. Increased water use under high O₃ exposure was reported to
26 reduce late-season modeled streamflow in three forested watersheds in eastern Tennessee
27 ([McLaughlin et al., 2007b](#)).

28 [Felzer et al. \(2009\)](#) used TEM-Hydro to assess the interactions of O₃, climate, elevated
29 CO₂ and N limitation on the hydrological cycle in the eastern U.S. They found that
30 elevated CO₂ decreased evapotranspiration by 2-4% and increased runoff by 3-7%, as
31 compared to the effects of climate alone. When O₃ damage and N limitation were
32 included, evapotranspiration was reduced by an additional 4-7% and runoff was increased
33 by an additional 6-11% ([Felzer et al., 2009](#)). Based upon simulation with INTRAST and
34 LINKAGES, [Hanson et al. \(2005\)](#) found that increasing O₃ concentration by 20 ppb
35 above the current ambient level yields a modest 3% reduction in water use. Those
36 ecological models were generally built on the assumption that O₃ induces stomatal
37 closure and have not incorporated possible stomatal sluggishness due to O₃ exposure.

1 Because of this assumption, results of those models normally found that O₃ reduced water
2 use.

9.4.5.1 Summary

3 Although the evidence was from a limited number of field and modeling studies, findings
4 showed an association between O₃ exposure and alteration of water use and cycling in
5 vegetation, and at the watershed level. There is not a clear consensus on the nature of
6 leaf-level stomatal conductance response to O₃ exposure. When measured under steady-
7 state high light conditions, leaf-level stomatal conductance is often found to be reduced
8 when plants are exposed to O₃. However, measurements of stomatal conductance under
9 dynamic light and VPD conditions indicate sluggish responses under elevated O₃
10 exposure, which could potentially lead to increased water loss from vegetation in some
11 situations. Field studies conducted by [McLaughlin et al. \(2007a\)](#); [\(2007b\)](#) suggested that
12 peak hourly O₃ exposure increased the rate of water loss from several tree species, and
13 led to a reduction in the late-season modeled stream flow in three forested watersheds in
14 eastern Tennessee. Sluggish stomatal responses during O₃ exposure was suggested as a
15 possible mechanism for increased water loss during peak O₃ exposure. Currently, the
16 O₃-induced reduction in stomatal aperture is the biological assumption for most process-
17 based models. Because of this assumption, results of those models normally found that
18 O₃ reduced water loss. For example, [Felzer et al. \(2009\)](#) found that O₃ damage and
19 N limitation together reduced evapotranspiration and increased runoff.

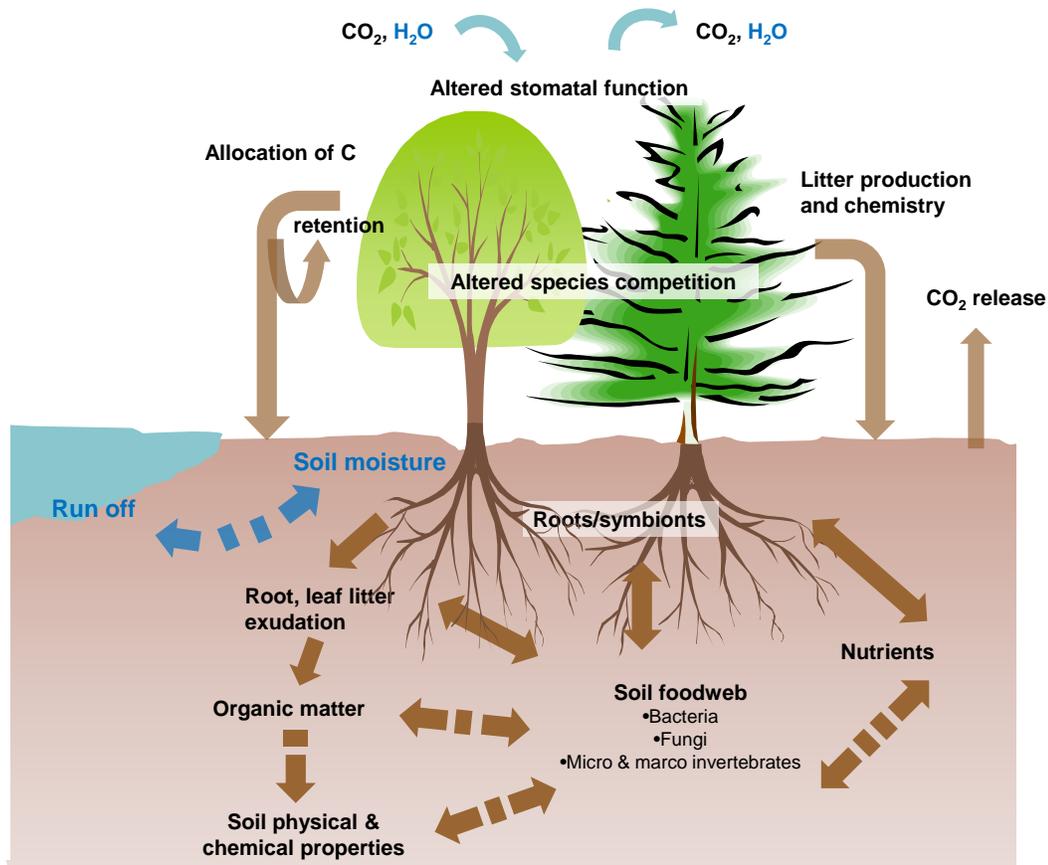
20 Although the direction of the response differed among studies, the evidence is sufficient
21 to conclude that there **is likely to be a causal relationship between O₃ exposure and**
22 **the alteration of ecosystem water cycling.**

9.4.6 Below-Ground Processes

23 Above-ground and below-ground processes are tightly interconnected. Because roots and
24 soil organisms are not exposed directly to O₃, below-ground processes are affected by O₃
25 through alterations in the quality and quantity of C supply from photosynthates and
26 litterfall ([Andersen, 2003](#)). Ozone can decrease leaf C uptake by reducing photosynthesis
27 (Section [9.3](#)). Ozone can also increase metabolic costs by stimulating the production of
28 chemical compounds for defense and repair processes, and by increasing the synthesis of
29 antioxidants to neutralize free radicals (see Section [9.3](#)), both of which increase the
30 allocation of carbon for above-ground processes. Therefore, O₃ could significantly reduce

1 the amount of C available for allocation to below-ground by decreasing C uptake while
 2 increasing C consumption of above-ground processes ([Andersen, 2003](#)).

3 Since the 2006 O₃ AQCD, there is additional evidence for O₃ effects on below-ground
 4 processes. Ozone has been found to alter root growth, soil food web structure,
 5 decomposer activities, C turnover, water cycling and nutrient flow ([Figure 9-8](#)). Ozone
 6 effects on root development and root biomass production and soil food web structure are
 7 reviewed in Section [9.4.3.1](#) and Section [9.4.9.2](#), respectively. The focus in this section is
 8 on the response of litter input, decomposer activities, soil respiration, soil C formation
 9 and nutrient cycling.



Note: Arrows denote C flux pathways that are affected by ozone. Dashed lines indicate where the impact of ozone is suspected but unknown.

Source: Modified from [Andersen \(2003\)](#).

Figure 9-8 Conceptual diagram showing where ozone alters C, water and nutrient flow in a tree-soil system, including transfer between biotic and abiotic components below ground that influence soil physical and chemical properties.

9.4.6.1 Litter Carbon Chemistry, Litter Nutrient and Their Ecosystem Budgets

1 Consistent with previous findings, recent studies show that, although the responses are
2 often species-dependent, O₃ tends to alter litter chemistry ([U.S. EPA, 2006b](#)). Alterations
3 in chemical parameters, such as changes in C chemistry and nutrient concentrations, were
4 observed in both leaf and root litter ([Table 9-6](#)).

5 At the Aspen FACE site, several studies investigated litter chemistry changes ([Parsons et](#)
6 [al., 2008](#); [Johnson and Pregitzer, 2007](#); [Chapman et al., 2005](#); [Liu et al., 2005](#)). In both
7 aspen and birch leaf litter, elevated O₃ increased the concentrations of soluble sugars,
8 soluble phenolics and condensed tannins ([Parsons et al., 2008](#); [Liu et al., 2005](#)).

9 Compared to other treatments, aspen litter under elevated O₃ had the highest fiber
10 concentration, with the lowest concentration associated with the birch litter under the
11 same conditions ([Parsons et al., 2008](#)). [Chapman et al. \(2005\)](#) measured chemical
12 changes in fine root litter and found that elevated O₃ decreased lignin concentration.
13 O₃-induced chemistry changes were also reported from other experimental sites. Results
14 from an OTC study in Finland suggested that elevated O₃ increased the concentration of
15 acid-soluble lignin, but had no significant impact on other chemicals such as total sugars,
16 hemicelluloses, cellulose or total lignin in the litter of silver birch ([Kasurinen et al.,](#)
17 [2006](#)). Results from the free air canopy O₃ exposure experiment at Kranzberg Forest
18 showed that O₃ increased starch concentrations but had no impact on cellulose and lignin
19 in beech and spruce leaf litter ([Aneja et al., 2007](#)). The effect of O₃ on three antioxidants
20 (ascorbate, glutathione and α-tocopherol) in fine roots of beech was also assessed at
21 Kranzberg Forest. The results indicated that O₃ had no significant effect on α-tocopherol
22 and ascorbate concentrations, but decreased glutathione concentrations in fine roots
23 ([Haberer et al., 2008](#)). In addition to changing C chemistry, O₃ also altered nutrient
24 concentrations in green leaves and litter ([Table 9-6](#)).

25 The combined effects of O₃ on biomass productivity and chemistry changes may alter
26 C chemicals and nutrient contents at the canopy or stand level. For example, although O₃
27 had different impacts on their concentrations, annual fluxes of C chemicals (soluble
28 sugar, soluble phenolics, condensed tannins, lipid and hemicelluloses), macro nutrients
29 (N, P, K and S) and micro nutrients (Mg, B, Cu and Zn) to soil were all reduced due to
30 lower litter biomass productivity at Aspen FACE ([Liu et al., 2007](#); [Liu et al., 2005](#)). In a
31 2-year growth chamber experiment in Germany, N content of a spruce canopy in a mixed
32 culture and Ca content of a beech canopy in a monoculture was increased due to elevated
33 O₃, although leaf production was not significantly altered by O₃ ([Rodenkirchen et al.,](#)
34 [2009](#)).

Table 9-6 The effect of elevated ozone on leaf/litter nutrient concentrations.

| Study Site | Species | O ₃ Concentration | Response | Reference |
|--|------------------|---|--|--|
| Suonenjoki Research Station, Finland | Silver birch | Ambient: 10-60 ppb Elevated: 2x ambient | Decreased the concentration of P, Mn, Zn and B in leaf litter | Kasurinen et al. (2006) |
| Aspen FACE | Aspen and birch | Ambient: 50-60 ppb Elevated: 1.5x ambient | Decreased the concentrations of P, S, Ca and Zn, but had no impact on the concentrations of N, K, Mg, Mn, B and Cu in leaf litter. | Liu et al. (2007)a) |
| Aspen FACE | Birch | Ambient: 50-60 ppb Elevated: 1.5x ambient | Increase N concentration in birch litter | Parsons et al. (2008) |
| Kranzberg Forest, Germany | Beech and spruce | Ambient: 9-41 ppb Elevated: 2x ambient | Increased N concentration in beech leaf, but not in spruce needle | Kozovits et al. (2005) |
| Kranzberg Forest, Germany | Beech and spruce | Ambient: 9-41 ppb Elevated: 2x ambient | (1) Had no significant effects on spruce needle chemistry; (2) increased Ca concentration in beech leaves in monoculture, but had no impacts on other nutrients | Rodenkirchen et al. (2009) |
| Salerno, Italy | Holm oak | Non-filtered OTC: 29 ppb Filtered OTC: 17ppb | O ₃ had no significant impacts on litter C, N, lignin and cellulose concentrations | Baldantoni et al. (2011) |
| Kuopio University Research Garden, Finland | Red Clover | Ambient: 25.7 ppb Elevated: 1.5x ambient | Increased the total phenolic content of leaves and had minor effects on the concentrations of individual phenolic compounds | Saviranta et al. (2010) |

9.4.6.2 Decomposer Metabolism and Litter Decomposition

1 The above- and below-ground physiological changes caused by O₃ exposure cascade
2 through the ecosystem and affect soil food webs. In the 2006 O₃ AQCD, there were very
3 few studies on the effect of O₃ on the structure and function of soil food webs, except two
4 studies conducted by [Larson et al. \(2002\)](#) and [Phillips et al. \(2002\)](#). Since the last O₃
5 AQCD, new studies have provided more information on how O₃ affects the metabolism
6 of soil microbes and soil fauna.

7 [Chung et al. \(2006\)](#) found that the activity of the cellulose-degrading enzyme
8 1,4-β-glucosidase was reduced by 25% under elevated O₃ at Aspen FACE. The decrease
9 in cellulose-degrading enzymatic activity was associated with the lower cellulose
10 availability under elevated O₃ ([Chung et al., 2006](#)). However, a later study at the same
11 site, which was conducted in the 10th year of the experiment, found that O₃ had no
12 impact on cellulolytic activity in soil ([Edwards and Zak, 2011](#)). In a lysimeter study of
13 beech trees (*Fagus sylvatica*) in Germany, soil enzyme activity was found to be
14 suppressed by O₃ exposure ([Esperschutz et al., 2009](#); [Pritsch et al., 2009](#)). Except for

1 xylosidase, enzyme activities involved in plant cell wall degradation (cellobiohydrolase,
2 beta-glucosidase and glucuronidase) were decreased in rhizosphere soil samples under
3 elevated O₃ (2 × ambient level) ([Pritsch et al., 2009](#)). Similarly, [Chen et al. \(2009\)](#) found
4 O₃ exposure, with a 3-month AOT40 of 21-44 ppm-h, decreased the microbial metabolic
5 capability in the rhizosphere and bulk soil of wheat, although the observed reduction in
6 bulk soil was not significant.

7 Ozone-induced change in soil organisms' activities could affect litter decomposition
8 rates. Results of recent studies indicated that O₃ slightly reduced or had no impacts on
9 litter decomposition ([Liu et al., 2009b](#); [Parsons et al., 2008](#); [Kasurinen et al., 2006](#))
10 ([Baldantoni et al., 2011](#)). The responses varied among species, sites and exposure length.
11 [Parsons et al. \(2008\)](#) collected litter from aspen and birch seedlings at Aspen FACE site,
12 and conducted a 23-month field litter incubation starting in 1999. They found that
13 elevated O₃ had different impacts on the decomposition of aspen and birch litter. Elevated
14 O₃ was found to reduce aspen litter decomposition. However, O₃ accelerated birch litter
15 decomposition under ambient CO₂, but reduced it under elevated CO₂ ([Parsons et al.,](#)
16 [2008](#)). [Liu et al. \(2009b\)](#) conducted another litter decomposition study at Aspen FACE
17 from 2003 to 2006, when stand leaf area index (LAI) reached its maximum. During the
18 935-day field incubation, elevated O₃ was shown to reduce litter mass loss in the first
19 year, but not in the second year. They suggested that higher initial tannin and phenolic
20 concentrations under elevated O₃ reduced microbial activity in the first year ([Liu et al.,](#)
21 [2009b](#)). In an OTC experiment, [Kasurinen et al. \(2006\)](#) collected silver birch leaf litter
22 from three consecutive growing seasons and conducted three separate litter-bag
23 incubation experiments. Litter decomposition was not affected by O₃ exposure in the first
24 two incubations, but a slower decomposition rate was found in the third incubation. Their
25 principle component analysis indicated that the litter chemistry changes caused by O₃
26 (decreased Mn, P, B and increased C:N) might be partially responsible for the decreased
27 mass loss of their third incubation. In another OTC experiment, [Baldantoni et al. \(2011\)](#)
28 found that O₃ significantly reduced leaf litter decomposition of *Quercus ilex* L, although
29 litter C, N, lignin and cellulose concentrations were not altered by O₃ exposure.

9.4.6.3 Soil Respiration and Carbon Formation

30 Ozone could reduce the availability of photosynthates for export to roots, and thus,
31 indirectly increase root mortality and turnover rates. Ozone has also been shown to
32 reduce above-ground litter productivity and alter litter chemistry, which would affect the
33 quality and quantity of the C supply to soil organisms (Section [9.4.6.1](#)). The complex
34 interactions among those changes make it difficult to predict the response of soil
35 C cycling under elevated O₃. The 2006 O₃ AQCD concluded that O₃ had no consistent

1 impact on soil respiration ([U.S. EPA, 2006b](#)). Ozone could increase or decrease soil
 2 respiration, depending on the approach and timing of the measurements. Ozone may also
 3 alter soil C formation. However, very few experiments directly measured changes in soil
 4 organic matter content under O₃ fumigation ([U.S. EPA, 2006b](#)). Recent studies on soil
 5 respiration and soil C content also found mixed responses. Most importantly, recent
 6 results from long-term fumigation experiments, such as the Aspen FACE experiment,
 7 suggest that ecosystem response to O₃ exposure can change over time. Observations
 8 made during the late exposure years can be inconsistent with those during the early years,
 9 highlighting the need for caution when assessing O₃ effects based on short-term studies
 10 ([Table 9-7](#)).

Table 9-7 The temporal variation of ecosystem responses to ozone exposure at Aspen FACE site

| Endpoint | Period of Measurement | Response | Reference |
|----------------------|-----------------------|---|---|
| Litter decomposition | 1999-2001 | O ₃ reduced aspen litter decomposition. However, O ₃ accelerated birch litter decomposition under ambient CO ₂ , but reduced it under elevated CO ₂ | Parsons et al. (2008) |
| | 2003-2006 | O ₃ reduced litter mass loss in the first year, but not in the second year. | Liu et al. (2009b) |
| Fine root production | 1999 | O ₃ had no significant impact on fine root biomass | King et al. (2001) |
| | 2002, 2005 | O ₃ increased fine root biomass | Pregitzer et al. (2008) |
| Soil respiration | 1998-1999 | Soil respiration under +CO ₂ +O ₃ treatment was lower than that under +CO ₂ treatment | King et al. (2001) |
| | 2003-2007 | Soil respiration under +CO ₂ +O ₃ treatment was 5-25% higher than under elevated CO ₂ treatment. | Pregitzer et al. (2008) ; Pregitzer et al. (2006) |
| Soil C formation | 1998-2001 | O ₃ reduced the formation rates of total soil C by 51% and acid-insoluble soil C by 48% | Loya et al. (2003) |
| | 2004-2008 | No significant effect of O ₃ on the new C formed under elevated CO ₂ | Talhelm et al. (2009) |

Soil Respiration

11 Ozone has shown inconsistent impacts on soil respiration. A sun-lit
 12 controlled-environment chamber study found that O₃ had no significant effects on soil
 13 respiration, fine root biomass or any of the soil organisms in a reconstructed ponderosa
 14 pine/soil-litter system ([Tingey et al., 2006](#)). In an adult European beech/Norway spruce
 15 forest at Kranzberg Forest, the free air O₃ fumigation (AOT40 of 10.2-117 ppm-h)
 16 increased soil respiration under both beech and spruce during a humid year ([Nikolova et
 17 al., 2010](#)). The increased soil respiration under beech has been accompanied by the

1 increase in fine root biomass and ectomycorrhizal fungi diversity and turnover ([Grebenc](#)
2 [and Kraigher, 2007](#)). The stimulating effect on soil respiration disappeared under spruce
3 in a dry year, which was associated with a decrease in fine root production in spruce
4 under drought. This finding suggested that drought was a more dominant stress than O₃
5 for spruce ([Nikolova et al., 2010](#)). [Andersen et al. \(2010\)](#) labeled the canopies of
6 European beech and Norway spruce with CO₂ depleted in ¹³C at the same site. They did
7 not observe any significant changes in soil respiration for either species.

8 The nearly 10 year long studies at Aspen FACE indicated that the response of soil
9 respiration to O₃ interacted with CO₂ exposure and varied temporally ([Table 9-7](#))
10 ([Pregitzer et al., 2008](#); [Pregitzer et al., 2006](#); [King et al., 2001](#)). Ozone treatment alone
11 generally had the lowest mean soil respiration rates, although those differences between
12 control and elevated O₃ were usually not significant. However, soil respiration rates were
13 different with O₃ alone and when acting in combination with elevated CO₂. In the first
14 five years (1998-2002), soil respiration under +CO₂+O₃ treatment was similar to that
15 under control and lower than that under +CO₂ treatment ([Pregitzer et al., 2006](#); [King et](#)
16 [al., 2001](#)). Since 2003, +CO₂+O₃ treatment started to show the greatest impact on soil
17 respiration. Compared to elevated CO₂, soil respiration rate under +CO₂+O₃ treatment
18 was 15-25% higher from 2003-2004, and 5-10% higher from 2005-2007 ([Pregitzer et al.,](#)
19 [2008](#); [Pregitzer et al., 2006](#)). Soil respiration was highly correlated with the biomass of
20 roots with diameters of <2 mm and <1 mm, across plant community and atmospheric
21 treatments. The authors suggested that the increase in soil respiration rate may be due to
22 +CO₂+O₃ increased fine root (<1.0 mm) biomass production ([Pregitzer et al., 2008](#)).

23 Changes in leaf chemistry and productivity due to O₃ exposure have been shown to affect
24 herbivore growth and abundance (See Section [9.4.9.1](#)). Canopy insects could affect soil
25 carbon and nutrient cycling through frass deposition, or altering chemistry and quantity
26 of litter input to the forest floor. A study at the Aspen FACE found that although elevated
27 O₃ affected the chemistry of frass and greenfall, these changes had small impact on
28 microbial respiration and no effect on nitrogen leaching ([Hillstrom et al., 2010a](#)).
29 However, respiratory carbon loss and nitrate immobilization were nearly double in
30 microcosms receiving herbivore inputs than those receiving no herbivore inputs
31 ([Hillstrom et al., 2010a](#)).

Soil Carbon Formation

32 Ozone-induced reductions in plant growth can result in reduced C input to soil and
33 therefore soil C content ([Andersen, 2003](#)). The simulations of most ecosystem models
34 support this prediction ([Ren et al., 2007b](#); [Zhang et al., 2007a](#); [Felzer et al., 2004](#)).
35 However, very few studies have directly measured soil C dynamics under elevated O₃.

1 After the first four years of fumigation (from 1998 to 2001) at the Aspen FACE site,
2 [Loya et al. \(2003\)](#) found that forest stands exposed to both elevated O₃ and CO₂
3 accumulated 51% less total soil C, and 48% less acid-insoluble soil C compared to stands
4 exposed only to elevated CO₂. Soil organic carbon (SOC) was continuously monitored at
5 the Aspen FACE site, and the later data showed that the initial reduction in new
6 C formation (soil C derived from plant litter since the start of the experiment) by O₃
7 under elevated CO₂ is only a temporary effect ([Table 9-7](#)) ([Talhelm et al., 2009](#)). The
8 amount of new soil C in the elevated CO₂ and the combined elevated CO₂ and O₃
9 treatments has converged since 2002. There was no significant effect of O₃ on the new C
10 formed under elevated CO₂ over the last four years of the study (2004-2008). [Talhelm et](#)
11 [al. \(2009\)](#) suggested the observed reduction in the early years of the experiment might be
12 driven by a suppression of C allocated to fine root biomass. During the early exposure
13 years, O₃ had no significant impact on fine root production ([King et al., 2001](#)). However,
14 the effect of O₃ on fine root biomass was observed later in the experiment. Ozone
15 increased fine root production and the highest fine root biomass was observed under the
16 combined elevated CO₂ and O₃ treatment in the late exposure years ([Table 9-7](#)) ([Pregitzer](#)
17 [et al., 2006](#)). This increase in fine root production was due to changes in community
18 composition, such as better survival of an O₃-tolerant aspen genotype, birch and maple,
19 rather than changes in C allocation at the individual tree level ([Pregitzer et al., 2008](#); [Zak](#)
20 [et al., 2007](#)).

9.4.6.4 Nutrient Cycling

21 Ozone can affect nutrient cycling by changing nutrient release from litter, nutrient uptake
22 by plants, and soil microbial activity. Nitrogen is the limiting nutrient for most temperate
23 ecosystems, and several studies examined N dynamics under elevated O₃. Nutrient
24 mineralization from decomposing organic matter is important for sustaining ecosystem
25 production. [Holmes et al. \(2006\)](#) found that elevated O₃ decreased gross N mineralization
26 at the Aspen FACE site, indicating that O₃ may reduce N availability. Other N cycling
27 processes, such as NH₄⁺ immobilization, gross nitrification, microbial biomass N and soil
28 organic N, were not affected by elevated O₃ ([Holmes et al., 2006](#)). Similarly, [Kanerva et](#)
29 [al. \(2006\)](#) found total N, NO₃⁻, microbial biomass N, potential nitrification and
30 denitrification in their meadow mesocosms were not affected by elevated O₃ (40-50 ppb).
31 Ozone was found to decrease soil mineral N content at SoyFACE, which was likely
32 caused by a reduction in plant material input and increased denitrification ([Pujol Pereira](#)
33 [et al., 2011](#)). Ozone also showed small impact on other micro and macro nutrients. [Liu et](#)
34 [al. \(2007\)a](#) assessed N, P, K, S, Ca, Mg, Mn, B, Zn and Cu release dynamics at Aspen
35 FACE, and they found that O₃ had no effects on most nutrients, except to decrease N and

1 Ca release from litter. These studies reviewed above suggest that soil N cycling processes
2 are not affected or slightly reduced by O₃ exposure. However, in a lysimeter study with
3 young beech trees, [Stoelken et al. \(2010\)](#) found that elevated O₃ stimulated N release
4 from litter which was largely attributed to an enhanced mobilization of inert nitrogen
5 fraction.

6 Using the Simple Nitrogen Cycle model (SINIC), [Hong et al. \(2006\)](#) evaluated the
7 impacts of O₃ exposure on soil N dynamics and streamflow nitrate flux. The detrimental
8 effect of O₃ on plant growth was found to reduce plant uptake of N and therefore increase
9 nitrate leaching. Their model simulation indicated that ambient O₃ exposure increased the
10 mean annual stream flow nitrate export by 12% (0.042 g N/m²/year) at the Hubbard
11 Brook Experimental Watershed from 1964-1994 ([Hong et al., 2006](#)).

9.4.6.5 Dissolved Organic Carbon and Biogenic Trace Gases Emission

12 The O₃-induced changes in plant growth, C and N fluxes to soil and microbial
13 metabolism can alter other biogeochemical cycling processes, such as soil dissolved
14 organic carbon (DOC) turnover and trace gases emission.

15 [Jones et al. \(2009\)](#) collected fen cores from two peatlands in North Wales, UK and
16 exposed them to one of four levels of O₃ (AOT40 of 0, 3.69, 5.87 and 13.80 ppm-h for
17 41 days). They found the concentration of porewater DOC in fen cores was significantly
18 decreased by increased O₃ exposure. A reduction of the low molecular weight fraction of
19 DOC was concurrent with the observed decrease in DOC concentration. Their results
20 suggested that O₃ damage to overlying vegetation may decrease utilizable C flux to soil.
21 Microbes, therefore, have to use labile C in the soil to maintain their metabolism, which,
22 the authors hypothesized, leads to a decreased DOC concentration with a shift of the
23 DOC composition to more aromatic, higher molecular weight organic compounds.

24 Several studies since the 2006 O₃ AQCD have examined the impacts of O₃ on nitrous
25 oxide (N₂O) and methane (CH₄) emission. [Kanerva et al. \(2007\)](#) measured the fluxes of
26 N₂O and CH₄ in meadow mesocosms, which were exposed to elevated CO₂ and O₃ in
27 OTCs in south-western Finland. They found that the daily N₂O fluxes were decreased in
28 the NF+O₃ (non-filtered air + elevated O₃, 40-50 ppb) after three seasons of exposure.
29 Elevated O₃ alone or combined with CO₂ did not have any significant effect on the daily
30 fluxes of CH₄ ([Kanerva et al., 2007](#)). In another study conducted in central Finland, the
31 4 year open air O₃ fumigation (AOT40 of 20.8-35.5 ppm-h for growing season) slightly
32 increased potential CH₄ oxidation by 15% in the peatland microcosms, but did not affect
33 the rate of potential CH₄ production or net CH₄ emissions, which is the net result of the

1 potential CH₄ production and oxidation ([Morsky et al., 2008](#)). However, several studies
2 found that O₃ could significantly reduce CH₄ emission. [Toet et al. \(2011\)](#) exposed
3 peatland mesocosms to O₃ in OTCs for two years, and found that CH₄ emissions were
4 significantly reduced by about 25% during midsummer periods of both years. In an OTC
5 study of rice paddy, [Zheng et al. \(2011\)](#) found that the daily mean CH₄ emissions were
6 significantly lower under elevated O₃ treatments than those in charcoal-filtered air and
7 nonfiltered air treatments. They found that the seasonal mean CH₄ emissions were
8 negatively related with AOT40, but positively related to the relative rice yield,
9 aboveground biomass and underground biomass.

9.4.6.6 Summary

10 Since the 2006 O₃ AQCD, more evidence has shown that although the responses are
11 often site specific, O₃ altered the quality and quantity of litter input to soil, microbial
12 community composition, and C and nutrient cycling. Biogeochemical cycling of below-
13 ground processes is fueled by C input from plants. Studies at the leaf and plant level have
14 provided biologically plausible mechanisms, such as reduced photosynthetic rates,
15 increased metabolic cost, and reduced root C allocation for the association of O₃ exposure
16 and the alteration of below-ground processes.

17 Results from Aspen FACE and other experimental studies consistently found that O₃
18 reduced litter production and altered C chemistry, such as soluble sugars, soluble
19 phenolics, condensed tannins, lignin, and macro/micro nutrient concentration in litter
20 ([Parsons et al., 2008](#); [Kasurinen et al., 2006](#); [Liu et al., 2005](#)). Under elevated O₃, the
21 changes in substrate quality and quantity could alter microbial metabolism and therefore
22 soil C and nutrient cycling. Several studies indicated that O₃ suppressed soil enzyme
23 activities ([Pritsch et al., 2009](#); [Chung et al., 2006](#)). However, the impact of O₃ on litter
24 decomposition was inconsistent and varied among species, sites and exposure length.
25 Similarly, O₃ had inconsistent impacts on dynamics of micro and macro nutrients.

26 Studies from the Aspen FACE experiment suggested that the response of below-ground
27 C cycle to O₃ exposure, such as litter decomposition, soil respiration and soil C content,
28 changed over time. For example, in the early part of the experiment (1998-2003), O₃ had
29 no impact on soil respiration but reduced the formation rates of total soil C under
30 elevated CO₂. However, after 10-11 years of exposure, O₃ was found to increase soil
31 respiration but have no significant impact on soil C formation under elevated CO₂.

32 The evidence is sufficient to infer that there **is a causal relationship between O₃**
33 **exposure and the alteration of below-ground biogeochemical cycles.**

9.4.7 Community Composition

1 The effects of O₃ on species competition (AX9.3.3.4) and community composition
2 (AX9.6.4) were summarized in the 2006 O₃ AQCD. Plant species differ in their
3 sensitivity to O₃. Further, different genotypes of a given species also vary in their
4 sensitivity. This differential sensitivity could change the competitive interactions that
5 lead to loss in O₃ sensitive species or genotypes. In addition, O₃ exposure has been found
6 to alter reproductive processes in plants (See Section [9.4.3.3](#)). Changes in reproductive
7 success could lead to changes in species composition. However, since ecosystem-level
8 responses result from the interaction of organisms with one another and with their
9 physical environment, it takes longer for a change to develop to a level of prominence at
10 which it can be identified and measured. A shift in community composition in forest and
11 grassland ecosystems noted in the 2006 O₃ AQCD has continued to be observed from
12 experimental and gradient studies. Additionally, research since the last review has shown
13 that O₃ can alter community composition and diversity of soil microbial communities.

9.4.7.1 Forest

14 In the San Bernardino Mountains in southern California, O₃ pollution caused a significant
15 decline in ponderosa pine (*Pinus ponderosa*) and Jeffrey pine (*Pinus jeffreyi*) ([U.S. EPA,](#)
16 [2006b](#)). Pine trees in the young mature age class group exhibited higher mortality rates
17 compared with mature trees at a site with severe O₃ visible foliar injury. The vulnerability
18 of young mature pines was most likely caused by the fact that trees in this age class were
19 emerging into the canopy, where higher O₃ concentrations were encountered ([McBride](#)
20 [and Laven, 1999](#)). Because of the loss of O₃-sensitive pines, mixed forests of ponderosa
21 pine, Jeffrey Pine and white fir (*Abies concolor*) shifted to predominantly white fir
22 ([Miller, 1973](#)). Ozone may have indirectly caused the decline in understory diversity in
23 coniferous forests in the San Bernardino Mountains through an increase in pine litterfall.
24 This increase in litterfall from O₃ exposure results in an understory layer that may
25 prohibit the establishment of native herbs, but not the exotic annual *Galium aparine*
26 ([Allen et al., 2007](#)).

27 Ozone damage to conifer forests has also been observed in several other regions. In the
28 Valley of Mexico, a widespread mortality of sacred fir (*Abies religiosa*) was observed in
29 the heavily polluted area of the Desierto de los Leones National Park in the early 1980s
30 ([de Lourdes de Bauer and Hernandez-Tejeda, 2007](#); [Fenn et al., 2002](#)). Ozone damage
31 was widely believed to be an important causal factor in the dramatic decline of sacred fir.
32 In alpine regions of southern France and the Carpathians Mountains, O₃ was also
33 considered as the major cause of the observed decline in cembran pine (*Pinus cembra*)

1 ([Wieser et al., 2006](#)). However, many environmental factors such as light, temperature,
2 nutrient and soil moisture, and climate extremes such as unusual dry and wet periods
3 could interact with O₃ and alter the response of forest to O₃ exposure. For those pollution
4 gradient studies, several confounding factors, such as drought, insect outbreak and forest
5 management, may also contribute to or even be the dominant factors causing the
6 mortality of trees ([de Lourdes de Bauer and Hernandez-Tejeda, 2007](#); [Wieser et al.,
7 2006](#)).

8 Recent evidence from long-term free O₃ fumigation experiments provided additional
9 support for the potential impacts of O₃ on species competition and community
10 composition changes in forest ecosystems. At the Aspen FACE site, community
11 composition at both the genetic and species levels was altered after seven years of
12 fumigation with O₃ ([Kubiske et al., 2007](#)). In the pure aspen community, O₃ fumigation
13 reduced growth and increased mortality of sensitive clone 259, while the O₃ tolerant
14 clone 8L emerged as the dominant clone. Growth of clone 8L was even greater under
15 elevated O₃ compared to controls, probably due to O₃ alleviated competitive pressure on
16 clone 8L by reducing growth of other clones. In the mixed aspen-birch and aspen-maple
17 communities, O₃ reduced the competitive capacity of aspen compared to birch and maple
18 ([Kubiske et al., 2007](#)). In a phytotron study, O₃ fumigation reduced growth of beech but
19 not spruce in mixed culture, suggesting a higher susceptibility of beech to O₃ under
20 interspecific competition ([Kozovits et al., 2005](#)).

9.4.7.2 Grassland and Agricultural Land

21 The response of managed pasture, often cultivated as a mixture of grasses and clover, to
22 O₃ pollution has been studied for many years. The tendency for O₃-exposure to shift the
23 biomass of grass-legume mixtures in favor of grass species, reported in the previous O₃
24 AQCD has been generally confirmed by recent studies. In a mesocosm study, *Trifolium*
25 *repens* and *Lolium perenne* mixtures were exposed to an episodic rural O₃ regime within
26 solardomes for 12 weeks. *T. repens* showed significant changes in biomass but not *L.*
27 *perenne*, and the proportion of *T. repens* decreased in O₃-exposed mixtures compared to
28 the control ([Hayes et al., 2009](#)). The changes in community composition of grass-legume-
29 forb mixtures were also observed at the Le Mouret FACE experiment, Switzerland.
30 During the 5-year O₃ fumigation (AOT40 of 13.3-59.5 ppm-h), the dominance of
31 legumes in fumigated plots declined more quickly than those in the control plots ([Volk et
32 al., 2006](#)). However, [Stampfli and Fuhrer \(2010\)](#) reanalyzed the species and soil data and
33 suggested that [Volk et al. \(2006\)](#) overestimated the O₃ effect. [Stampfli and Fuhrer \(2010\)](#)
34 found that the difference in the species dynamics between control and O₃ treatment was
35 more caused by heterogeneous initial conditions than O₃ exposure. Several studies also

1 suggested that mature/species-rich ecosystems were more resilient to O₃ exposure. At
2 another FACE experiment, located at Alp Flix, Switzerland, O₃ fumigation (AOT40 of
3 15.2-64.9 ppm-h) showed no significant impact on community composition of this
4 species-rich pasture ([Bassin et al., 2007b](#)). Although most studies demonstrated an
5 increase in grass:forb ratio with O₃ exposure ([Hayes et al., 2009](#); [U.S. EPA, 2006b](#)), a
6 study on a simulated upland grassland community showed that O₃ reduced the grass:forb
7 ratio ([Hayes et al., 2010](#)) which may be due to the grass species in this community. The
8 grass species studied by [Hayes et al. \(2010\)](#), *Anthoxanthum odoratum*, was more
9 sensitive to O₃ than other grass species such as *L. perenne* ([Hayes et al., 2009](#)). [Pfleeger](#)
10 [et al. \(2010\)](#) collected seed bank soil from an agricultural field and examined how the
11 plant community responded over several generations to elevated O₃ exposures. Sixty
12 plant species from 22 families emerged in the chambers over their four year study.
13 Overall, they found that O₃ appeared to have small impacts on seed germination and only
14 a minor effect on species richness of pioneer plant communities.

15 Several review papers have discussed the physiological and ecological characteristics of
16 O₃-sensitive herbaceous plants. [Hayes et al. \(2007\)](#) assessed species traits associated with
17 O₃ sensitivity by the changes in biomass caused by O₃ exposure. Plants of the therophyte
18 (e.g., annual) life form were particularly sensitive to O₃. Species with higher mature leaf
19 N concentration tended to be more sensitive than those with lower leaf N concentration.
20 Plants growing under high oxidative stress environments, such as high light or high
21 saline, were more sensitive to O₃. Using the same dataset from [Hayes et al. \(2007\)](#), [Mills](#)
22 [et al. \(2007b\)](#) identified the O₃ sensitive communities. They found that the largest number
23 of these O₃ sensitive communities were associated with grassland ecosystems. Among
24 grassland ecosystems, alpine grassland, sub-alpine grassland, woodland fringe, and dry
25 grassland were identified as the most sensitive communities.

9.4.7.3 Microbes

26 Several methods have been used to study microbial composition changes associated with
27 elevated O₃. Phospholipid fatty acid (PLFA) analysis is widely used to determine whether
28 O₃ elicits an overall effect on microbial community composition. However, since PLFA
29 markers cover a broad range of different fungi, resolution of this method may be not fine
30 enough to detect small changes in the composition of fungal communities. Methods, such
31 as microscopic analyses and polymerase chain reaction–denaturing gradient gel
32 electrophoresis (PCR–DGGE), have better resolution to specifically analyze the fungal
33 community composition. The resolution differences among those methods needs to be
34 considered when assessing the O₃ impact on microbial community composition.

1 [Kanerva et al. \(2008\)](#) found that elevated O₃ (40-50 ppb) decreased total, bacterial,
2 actinobacterial and fungal PLFA biomass values as well as fungal:bacterial PLFA
3 biomass ratio in their meadow mesocosms in south-western Finland. The relative
4 proportions of individual PLFAs between the control and elevated O₃ treatments were
5 significantly different, suggesting that O₃ modified the structure of the microbial
6 community. [Morsky et al. \(2008\)](#) exposed boreal peatland microcosms to elevated O₃,
7 with growing season AOT40 of 20.8-35.3 ppm-h, in an open-air O₃ exposure field in
8 Central Finland. They also found that microbial composition was altered after three
9 growing seasons with O₃ fumigation, as measured by PLFA. Ozone tended to increase
10 the presence of Gram-positive bacteria and the biomass of fungi in the peatland
11 microcosms. Ozone also resulted in higher microbial biomass, which co-occurred with
12 the increases in concentrations of organic acids and leaf density of sedges ([Morsky et al.,
13 2008](#)). In a lysimeter experiment in Germany, O₃ was found to alter the PLFA profiles in
14 the upper 0-20 cm rhizosphere soil of European beech. Elevated O₃ reduced bacterial
15 abundance but had no detectable effect on fungal abundance ([Pritsch et al., 2009](#)). Using
16 microscopic analyses, [Kasurinen et al. \(2005\)](#) found that elevated O₃, with 5 or 6 months
17 of AOT40 of 20.6-30.9 ppm-h, decreased the proportions of black and liver-brown
18 mycorrhizas and increased that of light brown/orange mycorrhizas. In an herbaceous
19 plant study, SSCP (single-strand conformation polymorphism) profiles indicated that O₃
20 stress (about 75 ppb) had a very small effect on the structural diversity of the bacterial
21 community in rhizospheres ([Dohrmann and Tebbe, 2005](#)). At the Aspen FACE site, O₃
22 had no significant effect on fungal relative abundance, as indicated by PLFA profile.
23 However, elevated O₃ altered fungal community composition, according to the
24 identification of 39 fungal taxonomic units from soil using polymerase chain reaction–
25 denaturing gradient gel electrophoresis (PCR-DGGE) ([Chung et al., 2006](#)). In another
26 study at Aspen FACE, phylogenetic analysis suggested that O₃ exposure altered the
27 agaricomycete community. The ectomycorrhizal communities developing under elevated
28 O₃ had higher proportions of *Cortinarius* and *Inocybe* species, and lower proportions of
29 *Laccaria* and *Tomentella* ([Edwards and Zak, 2011](#)). Ozone was found to change
30 microbial community composition in an agricultural system. [Chen et al. \(2010b\)](#) found
31 elevated O₃ (100-150 ppb) had significant effects on soil microbial composition
32 expressed as PLFA percentage in a rice paddy in China.

9.4.7.4 Summary

33 In the 2006 O₃ AQCD, the impact of O₃ exposure on species competition and community
34 composition was assessed. Ozone was found to cause a significant decline in ponderosa
35 and Jeffrey pine in the San Bernardino Mountains in southern California. Ozone exposure

1 also tended to shift the grass-legume mixtures in favor of grass species ([U.S. EPA,](#)
2 [2006b](#)). Since the 2006 O₃ AQCD, more evidence has shown that O₃ exposure changed
3 the competitive interactions and could lead to loss of O₃ sensitive species or genotypes.
4 Studies at plant level found that the severity of O₃ damage on growth, reproduction and
5 foliar injury varied among species, which provided the biological plausibility for the
6 alteration of community composition. Additionally, research since the last review has
7 shown that O₃ can alter community composition and diversity of soil microbial
8 communities.

9 The decline of conifer forests under O₃ exposure was continually observed in several
10 regions. Ozone damage was believed to be an important causal factor in the dramatic
11 decline of sacred fir in the valley of Mexico ([de Lourdes de Bauer and Hernandez-](#)
12 [Tejeda, 2007](#)), as well as cembran pine in southern France and the Carpathian Mountains
13 ([Wieser et al., 2006](#)). Results from the Aspen FACE site indicated that O₃ could alter
14 community composition of broadleaf forests as well. At the Aspen FACE site, O₃
15 reduced growth and increased mortality of a sensitive aspen clone, while the O₃ tolerant
16 clone emerged as the dominant clone in the pure aspen community. In the mixed aspen-
17 birch and aspen-maple communities, O₃ reduced the competitive capacity of aspen
18 compared to birch and maple ([Kubiske et al., 2007](#)).

19 The tendency for O₃-exposure to shift the biomass of grass-legume mixtures in favor of
20 grass species, was reported in the 2006 O₃ AQCD and has been generally confirmed by
21 recent studies. However, in a high elevation mature/species-rich grass-legume pasture, O₃
22 fumigation showed no significant impact on community composition ([Bassin et al.,](#)
23 [2007b](#)).

24 Ozone exposure not only altered community composition of plant species, but also
25 microorganisms. The shift in community composition of bacteria and fungi has been
26 observed in both natural and agricultural ecosystems, although no general patterns could
27 be identified ([Kanerva et al., 2008](#); [Morsky et al., 2008](#); [Kasurinen et al., 2005](#)).

28 The evidence is sufficient to conclude that there **is likely to be a causal relationship**
29 **between O₃ exposure and the alteration of community composition of some**
30 **ecosystems.**

9.4.8 Factors that Modify Functional and Growth Response

31 Many biotic and abiotic factors, including insects, pathogens, root microbes and fungi,
32 temperature, water and nutrient availability, and other air pollutants, as well as elevated
33 CO₂, influence or alter plant response to O₃. These modifying factors were

1 comprehensively reviewed in AX9.3 of the 2006 O₃ AQCD and thus, this section serves
2 mainly as a brief summary of the previous findings. A limited number of new studies
3 published since the 2006 O₃ AQCD add to the understanding of the role of these
4 interactions in modifying O₃-induced plant responses. Many of these modifying factors
5 and interactions are integrated into discussions elsewhere in this chapter and the reader is
6 directed to those sections.

9.4.8.1 Genetics

7 It is well known that species vary greatly in their responsiveness to O₃. Even within a
8 given species, individual genotypes or populations can also vary significantly with
9 respect to O₃ sensitivity ([U.S. EPA, 2006b](#)). Therefore, caution should be taken when
10 considering a species' degree of sensitivity to O₃. Plant response to O₃ is determined by
11 genes that are directly related to oxidant stress and to an unknown number of genes that
12 are not specifically related to oxidants, but instead control leaf and cell wall thickness,
13 stomatal conductance, and the internal architecture of the air spaces. It is rarely the case
14 that single genes are responsible for O₃ tolerance. Studies using molecular biological
15 tools and transgenic plants have positively verified the role of various genes and gene
16 products in O₃ tolerance and are continuing to increase the understanding of O₃ toxicity
17 and differences in O₃ sensitivity. See Section [9.3.3.2](#) of this document for a discussion of
18 recent studies related to gene expression changes in response to O₃.

9.4.8.2 Environmental Biological Factors

19 As stated in the 2006 O₃ AQCD, the biological factors within the plant's environment
20 that may influence its response to O₃ encompass insects and other animal pests, diseases,
21 weeds, and other competing plant species. Ozone may influence the severity of a disease
22 or infestation by a pest or weed, either by direct effects on the causal species, or
23 indirectly by affecting the host, or both. In addition, the interaction between O₃, a plant,
24 and a pest, pathogen, or weed may influence the response of the target host species to O₃
25 ([U.S. EPA, 2006b](#)). Several recent studies on the effects of O₃ on insects via their
26 interactions with plants are discussed in Section [9.4.9.1](#). In addition, O₃ has also been
27 shown to alter soil fauna communities (Section [9.4.9.2](#)).

28 In contrast to detrimental biological interactions, there are mutually beneficial
29 relationships or symbioses involving higher plants and bacteria or fungi. These include
30 (1) the nitrogen-fixing species *Rhizobium* and *Frankia* that nodulate the roots of legumes
31 and alder and (2) the mycorrhizae that infect the roots of many crop and tree species, all

1 of which may be affected by exposure of the host plants to O₃. Some discussion of
2 mycorrhizae can be found in Section [9.4.6](#).

3 In addition to the interactions involving animal pests, O₃ also has indirect effects on
4 higher herbivorous animals, e.g., livestock, due to O₃-induced changes in feed quality.
5 Recent studies on the effects of O₃ on nutritive quality of plants are discussed in
6 Section [9.4.4.2](#).

7 Intra- and interspecific competition are also important factors in determining vegetation
8 response to O₃. Plant competition involves the ability of individual plants to acquire the
9 environmental resources needed for growth and development: light, water, nutrients, and
10 space. Intraspecific competition involves individuals of the same species, typically in
11 monoculture crop situations, while interspecific competition refers to the interference
12 exerted by individuals of different species on each other when they are in a mixed
13 culture. This topic was previously reviewed in AX9.3.3.4 of the 2006 O₃ AQCD. Recent
14 studies on competition and its implications for community composition are discussed in
15 Section [9.4.7](#).

9.4.8.3 Physical Factors

16 Physical or abiotic factors play a large role in modifying plant response to O₃, and have
17 been extensively discussed in previous O₃ AQCDs. This section summarizes those
18 findings as well as recent studies published since the last review.

19 Although some studies have indicated that O₃ impact significantly increases with
20 increased ambient temperature ([Ball et al., 2000](#); [Mills et al., 2000](#)), other studies have
21 indicated that temperature has little effect ([Balls et al., 1996](#); [Fredericksen et al., 1996](#)). A
22 recent study by Riikonen et al. [Riikonen et al. \(2009\)](#) at the Ruohoniemi open air
23 exposure field in Kuopio, Finland found that the effects of temperature and O₃ on total
24 leaf area and photosynthesis of *Betula pendula* were counteractive. Elevated O₃ reduced
25 the saplings' ability to utilize the warmer growth environment by increasing the stomatal
26 limitation for photosynthesis and by reducing the redox state of ascorbate in the apoplast
27 in the combination treatment as compared to temperature alone ([Riikonen et al., 2009](#)).

28 Temperature affects the rates of all physiological processes based on enzyme catalysis
29 and diffusion; each process and overall growth (the integral of all processes) has a
30 distinct optimal temperature range. It is important to note that a plant's response to
31 changes in temperature will depend on whether it is growing near its optimum
32 temperature for growth or near its maximum temperature ([Rowland-Bamford, 2000](#)).

33 However, temperature is very likely an important variable affecting plant O₃ response in

1 the presence of the elevated CO₂ levels contributing to global climate change. In contrast,
2 some evidence suggests that O₃ exposure sensitizes plants to low temperature stress
3 ([Colls and Unsworth, 1992](#)) and, also, that O₃ decreases below-ground carbohydrate
4 reserves, which may lead to responses in perennial species ranging from rapid demise to
5 impaired growth in subsequent seasons (i.e., carry-over effects) ([Andersen et al., 1997](#)).

6 Light, a component of the plant's physical environment, is an essential "resource" of
7 energy content that drives photosynthesis and C assimilation. It has been suggested that
8 increased light intensity may increase the O₃ sensitivity of light-tolerant species while
9 decreasing that of shade-tolerant species, but this appears to be an oversimplification with
10 many exceptions. Several studies suggest that the interaction between O₃ sensitivity and
11 light environment is complicated by the developmental stage as well as the light
12 environment of individual leaves in the canopy ([Kitao et al., 2009](#); [Topa et al., 2001](#);
13 [Chappelka and Samuelson, 1998](#)).

14 Although the relative humidity of the ambient air has generally been found to increase the
15 effects of O₃ by increasing stomatal conductance (thereby increasing O₃ flux into the
16 leaves), abundant evidence also indicates that the ready availability of soil moisture
17 results in greater O₃ sensitivity ([Mills, 2002](#)). The partial "protection" against the effects
18 of O₃ afforded by drought has been observed in field experiments ([Low et al., 2006](#)) and
19 modeled in computer simulations ([Broadmeadow and Jackson, 2000](#)). Conversely,
20 drought may exacerbate the effects of O₃ on plants ([Pollastrini et al., 2010](#); [Grulke et al.,](#)
21 [2003b](#)). There is also some evidence that O₃ can predispose plants to drought stress
22 ([Maier-Maercker, 1998](#)). Hence, the nature of the response is largely species-specific and
23 will depend to some extent upon the sequence in which the stressors occur.

9.4.8.4 Interactions with other Pollutants

Ozone-nitrogen interactions

24 Elevated O₃ exposure and N deposition often co-occur. However, the interactions of O₃
25 exposure and N deposition on vegetation are complex and less well understood compared
26 to their independent effects. Consistent with the conclusion of the 2006 O₃ AQCD, the
27 limited number of studies published since the last review indicated that the interactive
28 effects of N and O₃ varied among species and ecosystems ([Table 9-8](#)). To better
29 understand these interactions in ecosystems across the U.S., more information is needed
30 considering combined O₃ exposure and N deposition related effects.

31 Nitrogen deposition could stimulate relative growth rate (RGR), and lead to increased
32 stomatal conductance. Therefore, plants might become more susceptible to O₃ exposure.

1 Alternatively, N deposition may increase the availability of photosynthates for use in
 2 detoxification and plants could become more tolerant to O₃ ([Bassin et al., 2007a](#)). Only a
 3 few recent studies have investigated the interactive effects of O₃ and N in the U.S. [Grulke](#)
 4 [et al. \(2005\)](#) measured stomatal conductance of California black oak (*Quercus kelloggii*)
 5 at a long-term N-enrichment site located in the San Bernardino Mountains, which is
 6 accompanied by high O₃ exposure (80 ppb, 24-h avg. over a six month growing season).
 7 The authors found that N amendment led to poor stomatal control in full sun in
 8 midsummer of the average precipitation years, but enhanced stomatal control in shade
 9 leaves of California black oak. In an OTC study, [Handley and Grulke \(2008\)](#) found that
 10 O₃ lowered photosynthetic ability and water-use efficiency, and increased leaf chlorosis
 11 and necrosis of California black oak. Nitrogen fertilization tended to reduce plant
 12 sensitivity to O₃ exposure; however, the interaction was not statistically significant. In
 13 another study, [Grulke et al. \(2008\)](#) reported that various lines of phenomenological and
 14 experimental evidence indicate that N deposition and O₃ pollution contribute to the
 15 susceptibility of forests to wildfire in the San Bernadino Mountains by increasing stress
 16 due to drought, weakening trees, and predisposing them to bark beetle infestation
 17 ([U.S. EPA, 2008](#); NO_x/SO_x ISA).

18 Studies conducted outside the U.S. are also summarized in [Table 9-8](#). Generally, the
 19 responses were species specific. The O₃-induced reduction in photosynthetic rate and
 20 biomass loss were greater in the relatively high N treatment for watermelon (*Citrillus*
 21 *lanants*) ([Calatayud et al., 2006](#)) and Japanese beech (*Fagus crenata*) seedlings
 22 ([Yamaguchi et al., 2007](#)). However, there was no significant interactive effect of O₃ and
 23 N on biomass production for *Quercus serrata* seedlings ([Watanabe et al., 2007](#)), young
 24 Norway spruce (*Picea abies*) trees ([Thomas et al., 2005](#)), and young European beech
 25 (*Fagus sylvatica*) trees [Thomas et al. \(2006\)](#).

Table 9-8 Response of plants to the interactive effects of elevated ozone exposure and nitrogen enrichment.

| Site | Species | Ozone exposure | N addition | Responses | References |
|--------------------------------|---|--------------------|-----------------------|--|---|
| San Bernardino Mountains, U.S. | California black oak (<i>Quercus kelloggii</i>) | 80 ppb | 0, and 50 kg N/ ha/yr | N-amended trees had lower late summer C gain and greater foliar chlorosis in the drought year, and poor stomatal control and lower leaf water use efficiency and in midsummer of the average precipitation year. | Grulke et al. (2005) |
| San Bernardino Mountains, U.S. | California black oak (<i>Quercus kelloggii</i>) | 0, 75, and 150 ppb | 0, and 50 kg N/ ha/yr | N fertilization tended to reduce plant sensitivity to O ₃ exposure; however the interaction was not statistically significant. | Handley and Grulke (2008) |

| Site | Species | Ozone exposure | N addition | Responses | References |
|-------------|---|---|-------------------------------|--|---|
| Switzerland | Spruce trees (<i>Picea abies</i>) | Filtered (19.4-28.1 ppb); ambient (37.6-47.4 ppb) | 0, 20, 40 and 80 kg N/ ha/yr | Higher N levels alleviated the negative impact of O ₃ on root starch concentrations | Thomas et al. (2005) |
| Switzerland | Beech trees (<i>Fagus sylvatica</i>) | Filtered (19.4-28.1 ppb); ambient (37.6-47.4 ppb) | 0, 20, 40 and 80 kg N/ ha/yr | N addition amplified the negative effects of O ₃ on leaf area and shoot elongation. | Thomas et al. (2006) |
| Switzerland | Alpine pasture | Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h) | 0, 5, 10, 25, 50 kg N/ ha/yr | The positive effects of N addition on canopy greenness were counteracted by accelerated leaf senescence in the highest O ₃ treatment. | Bassin et al. (2007b) |
| Switzerland | Alpine pasture | Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h) | 0, 5, 10, 25, 50 kg N/ha/yr | Only a small number of species showed significant O ₃ and N interactive effects on leaf chlorophyll concentration, leaf weight and change in ¹⁸ O, and the patterns were not consistent. | Bassin et al. (2009) |
| Switzerland | Alpine pasture | Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h) | 0, 5, 10, 25, 50 kg N/ ha/yr | The positive effects of N addition on canopy greenness were counteracted by accelerated leaf senescence in the highest O ₃ treatment. | Bassin et al. (2007b) |
| Switzerland | Alpine pasture | Ambient (AOT40 of 11.1-12.6 ppm-h); 1.2 ambient (AOT40 of 15.2-29.5 ppm-h) and 1.6 ambient (28.4-64.9 ppm-h) | 0, 5, 10, 25, 50 kg N/ ha/yr | Highest N addition resulted in carbon loss, but there was no interaction between O ₃ and N treatments. | Volk et al. (2011) |
| Spain | Watermelon (<i>Citrillus lanants</i>) | O ₃ free (AOT40 of 0 ppm-h), ambient (AOT40 of 5.1-6.3 ppm-h) and elevated O ₃ (AOT40 of 32.5-35.6 ppm-h) | 140, 280, and 436 kg N/ ha/yr | High N concentration enhanced the detrimental effects of O ₃ on Chlorophyll a fluorescence parameters, lipid peroxidation, and the total yield. | Calatayud et al. (2006) |
| Spain | Trifolium striatum | Filtered (24-h avg. of 8-22 ppb); ambient (29-34 ppb), elevated O ₃ (35-56 ppb) | 10, 30, and 60 kg N/ ha/yr | O ₃ reduced total aerial biomass. N fertilization counterbalanced O ₃ -induced effects only when plants were exposed to moderate O ₃ levels (ambient) but not under elevated O ₃ concentrations. | Sanz et al. (2007) |
| Japan | Japanese beech seedlings (<i>Fagus crenata</i>) | Filtered (24-h avg. of 10.3-13.2 ppb); ambient (42.0-43.3 ppb), 1.5 ambient (62.6-63.9 ppb) and 2.0 ambient (82.7-84.7 ppb) | 0, 20 and 50 kg N/ ha/yr | The O ₃ -induced reduction in net photosynthesis and whole-plant dry mass were greater in the relatively high N treatment than that in the low N treatment. | Yamaguchi et al. (2007) |
| Japan | <i>Quercus serrata</i> seedlings | Filtered (24-h avg. of 10.3-13.2 ppb); ambient (42.0-43.3 ppb), 1.5 ambient (62.6-63.9 ppb) and 2.0 ambient (82.7-84.7 ppb) | 0, 20 and 50 kg N/ ha/yr | No significant interactive effects of O ₃ and N load on the growth and net photosynthetic rate were detected. | Watanabe et al. (2007) |

Ozone-carbon dioxide interactions

1 Several decades of research has shown that exposure to elevated CO₂ increases
2 photosynthetic rates ([Bernacchi et al., 2006](#); [Bernacchi et al., 2005](#); [Tissue et al., 1999](#);
3 [Tissue et al., 1997](#); [Will and Ceulemans, 1997](#)), decreases stomatal conductance
4 ([Ainsworth and Rogers, 2007](#); [Paoletti et al., 2007](#); [Bernacchi et al., 2006](#); [Leakey et al.,](#)
5 [2006](#); [Medlyn et al., 2001](#)) and generally increases the growth of plants ([McCarthy et al.,](#)
6 [2009](#); [Norby et al., 2005](#)). This is in contrast to the decrease in photosynthesis and growth
7 in many plants that are exposed to elevated O₃. The interactive effects on vegetation have
8 been the subject of research in the past two decades due to the implications on
9 productivity and water use of ecosystems. This area of research was discussed in detail in
10 AX9.3.8.1 of the 2006 O₃ AQCD and the conclusions made then are still relevant ([U.S.](#)
11 [EPA, 2006b](#)).

12 The bulk of the available evidence shows that, under the various experimental conditions
13 used (which almost exclusively employed abrupt or “step” increases in CO₂
14 concentration, as discussed below), increased CO₂ levels (ambient + 200 to 400 ppm)
15 may protect plants from the negative effects of O₃ on growth. This protection may be
16 afforded in part by CO₂ acting together with O₃ in inducing stomatal closure, thereby
17 reducing O₃ uptake, and in part by CO₂ reducing the negative effects of O₃ on Rubisco
18 and its activity in CO₂-fixation. Although both CO₂-induced and O₃-induced decreases in
19 stomatal conductance have been observed primarily in short-term studies, recent data
20 show a long-term and sustained reduction in stomatal conductance under elevated CO₂
21 for a number of species ([Ainsworth and Long, 2005](#); [Ellsworth et al., 2004](#); [Gunderson et](#)
22 [al., 2002](#)). Instances of increased stomatal conductance have also been observed in
23 response to O₃ exposure, suggesting partial stomatal dysfunction after extended periods
24 of exposure ([Paoletti and Grulke, 2010](#); [Grulke et al., 2007a](#); [Maier-Maercker, 1998](#)).

25 Important caveats must be raised with regard to the findings presented in published
26 research. The first caveat concerns the distinctly different natures of the exposures to O₃
27 and CO₂ experienced by plants in the field. Changes in the ambient concentrations of
28 these gases have very different dynamics. In the context of climate change, CO₂ levels
29 increase relatively slowly (globally 2 ppm/year) and may change little over several
30 seasons of growth. On the other hand, O₃ presents a fluctuating stressor with considerable
31 hour-to-hour, day-to-day and regional variability ([Polle and Pell, 1999](#)). Almost all of the
32 evidence presented comes from experimentation involving plants subjected to an abrupt
33 step increase to a higher, steady CO₂ concentration. In contrast, the O₃ exposure
34 concentrations usually varied from day to day. [Luo and Reynolds \(1999\)](#), [Hui et al.](#)
35 [\(2002\)](#), and [Luo \(2001\)](#) noted the difficulties in predicting the likely effects of a gradual
36 CO₂ increase from experiments involving a step increase or those using a range of CO₂

1 concentrations. It is also important to note that the levels of elevated CO₂ in many of the
2 studies will not be experienced in the field for 30 or 40 years, but elevated levels of O₃
3 can occur presently in several areas of the U.S. Therefore, the CO₂ × O₃ interaction
4 studies may be less relevant for current ambient conditions.

5 Another caveat concerns the interactions of O₃ and CO₂ with other climatic variables,
6 such as temperature and precipitation. In light of the key role played by temperature in
7 regulating physiological processes and modifying plant response to increased CO₂ levels
8 ([Morison and Lawlor, 1999](#); [Long, 1991](#)) and the knowledge that relatively modest
9 increases in temperature may lead to dramatic consequences in terms of plant
10 development ([Lawlor, 1998](#)), it is important to consider that studying CO₂ and O₃
11 interactions alone may not create a complete understanding of effects on plants under
12 future climate change.

9.4.9 Insects and Other Wildlife

9.4.9.1 Insects

13 Insects may respond indirectly to changes in plants (i.e., increased reactive oxygen
14 species, altered phytochemistry, altered nutrient content) that occur under elevated O₃
15 conditions, or O₃ can have a direct effect on insect performance ([Menendez et al., 2009](#)).
16 Effects of O₃ on insects occur at the species level (i.e., growth, survival, reproduction,
17 development, feeding behavior) and at the population and community-level
18 (i.e., population growth rate, community composition). In general, effects of O₃ on
19 insects are highly context- and species-specific ([Lindroth, 2010](#); [Bidart-Bouzat and Imeh-
20 Nathaniel, 2008](#)). Furthermore, plant responses to O₃ exposure and herbivore attack have
21 been demonstrated to share signaling pathways, complicating characterization of these
22 stressors ([Lindroth, 2010](#); [Menendez et al., 2010, 2009](#)). Although both species-level and
23 population and community-level responses to elevated O₃ are observed in field and
24 laboratory studies discussed below, there is no consensus on how insects respond to
25 feeding on O₃-exposed plants.

Species-level responses

26 In considering insect growth, survival and reproduction in elevated O₃ conditions, several
27 studies have indicated an effect while others have found no correlation. The performance
28 of five herbivore species (three moths and two weevils) was assessed in an OTC
29 experiment at 2 × ambient concentration ([Peltonen et al., 2010](#)). Growth of larvae of the

1 Autumnal moth, *Epirrita autumnna*, was significantly decreased in the O₃ treatment while
2 no effects were observed in the other species. In an aphid oviposition preference study
3 using birch buds grown in a three year OTC experiment, O₃ had neither a stimulatory or
4 deterring effect on egg-laying ([Peltonen et al., 2006](#)). Furthermore, changes in birch bud
5 phenolic compounds associated with the doubled ambient concentrations of O₃ did not
6 correlate with changes in aphid oviposition ([Peltonen et al., 2006](#)). Reproduction in
7 *Popillia japonica*, that were fed soybeans and grown under elevated O₃ appeared to be
8 unaffected ([O'Neill et al., 2008](#)). In a meta-analysis of effects of elevated O₃ on 22
9 species of trees and 10 species of insects, the rates of survival, reproduction and food
10 consumption were typically unaffected while development times were reduced and pupal
11 masses were increased ([Valkama et al., 2007](#)).

12 At the Aspen FACE site insect performance under elevated (50-60 ppb) O₃ conditions
13 (approximately 1.5 × background ambient levels of 30-40 ppb O₃) have been considered
14 for several species. Cumulative fecundity of aphids (*Cepegilletta betulaefoliae*), that
15 were reared on O₃-exposed paper birch (*Betula papyrifera*) trees, was lower than aphids
16 from control plots ([Awmack et al., 2004](#)). No effects on growth, development, adult
17 weight, embryo number and birth weight of newborn nymphs were observed. In a study
18 conducted using three aspen genotypes, performance of the aspen beetle (*Chrysomela*
19 *crochi*) decreased across all parameters measured (development time, adult mass and
20 survivorship) under elevated O₃ ([Vigue and Lindroth, 2010](#)). There was an increase in the
21 development time of male and female aspen beetle larvae although the percentages varied
22 across genotypes. Decreased beetle adult mass and survivorship was observed across all
23 genotypes under elevated O₃ conditions. Another study from the Aspen FACE site did
24 not find any significant effects of elevated O₃ on performance (longevity, fecundity,
25 abundance) of the invasive weevil (*Polydrusus sericeus*) ([Hillstrom et al., 2010b](#)).

26 Since the 2006 O₃ AQCD, several studies have considered the effect of elevated O₃ on
27 feeding behavior of insects. In a feeding preference study, the common leaf weevil
28 (*Phyllobius pyri*) consumed significantly more leaf discs from one aspen clone when
29 compared to a second clone under ambient air conditions ([Freiwald et al., 2008](#)). In a
30 moderately elevated O₃ environment (1.5 × ambient), this preference for a certain aspen
31 clone was less evident, however, leaves from O₃-exposed trees were significantly
32 preferred to leaves grown under ambient conditions. Soybeans grown under enriched O₃
33 had significantly less loss of leaf tissue to herbivory in August compared to earlier in the
34 growing season (July) when herbivory was not affected ([Hamilton et al., 2005](#)). Other
35 plant-herbivore interactions have shown no effects of elevated O₃ on feeding. Feeding
36 behavior of Japanese beetles (*P. japonica*) appeared to be unchanged when beetles were
37 fed soybean leaves grown under elevated O₃ conditions ([O'Neill et al., 2008](#)). At the
38 Aspen FACE site, feeding by the invasive weevil (*Polydrusus sericeus*), as measured by

1 leaf area consumption, was not significantly different between foliage that was grown
2 under elevated O₃ versus ambient conditions ([Hillstrom et al., 2010b](#)).

Population-level and community-level responses

3 Recent data on insects provide evidence of population-level and community-level
4 responses to O₃. Elevated levels of O₃ can affect plant phytochemistry and nutrient
5 content which in turn can alter population density and structure of the associated
6 herbivorous insect communities and impact ecosystem processes ([Cornelissen, 2011](#);
7 [Lindroth, 2010](#)). In 72-hour exposures to elevated O₃, mean relative growth rate of the
8 aphid *Diuraphis noxia* increased with O₃ concentration suggesting that more rapid
9 population growth may occur when atmospheric O₃ is elevated ([Summers et al., 1994](#)). In
10 a long-term study of elevated O₃ on herbivore performance at the Aspen FACE site,
11 individual performance and population-level effects of the aphid *C. betulaefoliae* were
12 assessed. Elevated O₃ levels had a strong positive effect on the population growth rates of
13 the aphids; although effects were not detected by measuring growth, development, adult
14 weight, embryo number or birth weight of newborn nymphs ([Awmack et al., 2004](#)).
15 Conversely, a lower rate of population growth was observed in aphids previously
16 exposed to O₃ in an OTC ([Menendez et al., 2010](#)). No direct effects of O₃ were observed;
17 however, nymphs born from adults exposed to and feeding on O₃ exposed plants were
18 less capable of infesting new plants when compared to nymphs in the control plots
19 ([Menendez et al., 2010](#)). Elevated O₃ reduced total arthropod abundance by 17% at
20 Aspen FACE, largely as a result of the negative effects on parasitoids, although phloem-
21 feeding insects may benefit ([Hillstrom and Lindroth, 2008](#)). Herbivore communities
22 affected by O₃ and N were sampled along an air pollution gradient in the Los Angeles
23 basin ([Jones and Paine, 2006](#)). Abundance, diversity, and richness of herbivores were not
24 affected. However, a shift in community structure, from phloem-feeding to chewing
25 dominated communities, was observed along the gradient. No consistent effect of
26 elevated O₃ on herbivory or insect population size was detected at SoyFACE ([O'Neill et](#)
27 [al., 2010](#); [Dermody et al., 2008](#)).

28 Evidence of modification of insect populations and communities in response to elevated
29 O₃ includes genotypic and phenotypic changes. In a study conducted at the Aspen FACE
30 site, elevated O₃ altered the genotype frequencies of the pea aphid (*Acyrtosiphon pisum*)
31 grown on red clover (*Trifolium pratense*) over multiple generations ([Mondor et al.,](#)
32 [2005](#)). Aphid color was used to distinguish between the two genotypes. Ozone increased
33 the genotypic frequencies of pink-morph:green-morph aphids from 2:1 to 9:1, and
34 depressed wing-induction responses more strongly in the pink than the green genotype
35 ([Mondor et al., 2005](#)). Growth and development of individual green and pink aphids
36 reared as a single genotype or mixed genotypes were unaffected by elevated O₃ ([Mondor](#)

1 [et al., 2010](#)). However, growth of pea aphid populations is not readily predictable using
2 individual growth rates.

9.4.9.2 Wildlife

Herpetofauna

3 Since the 2006 O₃ AQCD, direct effects of O₃ exposure including physiological changes
4 and alterations of ecologically important behaviors such as feeding and thermoregulation
5 have been observed in wildlife. These studies have been conducted in limited laboratory
6 exposures, and the levels of O₃ treatment (e.g., 0.2-0.8 ppm) were often unrealistically
7 higher than the ambient levels. Amphibians may be especially vulnerable to airborne
8 oxidants due to the significant gas exchange that occurs across the skin ([Andrews et al.,
9 2008](#); [Dohm et al., 2008](#)). Exposure to 0.2 ppm to 0.8 ppm O₃ for 4 hours resulted in a
10 decrease of oxygen consumption and depressed lung ventilation in the California tree
11 frog *Pseudacris cadaverina* ([Mautz and Dohm, 2004](#)). Following a single 4-h inhalation
12 exposure to 0.8 ppm O₃, reduced pulmonary macrophage phagocytosis was observed at 1
13 and 24 hours postexposure in the marine toad (*Bufo marinus*) indicating an effect on
14 immune system function ([Dohm et al., 2005](#)). There was no difference in macrophage
15 function at 48 hours postexposure in exposed and control individuals.

16 Behavioral effects of O₃ observed in amphibians include responses to minimize the
17 surface area of the body exposed to the air and a decrease in feeding rates ([Dohm et al.,
18 2008](#); [Mautz and Dohm, 2004](#)). The adoption of a low-profile “water conservation
19 posture” during O₃ exposure was observed in experiments with the California tree frog
20 ([Mautz and Dohm, 2004](#)). Marine toads, *Bufo marinus*, exposed to 0.06 μL/L O₃ for
21 4 hours ate significantly fewer mealworms at 1 hour and 48 hours postexposure than
22 control toads ([Dohm et al., 2008](#)). In the same study, escape/exploratory behavior as
23 measured by total distance moved was not negatively affected in the O₃-exposed
24 individuals as compared to the controls ([Dohm et al., 2008](#)).

25 Water balance and thermal preference in herpetofauna are altered with elevated O₃.
26 Marine toads exposed to 0.8 ppm O₃ for 4 hours exhibited behavioral hypothermia when
27 temperature selection in the toads was assessed at 1, 24 and 48 hours postexposure
28 ([Dohm et al., 2001](#)). Ozone-exposed individuals lost almost 5g more body mass on
29 average than controls due to evaporative water loss. At 24 hours after exposure, the
30 individuals that had lost significant body mass selected lower body temperatures ([Dohm
31 et al., 2001](#)). Behavioral hypothermia was also observed in reptiles following 4-h
32 exposures to 0.6 ppm O₃. Exposure of the Western Fence Lizard (*Sceloporus*

1 *occidentalis*) at 25°C induced behavioral hypothermia that recovered to control
2 temperatures by 24 hours ([Mautz and Dohm, 2004](#)). The behavioral hypothermic
3 response persisted in lizards exposed to O₃ at 35°C at 24 hours postexposure resulting in a
4 mean body temperature of 3.3°C over controls.

Soil fauna communities

5 Ozone has also been shown to alter soil fauna communities ([Meehan et al., 2010](#);
6 [Kasurinen et al., 2007](#); [Loranger et al., 2004](#)). Abundance of Acari (mites and ticks)
7 decreased by 47% under elevated O₃ at Aspen FACE site, probably due to the higher
8 secondary metabolites and lower N concentrations in litter and foliage under elevated O₃
9 ([Loranger et al., 2004](#)). In another study from the Aspen FACE site, leaf litter collected
10 from aspen grown under elevated O₃ conditions was higher in fiber and lignin
11 concentrations than litter from trees grown under ambient conditions. These chemical
12 characteristics of the leaves were associated with increased springtail population growth
13 following 10 weeks in a laboratory microcosm ([Meehan et al., 2010](#)). Consumption rates
14 of earthworms fed on leaf litter for 6 weeks from trees grown under elevated O₃
15 conditions and ambient air did not vary significantly between treatments ([Meehan et al.,](#)
16 [2010](#)). In another study on juvenile earthworms *Lumbricus terrestris*, individual growth
17 was reduced when worms were fed high-O₃ birch litter from trees exposed for three years
18 to elevated O₃ in an OTC system ([Kasurinen et al., 2007](#)). In the same study no
19 significant growth or mortality effects were observed in isopods.

9.4.9.3 Indirect Effects on Wildlife

20 In addition to the direct effects of O₃ exposure on physiological and behavioral endpoints
21 observed in the laboratory, there are indirect effects to wildlife. These effects include
22 changes in biomass and nutritive quality of O₃-exposed plants (reviewed in Section [9.4.4](#))
23 that are consumed by wildlife. Reduced digestibility of O₃-exposed plants may alter
24 dietary intake and foraging strategies in herbivores. In a study using native highbush
25 blackberry (*Rubus argutus*) relative feed value of the plants decreased in bushes exposed
26 to double ambient concentrations of O₃ ([Ditchkoff et al., 2009](#)). Indirect effects of
27 elevated O₃ on wildlife include changes in chemical signaling important in ecological
28 interactions reviewed below.

Chemical signaling in ecological interactions

1 Ozone has been shown to degrade or alter biogenic VOC signals important to ecological
2 interactions including; (1) attraction of pollinators and seed dispersers; (2) defense
3 against herbivory; and (3) predator-prey interactions ([Pinto et al., 2010](#); [McFrederick et](#)
4 [al., 2009](#); [Yuan et al., 2009](#); [Pinto et al., 2007a](#); [Pinto et al., 2007b](#)). Each signal released
5 by emitters has an atmospheric lifetime and a unique chemical signature comprised of
6 different ratios of individual hydrocarbons that are susceptible to atmospheric oxidants
7 such as O₃ ([Yuan et al., 2009](#); [Wright et al., 2005](#)). Under elevated O₃ conditions, these
8 olfactory cues may travel shorter distances before losing their specificity ([McFrederick et](#)
9 [al., 2009](#); [McFrederick et al., 2008](#)). Additional non-phytogenic VOC-mediated
10 interrelationships with the potential to be modified by O₃ include territorial marking,
11 pheromones for attraction of mates and various social interactions including scent trails,
12 nestmate recognition and signals involved in aggregation behaviors ([McFrederick et al.,](#)
13 [2009](#)). For example, the alcohols, ketones and aldehydes comprising sex pheromones in
14 moths could be especially vulnerable to degradation by O₃, since some males travel >100
15 meters to find mates ([Carde and Haynes, 2004](#)). In general, effects of O₃ on scent-
16 mediated ecological interactions are highly context- and species-specific ([Lindroth, 2010](#);
17 [Bidart-Bouzat and Imeh-Nathaniel, 2008](#)).

Pollination and seed dispersal

18 Phytogenic VOC's attract pollinators and seed dispersers to flowers and fruits ([Dudareva](#)
19 [et al., 2006](#); [Theis and Raguso, 2005](#)). These floral scent trails in plant-insect interactions
20 may be destroyed or transformed by O₃ ([McFrederick et al., 2008](#)). Using a Lagrangian
21 model, the rate of destruction of phytogenic VOC's was estimated in air parcels at
22 increasing distance from a source in response to increased regional levels of O₃, hydroxyl
23 and nitrate radicals ([McFrederick et al., 2008](#)). Based on the model, the ability of
24 pollinators to locate highly reactive VOCs from emitting flowers may have decreased
25 from kilometers during pre-industrial times to <200 meters at current ambient conditions
26 ([McFrederick et al., 2008](#)). Scents that travel shorter distances (0-10 m) are less
27 susceptible to air pollutants, while highly reactive scents that travel longer distances (10
28 to 100's of meters), are at a higher risk for degradation ([McFrederick et al., 2009](#)). For
29 example, male euglossine bees can detect bait stations from a distance of at least one
30 kilometer ([Dobson, 1994](#)).

Defense against herbivory

1 Ozone can alter the chemical signature of VOCs emitted by plants and these VOCs are
2 subsequently detected by herbivores ([Blande et al., 2010](#); [Iriti and Faoro, 2009](#); [Pinto et](#)
3 [al., 2007a](#); [Vuorinen et al., 2004](#); [Jackson et al., 1999](#); [Cannon, 1990](#)). These
4 modifications can make the plant either more attractive or repellant to phytophagous
5 insects ([Pinto et al., 2010](#)). For example, under elevated O₃, the host plant preference by
6 forest tent caterpillars increased for birch compared to aspen ([Agrell et al., 2005](#)).
7 Ozone-induced emissions from red spruce needles were found to repel spruce budworm
8 larvae ([Cannon, 1990](#)). Transcriptional profiles of field grown soybean (*Glycine max*)
9 grown in elevated O₃ conditions were altered due to herbivory by Japanese beetles. The
10 herbivory resulted in a higher number of transcripts in the leaves of O₃-exposed plants
11 and upregulation of antioxidant metabolism associated with plant defense ([Casteel et al.,](#)
12 [2008](#)).

13 Ozone may modify signals involved in plant-to-plant interactions and plant defense
14 against pathogens ([Blande et al., 2010](#); [Pinto et al., 2010](#); [McFrederick et al., 2009](#); [Yuan](#)
15 [et al., 2009](#)). In a recent study with lima beans, 80 ppb O₃ degraded several
16 herbivore-induced VOCs, reducing the distance over which plant-to-plant signaling
17 occurred ([Blande et al., 2010](#)).

Predator-prey interactions

18 Elevated O₃ conditions are associated with disruption of pheromone-mediated
19 interactions at higher trophic levels (e.g., predators and parasitoids of herbivores). In a
20 study from the Aspen FACE site, predator escape behaviors of the aphid (*Chatophorus*
21 *stevensis*) were enhanced on O₃-fumigated aspen trees although the mechanism of this
22 response remains unknown ([Mondor et al., 2004](#)). The predatory mite *Phytoseiulus*
23 *persimilis* can distinguish between the VOC signature of ozonated lima bean plants and
24 ozonated lima bean plants simultaneously damaged by *T. urticae* ([Vuorinen et al., 2004](#))
25 however, other tritrophic interactions have shown no effect ([Pinto et al., 2007b](#)).

26 There are few studies that consider host location behaviors of parasites under elevated O₃.
27 In closed chambers fumigated with O₃, the searching efficiency and proportion of the
28 host larval fruit flies parasitized by *Asobara tabida* declined when compared to filtered
29 air controls ([Gate et al., 1995](#)). The host location behavior and rate of parasitism of the
30 wasp (*Coesia plutellae*) on *Plutella xylostella*-infested potted cabbage plants was tested
31 under ambient and doubled O₃ conditions in an open-air fumigation system ([Pinto et al.,](#)
32 [2008](#)). The number of wasps found in the field and the percentages of parasitized larvae
33 were not significantly different from controls under elevated O₃.

1 Elevated O₃ has the potential to perturb specialized food-web communication in
2 transgenic crops. In insect-resistant oilseed rape *Brassica napus* grown under 100 ppb O₃
3 in a growth chamber, reduced feeding damage by *Putella xylostella* led to decreased
4 attraction of the endoparasitoid (*Costesia vestalis*), however this tritrophic interaction
5 was influenced by the degree of herbivore feeding ([Himanen et al., 2009a](#); [Himanen et](#)
6 [al., 2009b](#)). Under chronic O₃-exposure, the insect resistance trait BT cry1Ac in
7 transgenic *B. napus* was higher than the control ([Himanen et al., 2009c](#)). There was a
8 negative relative growth rate of the Bt target herbivore, *P. xylostella*, in all O₃ treatments.

9.4.9.4 Summary

9 Recent information on O₃ effects on insects and other wildlife is limited to a few species
10 and there is no consensus on how these organisms respond to elevated O₃. Studies
11 published since the last review show impacts of elevated O₃ on both species-level
12 responses (reproduction, growth, feeding behavior) and community and ecosystem-level
13 responses (population growth, abundance, shift in community structure) in some insects
14 and soil fauna. Changes in ecologically important behaviors such as feeding and
15 thermoregulation have recently been observed with O₃ exposure in amphibians and
16 reptiles, however, these responses occur at concentrations of O₃ much higher than
17 ambient levels.

18 Recent information available since the last review considers the effects of O₃ on chemical
19 signaling in insect and wildlife interactions. Specifically, studies on O₃ effects on
20 pollination and seed dispersal, defenses against herbivory and predator-prey interactions
21 all consider the ability of O₃ to alter the chemical signature of VOCs emitted during these
22 pheromone-mediated events. The effects of O₃ on chemical signaling between plants,
23 herbivores and pollinators as well as interactions between multiple trophic levels is an
24 emerging area of study that may result in further elucidation of O₃ effects at the species,
25 community and ecosystem-level.

9.5 Effects-Based Air Quality Exposure Indices and Dose Modeling

9.5.1 Introduction

26 Exposure indices are metrics that quantify exposure as it relates to measured plant
27 damage (e.g., reduced growth). They are summary measures of monitored ambient O₃

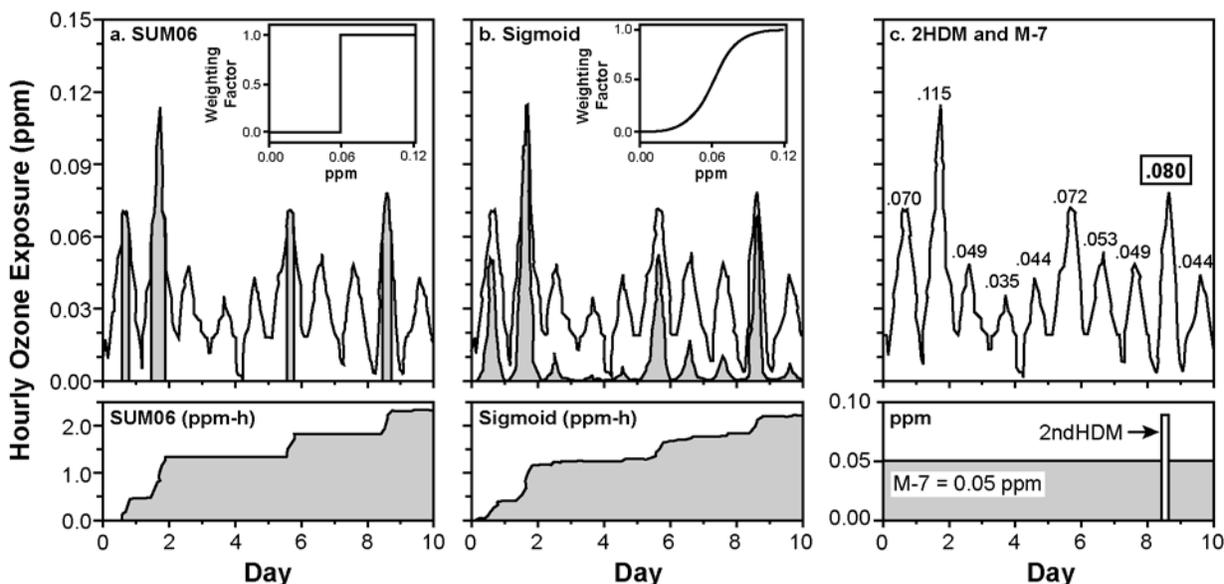
1 concentrations over time, intended to provide a consistent metric for reviewing and
2 comparing exposure-response effects obtained from various studies. Such indices may
3 also provide a basis for developing a biologically-relevant air quality standard for
4 protecting vegetation and ecosystems. Effects on plant growth and/or yield have been a
5 major focus of the characterization of O₃ impacts on plants for purposes of the air quality
6 standard setting process ([U.S. EPA, 2007b](#), [1996e](#), [1986](#)). The relationship of O₃ and
7 plant responses can be characterized quantitatively as “dose-response” or “exposure-
8 response.” The distinction is in how the pollutant concentration is expressed: “dose” is
9 the pollutant concentration absorbed by the leaf over some time period, and is very
10 difficult to measure directly, whereas “exposure” is the ambient air concentration
11 measured near the plant over some time period, and summarized for that period using an
12 index. Exposure indices have been most useful in considering the form of the secondary
13 O₃ NAAQS, in large part because they only require ambient air quality data rather than
14 more complex indirect calculations of dose to the plant. The attributes of exposure
15 indices that are most relevant to plant damage are the weighting of O₃ concentrations and
16 the daily and seasonal time-periods. Several different types of exposure indices are
17 discussed in Section [9.5.2](#).

18 From a theoretical perspective, a measure of plant O₃ uptake or dose from ambient air
19 (either rate of uptake or cumulative seasonal uptake) might be a better predictor of O₃
20 damage to plants than an exposure index and may be useful in improving risk assessment.
21 An uptake estimate would have to integrate all those environmental factors that influence
22 stomatal conductance, including but not limited to temperature, humidity, and soil water
23 status (Section [9.5.4](#)). Therefore, uptake values are generally obtained with simulation
24 models that require knowledge of species- and site-specific values for the variables
25 mentioned. However, a limitation of modeling dose is that environmental variables are
26 poorly characterized. In addition, it has also been recognized that O₃ detoxification
27 processes and the temporal dynamics of detoxification must be taken into account in dose
28 modeling ([Heath et al., 2009](#)) (Section [9.5.4](#)). Because of this, research has focused
29 historically on predictors of O₃ damage to plants based only on exposure as a summary
30 measure of monitored ambient pollutant concentration over some integral of time, rather
31 than dose ([U.S. EPA, 1996c](#); [Costa et al., 1992](#); [Lee et al., 1988b](#); [U.S. EPA, 1986](#);
32 [Lefohn and Benedict, 1982](#); [O’Gara, 1922](#)).

9.5.2 Description of Exposure Indices Available in the Literature

33 Mathematical approaches for summarizing ambient air quality information in biologically
34 meaningful forms for O₃ vegetation effects assessment purposes have been explored for
35 more than 80 years ([U.S. EPA, 1996b](#); [O’Gara, 1922](#)). In the context of national standards

1 that protect for “known or anticipated” effects on many plant species in a variety of
2 habitats, exposure indices provide a numerical summary of very large numbers of
3 ambient observations of concentration over extended periods. Like any summary statistic,
4 exposure indices retain information on some, but not all, characteristics of the original
5 observations. Several indices have been developed to attempt to incorporate some of the
6 biological, environmental, and exposure factors that influence the magnitude of the
7 biological response and contribute to observed variability ([Hogsett et al., 1988](#)). In the
8 1996 O₃ AQCD, the exposure indices were arranged into five categories; (1) One event,
9 (2) Mean, (3) Cumulative, (4) Concentration weighted, and (5) Multicomponent, and
10 were discussed in detail ([Lee et al., 1989](#)). [Figure 9-9](#) illustrates how several of the
11 indices weight concentration and accumulate exposure. For example, the SUM06 index
12 (panel a) is a threshold-based approach wherein concentrations below 0.06 ppm are given
13 a weight of zero and concentrations at or above 0.06 ppm are given a weight of 1.0 that is
14 summed, usually over 3 to 6 months. The Sigmoid approach (panel b), which is similar to
15 the W126 index ([Lefohn et al., 1988](#); [Lefohn and Runeckles, 1987](#)), is a non-threshold
16 approach wherein all concentrations are given a weight that increases from zero to 1.0
17 with increasing concentration and summed.



(a) SUM06: the upper graphic illustrates an episodic exposure profile; the shaded area under some of the peaks illustrates the concentrations greater than or equal to 0.06 ppm that are accumulated in the index. The insert shows the concentration weighting (0 or 1) function. The lower portion of the graphic illustrates how concentration is accumulated over the exposure period. (b) SIGMOID: the upper graphic illustrates an episodic exposure profile; the variable shaded area under the peaks illustrates the concentration-dependent weights that are accumulated in the index. The insert shows the sigmoid concentration weighting function. This is similar to the W126 function. The lower portion of the graphic illustrates how concentration is accumulated over the exposure period. (c) second HDM and M-7: the upper graphic illustrates an episodic exposure profile. The lower portion of the graphic illustrates that the second HDM considers only a single exposure peak, while the M-7 (average of 7-h daily means) applies a constant exposure value over the exposure period.

Source: Reprinted with permission of Air and Waste Management Association ([Tingey et al., 1991](#)).

Figure 9-9 Diagrammatic representation of several exposure indices illustrating how they weight concentration and accumulate exposure.

- 1 This section will primarily discuss SUM06, W126 and AOTx exposure metrics. Below
 2 are the definitions of the three cumulative index forms:
- 3 ▪ **SUM06:** Sum of all hourly O₃ concentrations greater than or equal to
 4 0.06 ppm observed during a specified daily and seasonal time window
 5 ([Figure 9-9a](#)).
 - 6 ▪ **AOTx:** Sum of the differences between hourly O₃ concentrations greater than
 7 a specified threshold during a specified daily and seasonal time window. For
 8 example, AOT40 is sum of the differences between hourly concentrations
 9 above 0.04 ppm.
 - 10 ▪ **W126:** Sigmoidally weighted sum of all hourly O₃ concentrations observed
 11 during a specified daily and seasonal time window ([Lefohn et al., 1988](#);
 12 [Lefohn and Runeckles, 1987](#)), similar to [Figure 9-9b](#)). The sigmoidal

1 weighting of hourly O₃ concentration is given in the equation below, where C
2 is the hourly O₃ concentration in ppm:

$$w_c = \frac{1}{1 + 4403e^{-126C}}$$

Equation 9-1

3 These indices have a variety of relevant time windows that may be applied and are
4 discussed in Section [9.5.3](#).

5 Various factors with known or suspected bearing on the exposure-response relationship,
6 including concentration, time of day, respite time, frequency of peak occurrence, plant
7 phenology, predisposition, etc., have been weighted with various functions in a large set
8 of indices. The resulting indices were evaluated by ranking them according to the
9 goodness-of-fit of a regression model of growth or yield response ([Lee et al., 1989](#)). The
10 statistical evaluations for each of these indices were completed using growth or yield
11 response data from many earlier exposure studies (e.g., NCLAN). This retrospective
12 approach was necessary because there were no studies specifically designed to test the
13 goodness-of-fit of the various indices. The goodness-of-fit of a set of linear and nonlinear
14 models for exposure-response was ranked as various proposed indices were used in turn
15 to quantify exposure. This approach provided evidence for the best indices. The results of
16 retrospective analyses are described below.

17 Most of the early retrospective studies reporting regression approaches used data from the
18 NCLAN program or data from Corvallis, Oregon or California ([Costa et al., 1992](#); [Lee et
19 al., 1988b](#); [Lefohn et al., 1988](#); [Musselman et al., 1988](#); [Lee et al., 1987](#); [U.S. EPA,
20 1986](#)). These studies were previously reviewed by the EPA ([U.S. EPA, 1996c](#); [Costa et
21 al., 1992](#)) and were in general agreement that the best fit to the data resulted from using
22 cumulative concentration-weighted exposure indices (e.g., W126, SUM06). [Lee et al.
23 \(1987\)](#) suggested that exposure indices that included all the 24-h data performed better
24 than those that used only 7 hours of data; this was consistent with the conclusions of
25 [Heagle et al. \(1987\)](#) that plants receiving exposures for an additional 5-h/day showed
26 10% greater yield loss than those exposed for 7-h/day. In an analysis using the National
27 Crop Loss Assessment Network (NCLAN) data, [Lefohn et al. \(1988\)](#) found several
28 indices which only cumulated and weighted higher concentrations (e.g., W126, SUM06,
29 SUM08, and AOT40) performed very well. Amongst this group no index had
30 consistently better fits than the other indices across all studies and species ([Heagle et al.,
31 1994b](#); [Lefohn et al., 1988](#); [Musselman et al., 1988](#)). [Lefohn et al. \(1988\)](#) found that
32 adding phenology weighting to the index somewhat improved the performance of the

1 indices. The “best” exposure index was a phenologically weighted cumulative index,
2 with sigmoid weighting on concentration and a gamma weighting function as a surrogate
3 for plant growth stage. This index provided the best statistical fit when used in the models
4 under consideration, but it required data on species and site conditions, making
5 specification of weighting functions difficult for general use.

6 Other factors, including predisposition time ([Hogsett et al., 1988](#); [McCool et al., 1988](#))
7 and crop development stage ([Tingey et al., 2002](#); [Heagle et al., 1991](#)) contributed to
8 variation in the biological response and suggested the need for weighting O₃
9 concentrations to account for predisposition time and phenology. However, the roles of
10 predisposition and phenology in plant response vary considerably with species and
11 environmental conditions; therefore, specification of a weighting function for general use
12 in characterizing plant exposure has not been possible.

13 European scientists took a similar approach in developing indices describing growth and
14 yield loss in crops and tree seedlings, using OTCs with modified ambient exposures, but
15 many fewer species and study locations were employed in the European studies. There is
16 evidence from some European studies that a lower ([Pleijel et al., 1997](#)) or higher ([Finnan
17 et al., 1997](#); [Finnan et al., 1996](#)) cutoff value in indices with a threshold may provide a
18 better statistical fit to the experimental data. [Finnan et al. \(1997\)](#) used seven exposure
19 studies of spring wheat to confirm that cumulative exposure indices emphasizing higher
20 O₃ concentrations were best related to plant response and that cumulative exposure
21 indices using weighting functions, including cutoff concentrations, allometric and
22 sigmoidal, provided a better fit and that the ranking of these indices differed depending
23 on the exposure-response model used. Weighting those concentrations associated with
24 sunshine hours in an attempt to incorporate an element of plant uptake did not improve
25 the index performance ([Finnan et al., 1997](#)). A more recent study using data from several
26 European studies of Norway spruce, analyzed the relationship between relative biomass
27 accumulation and several cumulative, weighted indices, including the AOT40 (area over
28 a threshold of 40ppb) and the SUM06 ([Skarby et al., 2004](#)). All the indices performed
29 relatively well in regressing biomass and exposure index, with the AOT20 and AOT30
30 doing slightly better than others ($r^2 = 0.46-0.47$). In another comparative study of four
31 independent data sets of potato yield and different cumulative uptake indices with
32 different cutoff values, a similarly narrow range of r^2 was observed ($r^2 = 0.3-0.4$) ([Pleijel
33 et al., 2004b](#)).

34 In Europe, the cutoff concentration-weighted index AOT40 was selected in developing
35 exposure-response relationships based on OTC studies of a limited number of crops and
36 trees ([Grunhage and Jager, 2003](#)). The United Nations Economic Commission for Europe
37 ([UNECE, 1988](#)) adopted the critical levels approach for assessment of O₃ risk to

1 vegetation across Europe. As used by the UNECE, the critical levels are not like the air
2 quality regulatory standards used in the U.S., but rather function as planning targets for
3 reductions in pollutant emissions to protect ecological resources. Critical levels for O₃ are
4 intended to prevent long-term deleterious effects on the most sensitive plant species
5 under the most sensitive environmental conditions, but not intended to quantify O₃
6 effects. A critical level was defined as “the concentration of pollutant in the atmosphere
7 above which direct adverse effects on receptors, such as plants, ecosystems, or materials
8 may occur according to present knowledge” ([UNECE, 1988](#)). The nature of the “adverse
9 effects” was not specified in the original definition, which provided for different levels
10 for different types of harmful effect (e.g., visible injury or loss of crop yield). There are
11 also different critical levels for crops, forests, and semi-natural vegetation. The caveat,
12 “according to present knowledge” is important because critical levels are not rigid; they
13 are revised periodically as new scientific information becomes available. For example,
14 the original critical level for O₃ specified concentrations for three averaging times, but
15 further research and debate led to the current critical level being stated as the cumulative
16 exposure (concentration × hours) over a cutoff concentration of 40 ppb (AOT40) ([Fuhrer
17 et al., 1997](#)).

18 More recently in Europe, a decision was made to work towards a flux-based approach
19 (see Section [9.5.4](#)) for the critical levels (“Level II”), with the goal of modeling O₃
20 flux-effect relationships for three vegetation types: crops, forests, and semi-natural
21 vegetation ([Grunhage and Jager, 2003](#)). Progress has been made in modeling flux ([U.S.
22 EPA, 2006b](#)) and the Mapping Manual is being revised ([Ashmore et al., 2004a, b](#);
23 [Grennfelt, 2004](#); [Karlsson et al., 2003](#)). The revisions may include a flux-based approach
24 for three crops: wheat, potatoes, and cotton. However, because of a lack of flux-response
25 data, a cumulative, cutoff concentration-based (AOT_x) exposure index will remain in use
26 for the near future for most crops and for forests and semi-natural herbaceous vegetation
27 ([Ashmore et al., 2004b](#)).

28 In both the U.S. and Europe, the adequacy of these numerical summaries of exposure in
29 relating biomass and yield changes have, for the most part, all been evaluated using data
30 from studies not necessarily designed to compare one index to another ([Skarby et al.,
31 2004](#); [Lee et al., 1989](#); [Lefohn et al., 1988](#)). Very few studies in the U.S. have addressed
32 this issue since the 2006 O₃ AQCD. [McLaughlin et al. \(2007a\)](#) reported that the
33 cumulative exposure index of AOT60 related well to reductions in growth rates at forest
34 sites in the southern Appalachian Mountains. However, the authors did not report an
35 analysis to compare multiple indices. Overall, given the available data from previous O₃
36 AQCDs and the few recent studies, the cumulative, concentration-weighted indices
37 perform better than the peak or mean indices. It is still not possible, however, to

1 distinguish the differences in performance among the cumulative, concentration-weighted
2 indices.

3 The main conclusions from the 1996 and 2006 O₃ AQCDs regarding an index based on
4 ambient exposure are still valid. No information has come forth since the 2006 O₃ AQCD
5 to alter those conclusions. These key conclusions can be restated as follows:

- 6 ▪ O₃ effects in plants are cumulative;
- 7 ▪ higher O₃ concentrations appear to be more important than lower
8 concentrations in eliciting a response;
- 9 ▪ plant sensitivity to O₃ varies with time of day and plant development stage;
10 and
- 11 ▪ quantifying exposure with indices that accumulate the O₃ hourly
12 concentrations and preferentially weight the higher concentrations improves
13 the explanatory power of exposure/response models for growth and yield, over
14 using indices based on mean and peak exposure values.

15 Following the 2006 criteria review process ([U.S. EPA, 2006b](#)), the EPA proposed an
16 alternative form of the secondary NAAQS for O₃ using a cumulative, concentration-
17 weighted exposure index to protect vegetation from damage (72 FR 37818). The EPA
18 considered two specific concentration-weighted indices: the cutoff concentration
19 weighted SUM06 and the sigmoid-weighted W126 exposure index ([U.S. EPA, 2007b](#)).
20 These two indices performed equally well in predicting the exposure-response
21 relationships observed in the crop and tree seedlings studies ([Lee et al., 1989](#)). At a
22 workshop convened to consider the science supporting these indices ([Heck and Cowling,](#)
23 [1997](#)) there was a consensus that these cumulative concentration-weighted indices being
24 considered were equally capable of predicting plant response. It should be noted that
25 there are some important differences between the SUM06 and W126. When considering
26 the response of vegetation to O₃ exposures represented by the threshold (e.g., SUM06)
27 and non-threshold (e.g., W126) indices, the W126 metric does not have a cut-off in the
28 weighting scheme as does SUM06 and thus it includes consideration of potentially
29 damaging exposures below 60 ppb. The W126 metric also adds increasing weight to
30 hourly concentrations from about 40 ppb to about 100 ppb ([Lefohn et al., 1988](#); [Lefohn](#)
31 [and Runeckles, 1987](#)). This is unlike cut-off metrics such as the SUM06 where all
32 concentrations above 60 ppb are treated equally. This is an important feature of the W126
33 since as hourly concentrations become higher, they become increasingly likely to
34 overwhelm plant defenses and are known to be more detrimental to vegetation (See
35 Section [9.5.3.1](#)).

9.5.3 Important Components of Exposure Indices

1 In the previous O₃ AQCDs it was established that higher hourly concentrations have
2 greater effects on vegetation than lower concentrations ([U.S. EPA, 2006b, 1996c](#)).
3 Further, it was determined that the diurnal and seasonal duration of exposure is important
4 for plant response. Weighting of hourly concentrations and the diurnal and seasonal time
5 window of exposure are the most important variables in a cumulative exposure index and
6 will be discussed below. However, these variables should be looked at in the context of
7 plant phenology, diurnal conductance rates, plant canopy structure, and detoxification
8 mechanisms of vegetation as well as the climate and meteorology, all of which are
9 determinants of plant response. These more specific factors will be discussed in the
10 uptake and dose modeling Section [9.5.4](#).

9.5.3.1 Role of Concentration

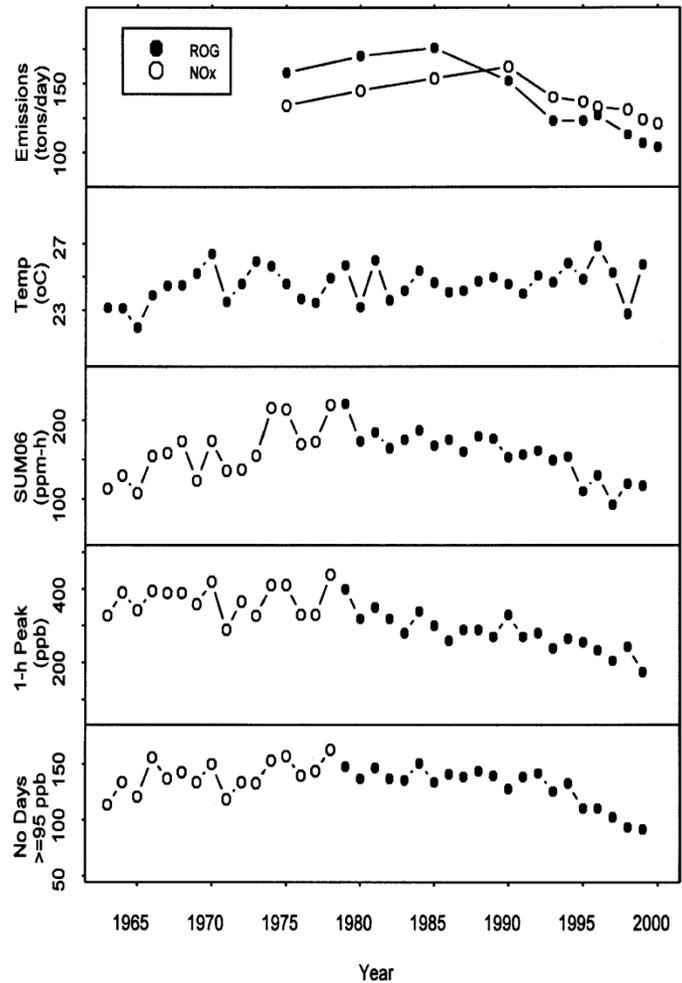
11 The significant role of peak O₃ concentrations was established based on several
12 experimental studies ([U.S. EPA, 1996c](#)). Several studies ([Oksanen and Holopainen,
13 2001](#); [Yun and Laurence, 1999](#); [Nussbaum et al., 1995](#)) have added support for the
14 important role that peak concentrations, as well as the pattern of occurrence, plays in
15 plant response to O₃. [Oksanen and Holopainen \(2001\)](#) found that the peak concentrations
16 and the shape of the O₃ exposure (i.e., duration of the event) were important determinants
17 of foliar injury in European white birch saplings, but growth reductions were found to be
18 more related to total cumulative exposure. Based on air quality data from 10 U.S. cities,
19 three 4-week exposure treatments having the same SUM06 value were constructed by
20 [Yun and Laurence \(1999\)](#). The authors used different exposure regimes to explore effects
21 of treatments with variable versus uniform peak occurrence during the exposure period.
22 The authors reported that the variable peak exposures were important in causing injury,
23 and that the different exposure treatments, although having the same SUM06, resulted in
24 very different patterns of foliar injury. [Nussbaum et al. \(1995\)](#) also found peak
25 concentrations and the pattern of occurrence to be critical in determining the measured
26 response. The authors recommended that to describe the effect on total forage yield, peak
27 concentrations >0.11 ppm must be emphasized by using an AOT with higher threshold
28 concentrations.

29 A greater role for peak concentrations in effects on plant growth might be inferred based
30 on air quality analyses for the southern California area ([Tingey et al., 2004](#); [Lee et al.,
31 2003a](#)). In the late 1960s and 1970s, extremely high O₃ concentrations had impacted the
32 San Bernardino National Forest. However, over the past 20+ years, significant reductions
33 in O₃ exposure have occurred ([Bytnerowicz et al., 2008](#); [Lee et al., 2003a](#); [Lefohn and](#)

1 [Shadwick, 2000](#); [Davidson, 1993](#)). An illustration of this improvement in air quality is
2 shown by the 37-year history of O₃ air quality at the Crestline site in the San Bernardino
3 Mountains ([Figure 9-10](#)) ([Lee et al., 2003a](#)). Ozone exposure increased from 1963 to
4 1979 concurrent with increased population and vehicular miles, followed by a decline to
5 the present mirroring decreases in precursor emissions. The pattern in exposure was
6 evident in various exposure indices including the cumulative concentration weighted
7 (SUM06), as well as maximum peak event (1-h peak), and the number of days having
8 hourly averaged O₃ concentrations greater than or equal to 95 ppb. The number of days
9 having hourly averaged O₃ concentrations greater than or equal to 95 ppb declined
10 significantly from 163 days in 1978 to 103 days in 1997. The changes in ambient O₃ air
11 quality for the Crestline site were reflected in the changes in frequency and magnitude of
12 the peak hourly concentration and the duration of exposure ([Figure 9-10](#)). Considering
13 the role of exposure patterns in determining response, the seasonal and diurnal patterns in
14 hourly O₃ concentration did not vary appreciably from year to year over the 37-year
15 period ([Lee et al., 2003a](#)).

16 The potential importance of exposure to peak concentrations comes both from results of
17 measures of tree conditions on established plots and from results of model simulations.
18 Across a broad area of the San Bernardino National Forest, the Forest Pest Management
19 (FPM) method of injury assessment indicated an improvement in crown condition from
20 1974 to 1988; and the area of improvement in injury assessment is coincident with an
21 improvement in O₃ air quality ([Miller and Rechel, 1999](#)). A more recent analysis of forest
22 changes in the San Bernardino National Forest, using an expanded network of monitoring
23 sites, has verified significant changes in growth, mortality rates, basal area, and species
24 composition throughout the area since 1974 ([Arbaugh et al., 2003](#)). A model simulation
25 of ponderosa pine growth over the 40-year period in the San Bernardino National Forest
26 showed a significant impact of O₃ exposure on tree growth and indicates improved
27 growth with reduced O₃ concentrations. This area has also experienced elevated
28 N deposition and based on a number of environmental indicators, it appears that this area
29 is experiencing N saturation ([Fenn et al., 1996](#)). To account for this potential interaction,
30 the model simulations were conducted under conditions of unlimited soil N. The actual
31 interactions are not known. The improvement in growth over the years was attributed to
32 improved air quality, but no distinction was made regarding the relative role of
33 “mid-range” and higher hourly concentrations, only that improved growth tracked
34 decreasing SUM06, maximum peak concentration, and number of days of hourly O₃
35 >95 ppb ([Tingey et al., 2004](#)). A summary of air quality data from 1980 to 2000 for the
36 San Bernardino National Forest area of the number of “mid-range” hourly concentrations
37 indicated no dramatic changes over this 20-year period, ranging from about 1,500 to
38 2,000 hours per year ([Figure 9-11](#)). There was a slow increase in the number of
39 “mid-range” concentrations from 1980 to 1986, which corresponds to the period after

1 implementation of the air quality standard. Another sharper increase was observed in the
2 late 1990s. This pattern of occurrence of mid-range hourly concentrations suggests a
3 lesser role for these concentration ranges compared to the higher values in either of the
4 ground-level tree injury observations of the model simulation of growth over the 40-year
5 period.



Note: Annual ROG and NO_x emissions data for San Bernardino County were obtained from [Alexis et al. \(2001a\)](#) and the California Air Resource Board's emission inventory available at <http://www.arb.ca.gov/html/ds.htm> ([Cal EPA, 2010](#)).
Source: Reprinted with permission of Elsevier Science Ltd. ([Lee et al., 2003a](#)).

Figure 9-10 Trends in May to September: 12-hour SUM06, Peak 1-hour ozone concentration and number of daily exceedances of 95 ppb for the Crestline site in 1963 to 1999; in relation to trends in mean daily maximum temperature for Crestline and daily reactive organic gases (ROG) and oxides of nitrogen (NO_x) for San Bernardino County.

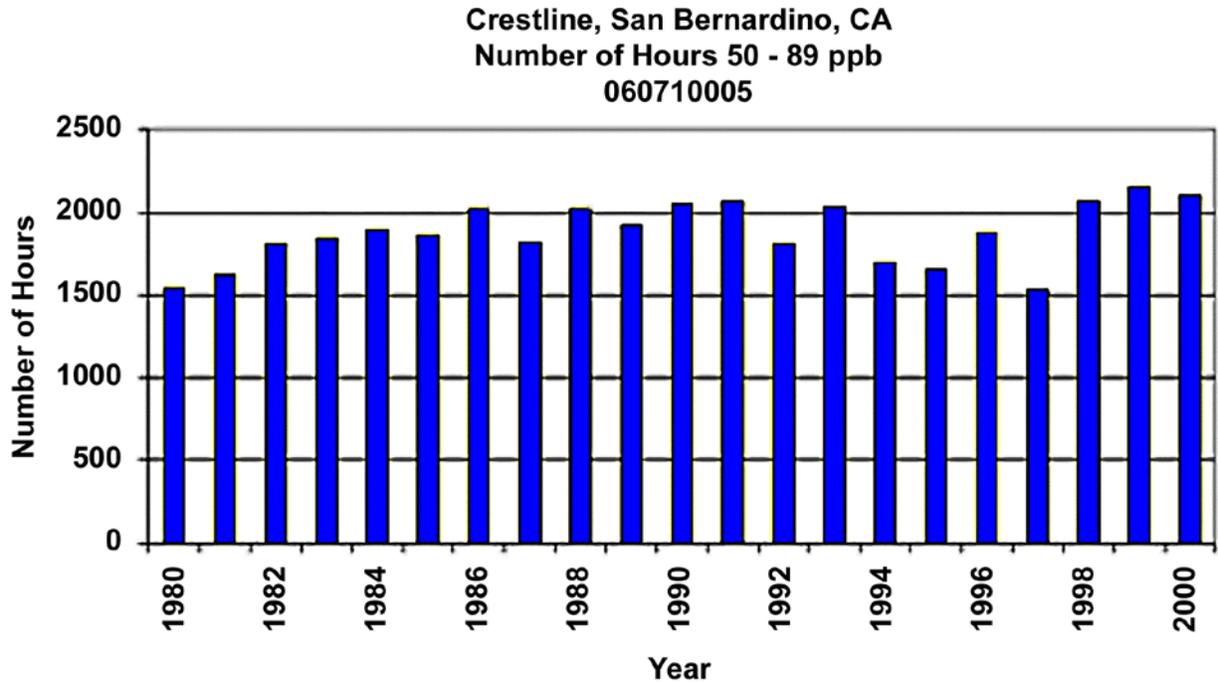


Figure 9-11 The number of hourly average concentrations between 50 and 89 ppb for the period 1980-2000 for the Crestline, San Bernardino County, CA, monitoring site.

9.5.3.2 Diurnal and Seasonal Exposure

Diurnal Exposure

1 The diurnal patterns of maximal leaf/needle conductance and occurrence of higher
 2 ambient concentrations can help determine which hours during the day over a season
 3 should be included in an exposure index. Stomatal conductance is species and phenology
 4 dependent and is linked to both diurnal and seasonal meteorological activity as well as to
 5 soil/site conditions (e.g., VPD, soil moisture). Daily patterns of leaf/needle conductance
 6 are often highest in midmorning, whereas higher ambient O₃ concentrations generally
 7 occur in early to late afternoon when stomata are often partially closed and conductances
 8 are lower. Total O₃ flux depends on atmospheric and boundary layer resistances, both of
 9 which exhibit variability throughout the day. Experimental studies with tree species
 10 demonstrated the decoupling of ambient O₃ exposure, peak occurrence, and gas
 11 exchange, particularly in areas of drought ([Panek, 2004](#)). Several studies have suggested
 12 that ponderosa pine trees in the southern and northern Sierra Nevada Mountains may not
 13 be as susceptible to high O₃ concentrations as to lower concentrations, due to reduced

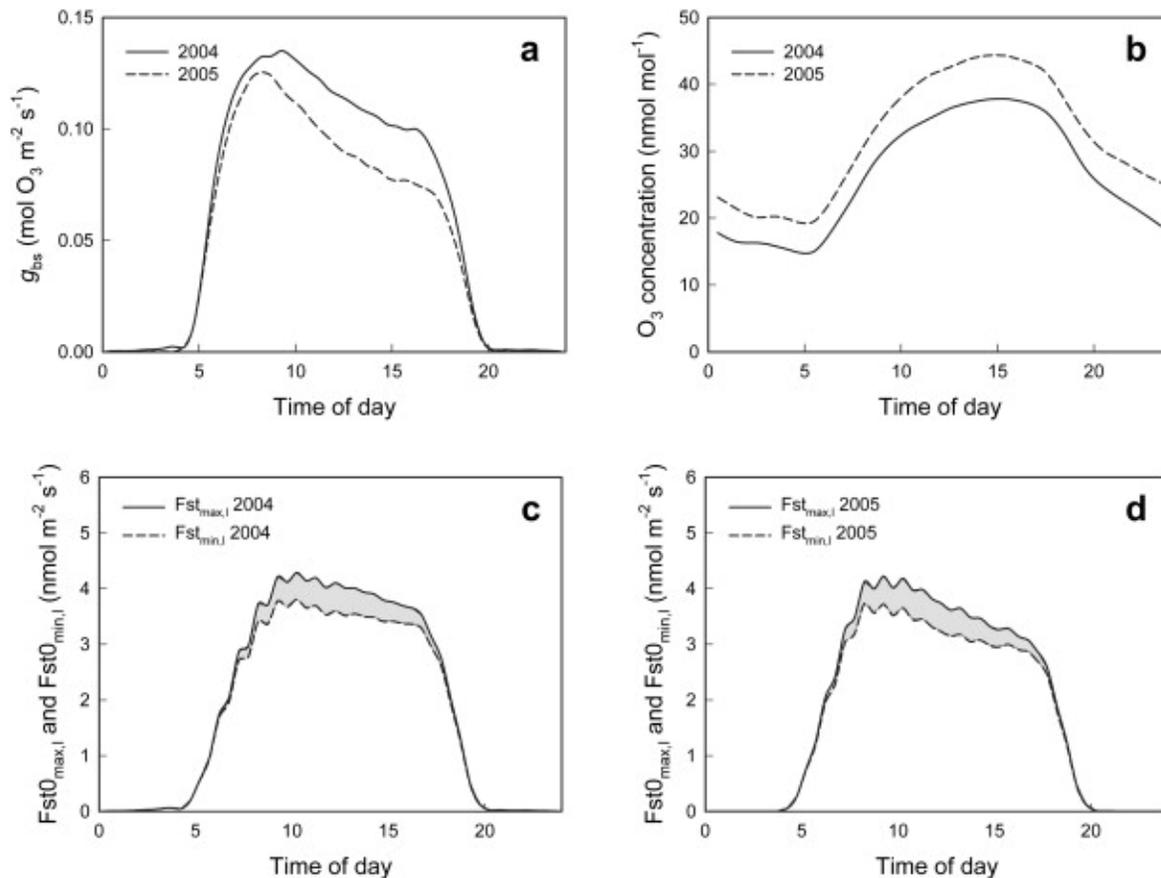
1 needle conductance and O₃ uptake during the period when the highest concentrations
2 occur ([Panek et al., 2002](#); [Panek and Goldstein, 2001](#); [Bauer et al., 2000](#); [Arbaugh et al.,
3 1998](#)). [Panek et al. \(2002\)](#) compared direct O₃ flux measurements into a canopy of
4 ponderosa pine and demonstrated a lack of correlation of daily patterns of conductance
5 and O₃ occurrence, especially in the late season drought period; the authors concluded
6 that a consideration of climate or season was essential, especially considering the role of
7 soil moisture and conductance/uptake. In contrast, [Grulke et al. \(2002\)](#) reported high
8 conductance when O₃ concentrations were high in the same species, but under different
9 growing site conditions. The longer-term biological responses reported by [Miller and
10 Rechel \(1999\)](#) for ponderosa pine in the same region, and the general reduction in recent
11 years in ambient O₃ concentrations, suggest that stomatal conductance alone may not be a
12 sufficient indicator of potential vegetation injury or damage. Another consideration for
13 the effect of O₃ uptake is the diurnal pattern of detoxification capacity of the plant. The
14 detoxification capacity may not follow the same pattern as stomatal conductance ([Heath
15 et al., 2009](#)).

16 The use of a 12-h (8:00 a.m. to 8:00 p.m.) daylight period for a W126 cumulating
17 exposure was based primarily on evidence that the conditions for uptake of O₃ into the
18 plant occur mainly during the daytime hours. In general, plants have the highest stomatal
19 conductance during the daytime and in many areas atmospheric turbulent mixing is
20 greatest during the day as well ([Uddling et al., 2010](#); [U.S. EPA, 2006b](#)). However,
21 notable exceptions to maximum daytime conductance are cacti and other plants with
22 crassulacean acid metabolism (CAM photosynthesis) which only open their stomata at
23 night. This section will focus on plants with C3 and C4 photosynthesis, which generally
24 have maximum stomatal conductance during the daytime.

25 Recent reviews of the literature reported that a large number of species had varying
26 degrees of nocturnal stomatal conductance ([Caird et al., 2007](#); [Dawson et al., 2007](#);
27 [Musselman and Minnick, 2000](#)). The reason for night-time water loss through stomata is
28 not well understood and is an area of active research (e.g., [Christman et al., 2009](#);
29 [Howard et al., 2009](#)). Night-time stomatal opening may be enhanced by O₃ damage that
30 could result in loss of stomatal control, and less complete closure of stomata, than under
31 low O₃ conditions ([Caird et al., 2007](#); [Grulke et al., 2007b](#)). In general, the rate of
32 stomatal conductance at night is much lower than during the day ([Caird et al., 2007](#)).
33 Atmospheric turbulence at night is also often low, which results in stable boundary layers
34 and unfavorable conditions for O₃ uptake into vegetation ([Finkelstein et al., 2000](#)).
35 Nevertheless, nocturnal turbulence does intermittently occur and may result in
36 non-negligible O₃ flux into the plants. In addition, plants might be more susceptible to O₃
37 exposure at night than during the daytime, because of potentially lower plant defenses
38 ([Heath et al., 2009](#); [Loreto and Fares, 2007](#); [Musselman et al., 2006](#); [Musselman and](#)

1 [Minnick, 2000](#)). For significant nocturnal stomatal flux and O₃ effects to occur, specific
2 conditions must exist. A susceptible plant with nocturnal stomatal conductance and low
3 defenses must be growing in an area with relatively high night-time O₃ concentrations
4 and appreciable nocturnal atmospheric turbulence. It is unclear how many areas there are
5 in the U.S. where these conditions occur. It may be possible that these conditions exist in
6 mountainous areas of southern California, front-range of Colorado ([Turnipseed et al.,
7 2009](#)) and the Great Smoky Mountains of North Carolina and Tennessee. [Tobiessen
8 \(1982\)](#) found that shade intolerant tree species showed opening of stomata in the dark and
9 did not find this in shade tolerant species. This may indicate shade intolerant trees may be
10 more likely to be susceptible to O₃ exposure at night. More information is needed in
11 locations with high night-time O₃ to assess the local O₃ patterns, micrometeorology and
12 responses of potentially vulnerable plant species.

13 Several field studies have attempted to quantify night-time O₃ uptake with a variety of
14 methods. However, many of these studies have not linked the night-time flux to measured
15 effects on plants. [Grulke et al. \(2004\)](#) showed that the stomatal conductance at night for
16 ponderosa pine in the San Bernardino National Forest (CA) ranged from one tenth to one
17 fourth that of maximum daytime stomatal conductance. In June, at a high-elevation site, it
18 was calculated that 11% of the total daily O₃ uptake of pole-sized trees occurred at night.
19 In late summer, however, O₃ uptake at night was negligible. However, this study did not
20 consider the turbulent conditions at night. [Finkelstein et al. \(2000\)](#) investigated O₃
21 deposition velocity to forest canopies at three different sites. The authors found the total
22 flux (stomatal and non-stomatal) to the canopy to be very low during night-time hours as
23 compared to day-time hours. However, the authors did note that higher nocturnal
24 deposition velocities at conifer sites may be due to some degree of stomatal opening at
25 night ([Finkelstein et al., 2000](#)). Work by [Mereu et al. \(2009\)](#) in Italy on Mediterranean
26 species indicated that nocturnal uptake was from 10 to 18% of total daily uptake during a
27 weak drought and up to 24% as the drought became more pronounced. The proportion of
28 night-time uptake was greater during the drought due to decreases in daytime stomatal
29 conductance ([Mereu et al., 2009](#)). In a study conducted in California, ([Fares et al., 2011](#))
30 reported that calculated mean percentages of nocturnal uptake were 5%, 12.5%, 6.9% of
31 total O₃ uptake for lemon, mandarin, and orange, respectively. In another recent study at
32 the Aspen FACE site in Wisconsin, calculated leaf-level stomatal O₃ flux was near zero
33 from the night-time hours of 8:00 p.m. to 5:00 a.m. ([Uddling et al., 2010](#)). This was likely
34 due to low horizontal wind speed (>1 meter/sec) and low O₃ concentrations (<25 ppb)
35 during those same night-time hours ([Figure 9-12](#)).



Note: Subscripts “max” and “min” refer to stomatal fluxes calculated neglecting and accounting for potential non-stomatal ozone flux, respectively.

Source: Reprinted with permission of Elsevier Ltd. ([Uddling et al., 2010](#)).

Figure 9-12 Diurnal (a) conductance through boundary layer and stomata (g_{bs}), (b) ozone concentration, and leaf-level stomatal ozone flux (FstO) in control plots from mid-June through August in (c) 2004 and (d) 2005 in the Aspen FACE experiment.

1 A few studies have tested the biological effects of night-time O_3 exposure on vegetation
 2 in controlled chambers. Biomass of ponderosa pine seedlings was significantly reduced
 3 when seedlings were exposed to either daytime or nighttime episodic profiles ([Lee and](#)
 4 [Hogsett, 1999](#)). However, the biomass reductions were much greater with daytime peak
 5 concentrations than with nighttime peak concentrations. Similarly, birch cuttings grown
 6 in field chambers that were exposed to O_3 at night only, daytime only, and 24 hours
 7 showed similar reductions in biomass in night only and day only treatments. Birch
 8 seedling showed greater reductions in growth in 24-h exposures than those exposed to O_3
 9 at night or day only ([Matyssek et al., 1995](#)). Field mustard (*Brassica rapa*) plants
 10 exposed to O_3 during the day or night showed little significant difference in the amounts

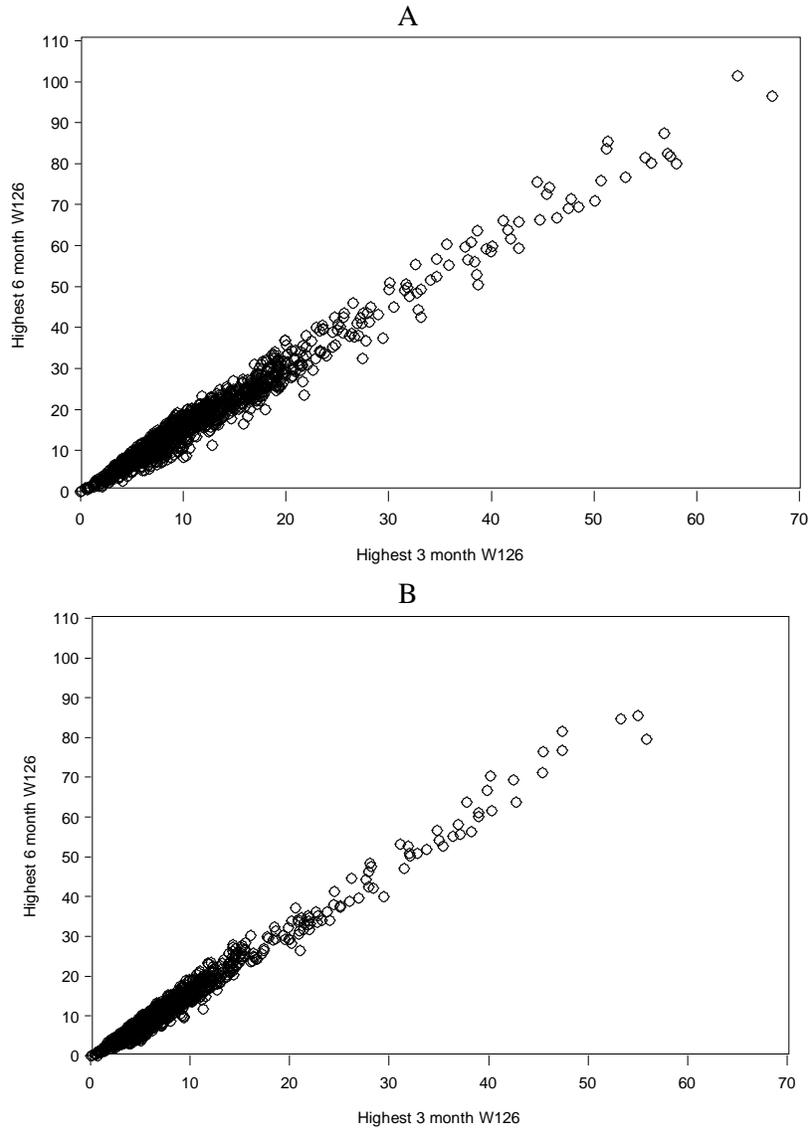
1 of injury or reduced growth response to O₃ treatment, although the stomatal conductance
2 was 70-80% lower at night ([Winner et al., 1989](#)). These studies show that effects can be
3 seen with night-time exposures to O₃ but when atmospheric conditions are stable at night,
4 it is uncertain how these exposures may affect plants and trees with complex canopies in
5 the field.

Seasonal exposure

6 Vegetation across the U.S. has widely varying periods of physiological activity during the
7 year due to variability in climate and phenology. In order for a particular plant to be
8 vulnerable to O₃ pollution, it must have foliage and be physiologically active. Annual
9 crops are typically grown for periods of two to three months. In contrast, perennial
10 species may be photosynthetically active longer (up to 12 months each year for some
11 species) depending on the species and where it is grown. In general, the period of
12 maximum physiological activity and thus, potential O₃ uptake for vegetation coincides
13 with some or all of the intra-annual period defined as the O₃ season, which varies on a
14 state-by-state basis ([Figure 3-24](#)). This is because the high temperature and high light
15 conditions that typically promote the formation of tropospheric O₃ also promote
16 physiological activity in vegetation. There are very limited exceptions to this pattern
17 where O₃ can form in the winter in areas in the western U.S. with intense natural gas
18 exploration ([Pinto, 2009](#)), but this is typically when plants are dormant and there is little
19 chance of O₃ uptake. Given the significant variability in growth patterns and lengths of
20 growing season among the wide range of vegetation species that may experience adverse
21 effects associated with O₃ exposure, no single time window of exposure can work
22 perfectly for all types of vegetation.

23 Various intra-annual averaging and accumulation time periods have been considered for
24 the protection of vegetation. The 2007 proposal for the secondary O₃ standard (75 FR
25 37818) proposed to use the maximum consecutive 3-month period within the O₃ season.
26 The U.S. Forest Service and federal land managers have used a 24-h W126 accumulated
27 for 6 months from April through September ([U.S. Forest Service, 2000](#)). However, some
28 monitors in the U.S. are operational for as little as four months and would not have
29 enough data for a 6-month seasonal window. The exposure period in the vast majority of
30 O₃ exposure studies conducted in the U.S. has been much shorter than 6 months. Most of
31 the crop studies done through NCLAN had exposures less than three months with an
32 average of 77 days. Open-top chamber studies of tree seedlings, compiled by the EPA,
33 had an average exposure of just over three months or 99 days. In more recent FACE
34 experiments, SoyFACE exposed soybeans for an average of approximately 120 days per
35 year and the Aspen FACE experiment exposed trees to an average of approximately
36 145 days per year of elevated O₃, which included the entire growing season at those

1 particular sites. Despite the possibility that plants may be exposed to ambient O₃ longer
2 than 3 months in some locations, there is generally a lack of exposure experiments
3 conducted for longer than 3 months.



Note: Data are from the AQS and CASTNET monitors for the years 2008 and 2009. (A) W126, 3 month versus 6 month, 2008 (Pearson correlation = 0.99); (B) W126, 3 month versus 6 month, 2009 (Pearson correlation = 0.99).

Figure 9-13 Maximum 3-month, 12-h W126 plotted against maximum 6-month, 12-h W126.

1 In an analysis of the 3- and 6-month maximum W126 values calculated for over 1,200
2 AQS (Air Quality System) and CASTNET (Clean Air Status and Trend Network) EPA
3 monitoring sites for the years 2008-2009, it was found that these 2 accumulation periods
4 resulted in highly correlated metrics ([Figure 9-13](#)). The two accumulation periods were
5 centered on the yearly maximum for each monitoring site, and it is possible that this
6 correlation would be weaker if the two periods were not temporally aligned. In the U.S.,
7 W126 cumulated over 3 months, and W126 cumulated over 6 months are proxies of one
8 another, as long as the period in which daily W126 is accumulated corresponds to the
9 seasonal maximum. Therefore, it is expected that either statistic will predict vegetation
10 response equally well. In other words, the strength of the correlation between maximum
11 3-month W126 and maximum 6-month W126 is such that there is no material difference
12 in their predictive value for vegetation response.

9.5.4 Ozone Uptake/Dose Modeling for Vegetation

13 Another approach for improving risk assessment of vegetation response to ambient O₃ is
14 based on estimating the O₃ concentration from the atmosphere that enters the leaf
15 (i.e., flux or deposition). Interest has been increasing in recent years, particularly in
16 Europe, in using mathematically tractable flux models for O₃ assessments at the regional,
17 national, and European scale ([Matyssek et al., 2008](#); [Paoletti and Manning, 2007](#); [ICP
18 M&M, 2004](#); [Emberson et al., 2000b](#); [Emberson et al., 2000a](#)). Some researchers have
19 claimed that using flux models can be used to better predict vegetation responses to O₃
20 than exposure-based approaches ([Matyssek et al., 2008](#)). However, other research has
21 suggested that flux models do not predict vegetation responses to O₃ better than
22 exposure-based models, such as AOT40 ([Gonzalez-Fernandez et al., 2010](#)). While some
23 efforts have been made in the U.S. to calculate O₃ flux into leaves and canopies ([Fares et
24 al., 2010a](#); [Turnipseed et al., 2009](#); [Uddling et al., 2009](#); [Bergweiler et al., 2008](#); [Hogg et
25 al., 2007](#); [Grulke et al., 2004](#); [Grantz et al., 1997](#); [Grantz et al., 1995](#)), little information
26 has been published relating these fluxes to effects on vegetation. The lack of flux data in
27 the U.S. and the lack of understanding of detoxification processes have made this
28 technique less viable for vulnerability and risk assessments in the U.S.

29 Flux calculations are data intensive and must be carefully implemented. Reducing
30 uncertainties in flux estimates for areas with diverse surface or terrain conditions to
31 within ± 50% requires “very careful application of dry deposition models, some model
32 development, and support by experimental observations” ([Wesely and Hicks, 2000](#)). As
33 an example, the annual average deposition velocity of O₃ among three nearby sites in
34 similar vegetation was found to vary by ± 10%, presumably due to terrain ([Brook et al.,
35 1997](#)). Moreover, the authors stated that the actual variation was even greater, because

1 stomatal uptake was unrealistically assumed to be the same among all sites, and flux is
2 strongly influenced by stomatal conductance ([Brook et al., 1997](#); [Massman and Grantz,](#)
3 [1995](#); [Fuentes et al., 1992](#); [Reich, 1987](#); [Leuning et al., 1979](#)). This uptake-based
4 approach to quantify the vegetation impact of O₃ requires inclusion of those factors that
5 control the diurnal and seasonal O₃ flux to vegetation (e.g., climate patterns, species
6 and/or vegetation-type factors and site-specific factors). The models have to distinguish
7 between stomatal and non-stomatal components of O₃ deposition to adequately estimate
8 actual concentration reaching the target tissue of a plant to elicit a response ([Uddling et](#)
9 [al., 2009](#)). Determining this O₃ uptake via canopy and stomatal conductance relies on
10 models to predict flux and ultimately the “effective” flux ([Grunhage et al., 2004](#);
11 [Massman, 2004](#); [Massman et al., 2000](#)). “Effective flux” has been defined as the balance
12 between O₃ flux and detoxification processes ([Heath et al., 2009](#); [Musselman and](#)
13 [Massman, 1999](#); [Grunhage and Haenel, 1997](#); [Dammgen et al., 1993](#)). The
14 time-integrated “effective flux” is termed “effective dose.” The uptake mechanisms and
15 the resistances in this process, including stomatal conductance and biochemical defense
16 mechanisms, are discussed below. The flux-based index is the goal for the “Level II”
17 critical level for assessment of O₃ risk to vegetation and ecosystems across Europe
18 ([Ashmore et al., 2004a](#)).

19 An important consideration in both O₃ exposure and uptake is how the O₃ concentration
20 at the top of low vegetation such as, crops and tree seedlings may be lower than the
21 height at which the measurement is taken. Ambient monitor inlets in the U.S. are
22 typically at heights of 3 to 5 meters. During daytime hours, the vertical O₃ gradient can
23 be relatively small because turbulent mixing maintains the downward flux of O₃. For
24 example, [Horvath et al. \(1995\)](#) calculated a 7% decrease in O₃ going from a height of 4
25 meters down to 0.5 meters above the surface during unstable (or turbulent) conditions in
26 a study over low vegetation in Hungary [see Section AX3.3.2. of the 2006 O₃ AQCD
27 ([U.S. EPA, 2006b](#))]. There have been several studies indicating decreased O₃
28 concentrations under tree canopies ([Kolb et al., 1997](#); [Samuelson and Kelly, 1997](#); [Joss](#)
29 [and Graber, 1996](#); [Fredericksen et al., 1995](#); [Lorenzini and Nali, 1995](#); [Enders, 1992](#);
30 [Fontan et al., 1992](#); [Neufeld et al., 1992](#)). In contrast, for forests, measured data may
31 underestimate O₃ concentration at the top of the canopy. The difference between
32 measurement height and canopy height is a function of several factors, the intensity of
33 turbulent mixing in the surface layer and other meteorological factors, canopy height and
34 total deposition to the canopy. Some researchers have used deposition models to estimate
35 O₃ concentration at canopy-top height based on concentrations at measurement height
36 ([Emberson et al., 2000a](#)). However, deposition models usually require meteorological
37 data inputs that are not always available or well characterized across large geographical
38 scales.

1 Soil moisture is a critical factor in controlling O₃ uptake through its effect on plant water
2 status and stomatal conductance. In an attempt to relate uptake, soil moisture, and
3 ambient air quality to identify areas of potential risk, available O₃ monitoring data for
4 1983 to 1990 were used along with literature-based seedling exposure-response data from
5 regions within the southern Appalachian Mountains that might have experienced O₃
6 exposures sufficient to inhibit growth ([Lefohn et al., 1997](#)). In a small number of areas
7 within the region, O₃ exposures and soil moisture availability were sufficient to possibly
8 cause growth reductions in some O₃ sensitive species (e.g., black cherry). The
9 conclusions were limited, however, because of the uncertainty in interpolating O₃
10 exposures in many of the areas and because the hydrologic index used might not reflect
11 actual water stress.

12 The non-stomatal component of plant defenses are the most difficult to quantify, but
13 some studies are available ([Heath et al., 2009](#); [Barnes et al., 2002](#); [Plochl et al., 2000](#);
14 [Chen et al., 1998](#); [Massman and Grantz, 1995](#)). [Massman et al. \(2000\)](#) developed a
15 conceptual model of a dose-based index to determine how plant injury response to O₃
16 relates to the traditional exposure-based parameters. The index used time-varying-
17 weighted fluxes to account for the fact that flux was not necessarily correlated with plant
18 injury or damage. The model applied only to plant foliar injury and suggested that
19 application of flux-based models for determining plant damage (yield or biomass) would
20 require a better understanding and quantification of the relationship between injury and
21 damage.

9.5.5 Summary

22 Exposure indices are metrics that quantify exposure as it relates to measured plant
23 damage (i.e., reduced growth). They are summary measures of monitored ambient O₃
24 concentrations over time intended to provide a consistent metric for reviewing and
25 comparing exposure-response effects obtained from various studies. No recent
26 information is available since 2006 that alters the basic conclusions put forth in the 2006
27 and 1996 O₃ AQCDs. These AQCDs focused on the research used to develop various
28 exposure indices to help quantify effects on growth and yield in crops, perennials, and
29 trees (primarily seedlings). The performance of indices was compared through regression
30 analyses of earlier studies designed to support the estimation of predictive O₃ exposure-
31 response models for growth and/or yield of crops and tree (seedling) species.

32 Another approach for improving risk assessment of vegetation response to ambient O₃ is
33 based on determining the O₃ concentration from the atmosphere that enters the leaf
34 (i.e., flux or deposition). Interest has been increasing in recent years, particularly in

1 Europe, in using mathematically tractable flux models for O₃ assessments at the regional,
2 national, and European scale ([Matyssek et al., 2008](#); [Paoletti and Manning, 2007](#); [ICP](#)
3 [M&M, 2004](#); [Emberson et al., 2000b](#); [Emberson et al., 2000a](#)). While some efforts have
4 been made in the U.S. to calculate O₃ flux into leaves and canopies ([Turnipseed et al.,](#)
5 [2009](#); [Uddling et al., 2009](#); [Bergweiler et al., 2008](#); [Hogg et al., 2007](#); [Grulke et al., 2004](#);
6 [Grantz et al., 1997](#); [Grantz et al., 1995](#)), little information has been published relating
7 these fluxes to effects on vegetation. There is also concern that not all O₃ stomatal uptake
8 results in a yield reduction, which depends to some degree on the amount of internal
9 detoxification occurring with each particular species. Those species having high amounts
10 of detoxification potential may, in fact, show little relationship between O₃ stomatal
11 uptake and plant response ([Musselman and Massman, 1999](#)). The lack of data in the U.S.
12 and the lack of understanding of detoxification processes have made this technique less
13 viable for vulnerability and risk assessments in the U.S.

14 The main conclusions from the 1996 and 2006 O₃ AQCDs regarding indices based on
15 ambient exposure are still valid. These key conclusions can be restated as follows:

- 16 ▪ O₃ effects in plants are cumulative;
- 17 ▪ higher O₃ concentrations appear to be more important than lower
18 concentrations in eliciting a response;
- 19 ▪ plant sensitivity to O₃ varies with time of day and plant development stage;
20 and
- 21 ▪ quantifying exposure with indices that accumulate the O₃ hourly
22 concentrations and preferentially weight the higher concentrations improves
23 the explanatory power of exposure/response models for growth and yield, over
24 using indices based on mean and peak exposure values.

25 Various weighting functions have been used, including threshold-weighted
26 (e.g., SUM06) and continuous sigmoid-weighted (e.g., W126) functions. Based on
27 statistical goodness-of-fit tests, these cumulative, concentration-weighted indices could
28 not be differentiated from one another using data from previous exposure studies.
29 Additional statistical forms for O₃ exposure indices have been discussed in [Lee et al.](#)
30 [\(1988b\)](#). The majority of studies published since the 2006 O₃ AQCD do not change
31 earlier conclusions, including the importance of peak concentrations, and the duration
32 and occurrence of O₃ exposures in altering plant growth and yield.

33 Given the current state of knowledge and the best available data, exposure indices that
34 cumulate and differentially weight the higher hourly average concentrations and also
35 include the “mid-level” values continue to offer the most defensible approach for use in

1 developing response functions and comparing studies, as well as for defining future
2 indices for vegetation protection.

9.6 Ozone Exposure-Plant Response Relationships

9.6.1 Introduction

3 The adequate characterization of the effects of O₃ on plants for the purpose of setting air
4 quality standards is contingent not only on the choice of the index used (i.e., SUM06,
5 W126) to summarize O₃ concentrations (Section 9.5), but also on quantifying the
6 response of the plant variables of interest at specific values of the selected index. The
7 many factors that determine the response of plants to O₃ exposure have been discussed in
8 previous sections. They include species, genotype and other genetic characteristics
9 (Section 9.3), biochemical and physiological status (Section 9.3), previous and current
10 exposure to other stressors (Section 9.4.8), and characteristics of the exposure itself
11 (Section 9.5). Establishing a secondary air quality standard entails the capability to
12 generalize those observations, in order to obtain predictions that are reliable enough
13 under a broad variety of conditions, taking into account these factors. This section
14 reviews results that have related specific quantitative observations of O₃ exposure with
15 quantitative observations of plant responses, and the predictions of responses that have
16 been derived from those observations through empirical models.

17 For four decades, exposure to O₃ at ambient concentrations found in many areas of the
18 U.S. has been known to cause detrimental effects in plants (U.S. EPA, 2006b, 1996b,
19 1984, 1978a). Results published after the 2006 O₃ AQCD continue to support this
20 finding, and the following sections deal with the quantitative characterizations of the
21 relationship, and what new insights may have appeared since 2006. Detrimental effects
22 on plants include visible injury, decreases in the rate of photosynthesis, reduced growth,
23 and reduced yield of marketable plant parts. Most published exposure-response data have
24 reported O₃ effects on the yield of crops and the growth of tree seedlings, and those two
25 variables have been the focus of the characterization of ecological impacts of O₃ for the
26 purpose of setting secondary air quality standards. In order to support quantitative
27 modeling of exposure-response relationships, data should preferably include more than
28 three levels of exposure, and some control of potential confounding or interacting factors
29 should be present in order to model the relationship with sufficient accuracy. Letting
30 potential confounders, such as other stressors, vary freely when generating O₃ exposure-
31 response data might improve the ‘realism’ of the data, but it also greatly increases the
32 amount of data necessary to extract a clear quantitative description of the relationship.

1 Conversely however, experimental settings should not be so exhaustively restrictive as to
2 make generalization outside of them problematic. During the last four decades, many of
3 the studies of the effects of O₃ on growth and yield of plants have not included enough
4 levels of O₃ to parameterize more than the simplest linear model. The majority of these
5 studies have only contrasted two levels, ambient and elevated, or sometimes three by
6 adding carbon filtration in OTC studies, with little or no consideration of quantitatively
7 relating specific values of exposure to specific values of growth or yield. This is not to
8 say that studies that did not include more than two or three levels of O₃ exposure, or
9 studies that were conducted in uncontrolled environments, do not provide exposure-
10 response information that is highly relevant to reviewing air quality standards. In fact,
11 they can be essential in verifying the agreement between predictions obtained through the
12 empirical models derived from experiments such as NCLAN, and observations. The
13 consensus of model predictions and observations from a variety of studies conducted in
14 other locations, at other times, and using different exposure methods, greatly increases
15 confidence in the reliability of both. Furthermore, if they are considered in the aggregate,
16 studies with few levels of exposure or high unaccounted variability can provide
17 additional independent estimates of decrements in plant growth and yield, at least within
18 a few broad categories of exposure.

19 Extensive exposure-response information on a wide variety of plant species has been
20 produced by two long-term projects that were designed with the explicit aim of obtaining
21 quantitative characterizations of the response of such an assortment of crop plants and
22 tree seedlings to O₃ under North American conditions: the NCLAN project for crops, and
23 the EPA National Health and Environmental Effects Research Laboratory, Western
24 Ecology Division tree seedling project (NHEERL/WED). The NCLAN project was
25 initiated by the EPA in 1980 primarily to improve estimates of yield loss under field
26 conditions and to estimate the magnitude of crop losses caused by O₃ throughout the U.S.
27 ([Heck et al., 1991](#); [1982](#)). The cultural conditions used in the NCLAN studies
28 approximated typical agronomic practices, and the primary objectives were: (1) to define
29 relationships between yields of major agricultural crops and O₃ exposure as required to
30 provide data necessary for economic assessments and development of O₃ NAAQS; (2) to
31 assess the national economic consequences resulting from O₃ exposure of major
32 agricultural crops; and (3) to advance understanding of cause-and-effect relationships that
33 determine crop responses to pollutant exposures.

34 NCLAN experiments yielded 54 exposure-response curves for 12 crop species, some of
35 which were represented by multiple cultivars at several of 6 locations throughout the U.S.
36 The NHEERL/WED project was initiated by EPA in 1988 with similar objectives for tree
37 species, and yielded 49 exposure-responses curves for multiple genotypes of 11 tree
38 species grown for up to three years in Oregon, Michigan, and the Great Smoky

1 Mountains National Park. Both projects used OTCs to expose plants to three to five
2 levels of O₃. Eight of the 54 crop datasets were from plants grown under a combination
3 of O₃ exposure and experimental drought conditions. [Figure 9-14](#) through [Figure 9-17](#)
4 summarize some of the NCLAN and NHEERL/WED results.

5 It should be noted that data from FACE experiments might also be used for modeling
6 exposure-response. They only use two levels of O₃ (ambient concentration at the site and
7 a multiple of it), but given that the value of both levels of exposure changes every year,
8 and that they are typically run for many consecutive years, aggregating data over time
9 produces twice as many levels of O₃ as there are years. As described in Section [9.2.4](#),
10 FACE experiments seek to impose fewer constraints on the growth environment than
11 OTCs. As a consequence, FACE studies have to contend with larger variability,
12 especially year-to-year variability, but the difference in experimental conditions between
13 the two methodologies makes comparisons between their results especially useful.

14 Growth and yield of at least one crop (soybean) has been investigated in yearly
15 experiments since 2001 at a FACE facility in Illinois ([UIUC, 2010](#); [Morgan et al., 2006](#)).
16 However, almost all analyses of SoyFACE published so far have been based on subsets
17 of one or two years, and have only contrasted ambient versus elevated O₃ as categorical
18 variables. They have not modeled the response of growth and yield to O₃ exposure
19 continuously over the range of exposure values that have occurred over time. The only
20 exception is a study by [Betzelberger et al. \(2010\)](#), who used a linear regression model on
21 data pooled over 2 years. Likewise, trees of three species (trembling aspen, paper birch,
22 and sugar maple) were grown between 1998 and 2009 in a FACE experiment located in
23 Rhinelander, Wisconsin ([Pregitzer et al., 2008](#); [Dickson et al., 2000](#)). The Aspen FACE
24 experiment has provided extensive data on responses of trees beyond the seedling stage
25 under long-term exposure, and also on ecosystem-level responses (Section [9.4](#)), but the
26 only attempt to use those data in a continuous model of the response of tree growth to O₃
27 exposure ([Percy et al., 2007](#)) suffered from severe methodological problems, some of
28 which are discussed in Section [9.6.3](#). Finally, one experiment was able to exploit a
29 naturally occurring gradient of O₃ concentrations to fit a linear regression model to the
30 growth of cottonwood ([Gregg et al., 2006, 2003](#)). Factors such as genotype, soil type and
31 soil moisture were under experimental control, and the authors were able to partition out
32 the effects of potential confounders such as temperature, atmospheric N deposition, and
33 ambient CO₂.

34 A serious difficulty in assessing results of exposure-response research is the multiplicity
35 of O₃ metrics that have been used in reporting. As described in Section [9.5](#), metrics that
36 entail either weighting or thresholding of hourly values cannot be algebraically converted
37 into one another, or into unweighted metrics such as hourly average. When computing O₃

1 exposure using weighted or thresholded metrics, each metric has to be computed
2 separately from the original hourly data. Comparisons of exposure-response models can
3 only be made between studies that used the same metric, and the value of exposure at
4 which a given plant response is expected using one metric of exposure cannot be exactly
5 converted to another metric. Determining the exposure value at which an effect would be
6 observed in a different metric can only be accomplished by first computing the
7 experimental exposures in this metric from the hourly data, then estimating (fitting)
8 model coefficients again. This problem is irremediable, although useful comparisons
9 might be made using categorical exposures such as ‘current ambient exposure’ or ‘2050
10 projected exposure’, which can serve as a common reference for quantitative values
11 expressed in various metrics. Studies that contained growth or yield exposure-response
12 data at few levels of exposure, and/or using metrics other than W126 are summarized in
13 [Table 9-18](#) and [Table 9-19](#).

9.6.2 Estimates of Crop Yield Loss and Tree Seedling Biomass Loss in the 1996 and 2006 Ozone AQCDs

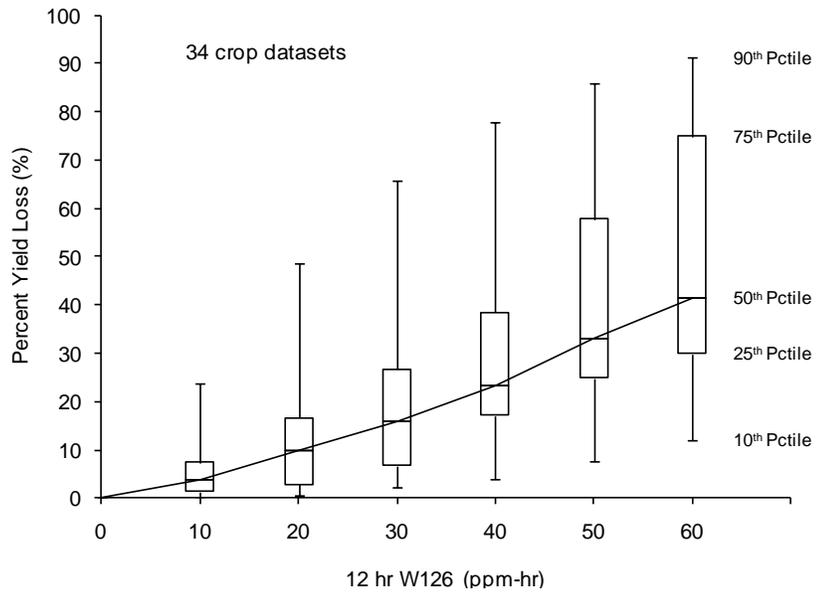
14 The 1996 and 2006 O₃ AQCDs relied extensively on analyses of NCLAN and
15 NHEERL/WED by [Lee et al. \(1994\)](#); ([1989](#), [1988b](#), [1987](#)), [Hogsett et al. \(1997\)](#), [Lee and](#)
16 [Hogsett \(1999\)](#), [Heck et al. \(1984\)](#), ([Rawlings and Cure, 1985](#)), ([Lesser et al., 1990](#)), and
17 ([Gumpertz and Rawlings, 1992](#)). Those analyses concluded that a three-parameter
18 Weibull model –

$$Y = \alpha e^{-\left(\frac{W126}{\eta}\right)^\beta}$$

Equation 9-2

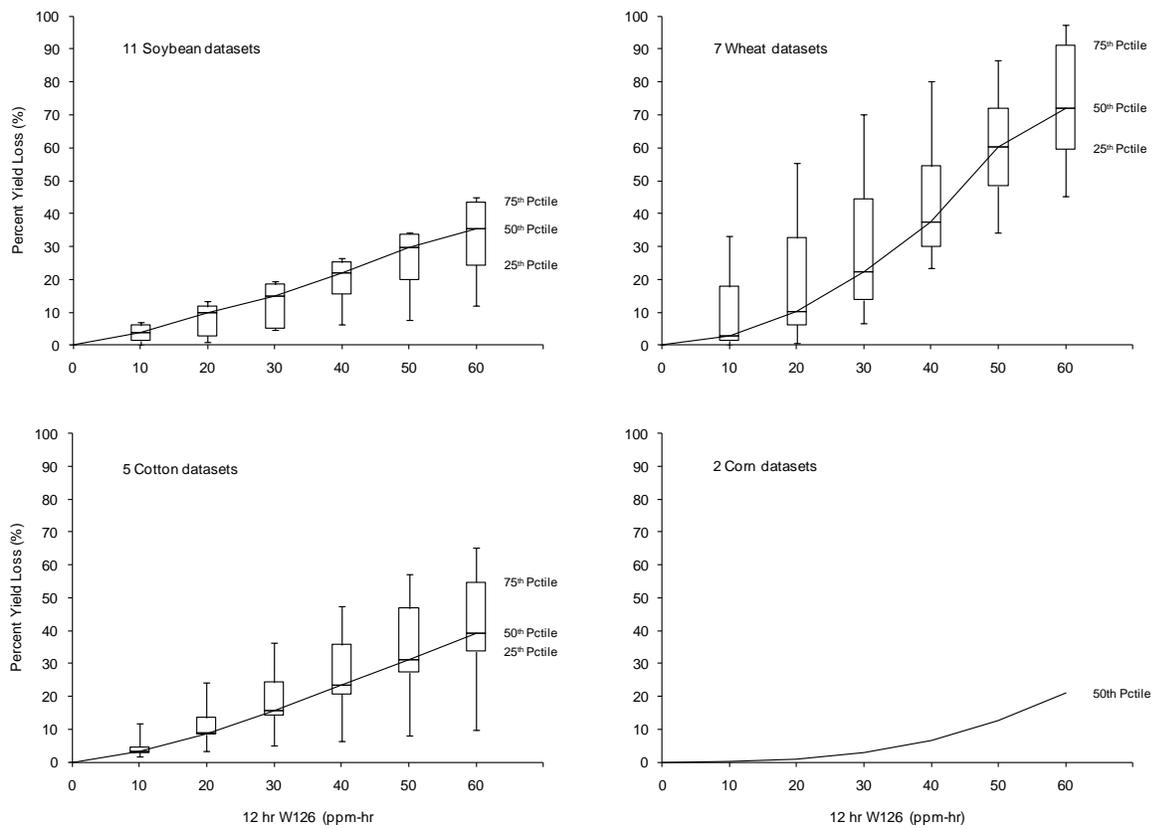
19 is the most appropriate model for the response of absolute yield and growth to O₃
20 exposure, because of the interpretability of its parameters, its flexibility (given the small
21 number of parameters), and its tractability for estimation. In addition, removing the
22 intercept α results in a model of relative yield (yield relative to [yield at exposure=0])
23 without any further reparameterization. Formulating the model in terms of relative yield
24 or relative yield loss (yield loss=[1 – relative yield]) is essential in comparing exposure-
25 response across species, genotypes, or experiments for which absolute values of the
26 response may vary greatly. In the 1996 and 2006 O₃ AQCDs, the two-parameter model of
27 relative yield was used in deriving common models for multiple species, multiple
28 genotypes within species, and multiple locations.

1 Given the disparate species, genotypes, and locations that were included in the NCLAN
2 and NHEERL/WED projects, and in the absence of plausible distributional assumptions
3 with respect to those variables, a three step process using robust methods was used to
4 obtain parameter estimates that could be generalized. The models that were derived for
5 each species or group of species were referred to as median composite functions. In the
6 first step, the three parameters of the Weibull model were computed for absolute yield or
7 biomass data from each NCLAN and NHEERL/WED experiment (54 crop datasets and
8 49 tree seedling datasets), using nonlinear regression. When data were only available for
9 three levels of exposure because of experimental problems, the shape parameter β was
10 constrained to 1, reducing the model to an exponential decay model. In the second step, α
11 was dropped, and predicted values of relative yield or biomass were then computed for
12 12-hour W126 exposures between 0 and 60 ppm-h. At each of these W126 exposure
13 values, the 25th, 50th, and 75th percentiles of the response were identified among the
14 predicted curves of relative response. For example, for the 34 NCLAN studies of 12 crop
15 species grown under non-droughted conditions for a complete cropping cycle
16 ([Figure 9-14](#)), the 3 quartiles of the response were identified at every integer value of
17 W126 between 0 and 60. The third step fitted a two-parameter Weibull model to those
18 percentiles, yielding the median composite function for the relative yield or biomass
19 response to O₃ exposure for each grouping of interest (e.g., all crops, all trees, all datasets
20 for one species), as well as composite functions for the other quartiles. In the 1996 and
21 2006 O₃ AQCDs this modeling of crop yield loss and tree seedling biomass loss was
22 conducted using the SUM06 metric for exposure. This section updates those results by
23 using the 12-hour W126 as proposed in 2007 (72 FR 37818) and 2010 (75 FR 2938, page
24 3003). [Figure 9-14](#) through [Figure 9-17](#) present quantiles of predicted relative yield or
25 biomass loss at seven values of the 12-h W126 for some representative groupings of
26 NCLAN and NHEERL/WED results. [Table 9-9](#) through [Table 9-11](#) give the 90-day 12-h
27 W126 O₃ exposure values at which 10 and 20% yield or biomass losses are predicted in
28 50 and 75% of crop or tree species using the composite functions.



Note: Quantiles of the predicted relative yield loss at 7 values of 12-hour W126 for 34 Weibull curves estimated using nonlinear regression on data from 34 studies of 12 crop species grown under well-watered conditions for the full duration of 1 cropping cycle. Source of Weibull parameters: [Lee and Hogsett \(1996\)](#).

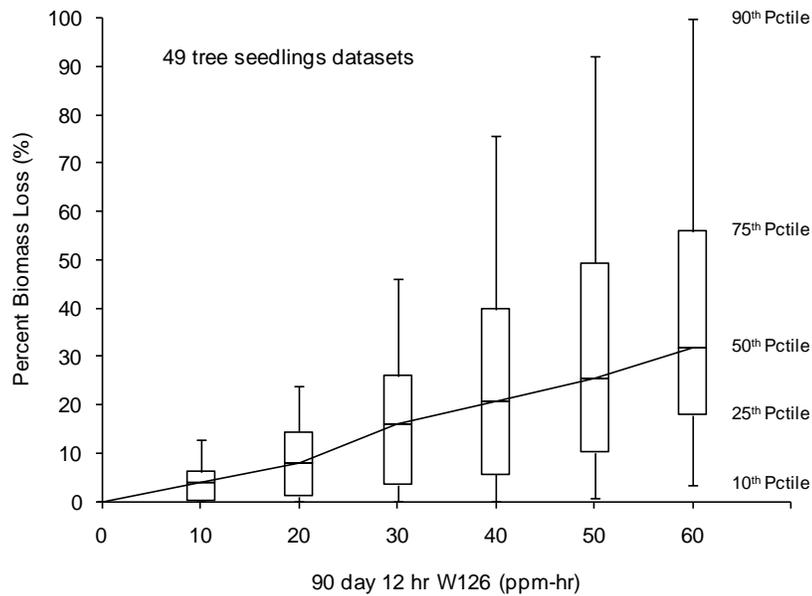
Figure 9-14 Quantiles of predicted relative yield loss for 34 NCLAN crop experiments.



Notes: Quantiles of the predicted relative yield loss at 7 values of 12-h W126 for Weibull curves estimated using nonlinear regression for 4 species grown under well-watered conditions for the full duration of 1 cropping cycle. The number of studies available for each species is indicated on each plot.

Source of Weibull parameters: [Lee and Hogsett \(1996\)](#).

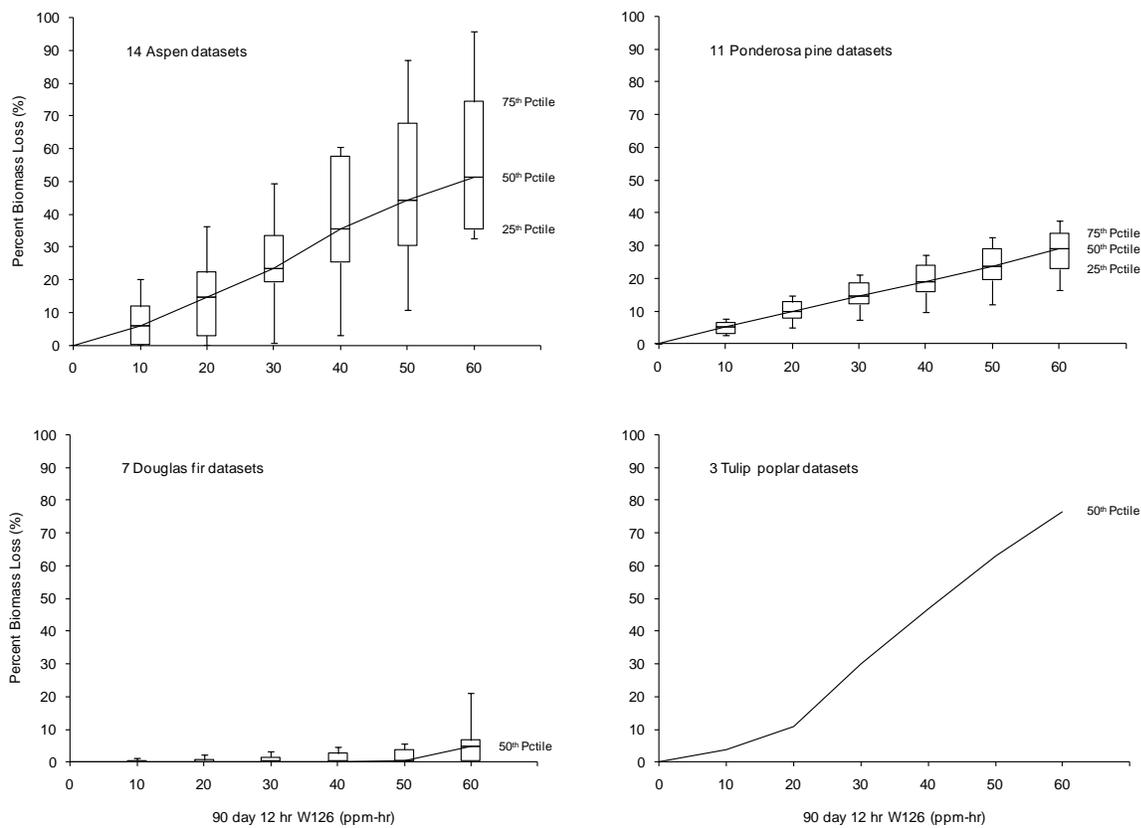
Figure 9-15 Quantiles of predicted relative yield loss for 4 crop species in NCLAN experiments.



Note: Quantiles of the predicted relative above-ground biomass loss at 7 values of 12-h W126 for 49 Weibull curves estimated using nonlinear regression on data from 49 studies of 11 tree species grown under well-watered conditions for 1 or 2 years. Curves were standardized to 90-day W126.

Source of Weibull parameters: [Lee and Hogsett \(1996\)](#).

Figure 9-16 Quantiles of predicted relative biomass loss for 49 tree species in NHEERL/WED experiments.



Note: Quantiles of the predicted relative above-ground biomass loss at 7 exposure values of 12-h W126 for Weibull curves estimated using nonlinear regression on data for 4 tree species grown under well-watered conditions for 1 or 2 year. Curves were standardized to 90-day W126. The number of studies available for each species is indicated on each plot.

Source of Weibull parameters: [Lee and Hogsett \(1996\)](#).

Figure 9-17 Quantiles of predicted relative biomass loss for 4 tree species in NHEERL/WED experiments.

Table 9-9 Ozone exposures at which 10 and 20% yield loss is predicted for 50 and 75% of crop species.

| Predicted Yield Loss for Crop Species ^a | 90-day 12-h W126 for 10% yield loss (ppm-h) | 90-day 12-h W126 for 20% yield loss (ppm-h) |
|--|---|---|
| Model for the 50th Percentile of 34 curves | | |
| Relative yield= $\exp(-(W126/104.82)^{1.424})$ | 22 | 37 |
| Model for the 75th Percentile of 34 curves | | |
| Relative yield= $\exp(-(W126/78.12)^{1.415})$ | 16 | 27 |

^aBased on composite functions for the 50th and 75th percentiles of 34 Weibull curves for relative yield loss data from 34 non-droughted NCLAN studies of 12 crop species; curves were standardized to 90-day W126.

Source of parameters for the 34 curves: [Lee and Hogsett \(1996\)](#).

Table 9-10 Ozone exposures at which 10 and 20% yield loss is predicted for 50 and 75% of crop species (Droughted versus Watered conditions).

| Predicted Yield Loss for Crop Species ^a | 90 day 12-h W126 for 10% yield loss (ppm-h) | 90 day 12-h W126 for 20% yield loss (ppm-h) |
|---|---|---|
| Model for the 50th Percentile of 2x8 curves | | |
| Watered Relative yield= $\exp(-(W126/132.86)^{1.170})$ | 19 | 37 |
| Droughted Relative yield= $\exp(-(W126/179.84)^{1.713})$ | 48 | 75 |
| Model for the 75th Percentile of 2x8 curves | | |
| Watered Relative yield= $\exp(-(W126/90.43)^{1.310})$ | 16 | 29 |
| Droughted Relative yield= $\exp(-(W126/105.16)^{1.833})$ | 31 | 46 |

^aUnder drought conditions and adequate moisture based on composite functions for the 50th and 75th percentiles of 16 Weibull curves for relative yield loss data from 8 NCLAN studies that paired droughted and watered conditions for the same genotype; curves were standardized to 90-day W126.

Source of parameters for the 16 curves: [Lee and Hogsett \(1996\)](#).

Table 9-11 Ozone exposures at which 10 and 20% biomass loss is predicted for 50 and 75% of tree species.

| Predicted Biomass Loss for Tree Species ^a | 90 day 12 h W126 for 10% yield loss (ppm-h) | 90 day 12 h W126 for 20% yield loss (ppm-h) |
|--|---|---|
| Model for the 50th Percentile of 49 curves | | |
| Relative yield= $\exp(-(W126/131.57)**1.242)$ | 21 | 39 |
| Model for the 75th Percentile of 49 curves | | |
| Relative yield= $\exp(-(W126/65.49)**1.500)$ | 15 | 24 |

^aBased on composite functions for the 50th and 75th percentiles of 49 Weibull curves for relative above-ground biomass loss data from 49 studies of 11 tree species grown under well-watered conditions for 1 or 2 year; curves were standardized to 90-day W126. Source of parameters for the 49 curves: [Lee and Hogsett \(1996\)](#).

9.6.3 Validation of 1996 and 2006 Ozone AQCD Models and Methodology Using the 90 day 12-h W126 and Current FACE Data

1 Since the completion of the NCLAN and NHEERL/WED projects, almost no studies
 2 have been published that could provide a basis for estimates of exposure-response that
 3 can be compared to those of the 1996 and 2006 O₃ AQCDs. Most experiments, regardless
 4 of exposure methodology, include only two levels of exposure. In addition, very few
 5 studies have included measurements of exposure using the W126 metric, or the hourly O₃
 6 concentration data that would allow computing exposure using the W126. Two FACE
 7 projects, however, were conducted over multiple years, and by adding to the number of
 8 exposure levels over time, can support independent model estimation and prediction
 9 using the same model and the same robust process as summarized in Section [9.6.2](#).
 10 Hourly O₃ data were available from both FACE projects.

11 The SoyFACE project is situated near Champaign, IL, and comprises 32 octagonal rings
 12 (20m-diameter), 4 of which in a given year are exposed to ambient conditions, and 4 of
 13 which are exposed to elevated O₃ as a fixed proportion of the instantaneous ambient
 14 concentration ([Betzberger et al., 2010](#); [UIUC, 2010](#); [Morgan et al., 2006](#); [Morgan et al., 2004](#)).
 15 Since 2002, yield data have been collected for up to 8 genotypes of soybean
 16 grown in subplots within each ring. The Aspen FACE project is situated in Rhinelander,
 17 WI, and comprises 12 rings (30m-diameter), 3 of which are exposed to ambient
 18 conditions, and 3 of which are exposed to O₃ as a fixed proportion of the instantaneous
 19 ambient concentration ([Pregitzer et al., 2008](#); [Karnosky et al., 2005](#); [Dickson et al., 2000](#)).
 20 In the summer of 1997, half the area of each ring was planted with small (five to
 21 seven leaf sized) clonally propagated plants of five genotypes of trembling aspen, which
 22 were left to grow in those environments until 2009. Biomass data are currently available

1 for the years 1997-2005 ([King et al., 2005](#)). Ozone exposure in these two FACE projects
2 can be viewed as a categorical variable with two levels: ambient, and elevated. However,
3 this overlooks the facts that not only do both ambient and elevated exposure vary from
4 year to year, but the proportionality between them also changes yearly. This change has
5 two sources: first, the dispensing of O₃ into the elevated exposure rings varies from the
6 set point for the ambient/elevated proportionality to some extent, and for SoyFACE, the
7 set point changed between years. Second, when using threshold or concentration-
8 weighted cumulative metrics (such as AOT40, SUM06 or W126), the proportionality
9 does not propagate regularly from the hourly data to the yearly value. For example,
10 hourly average elevated exposures that are a constant 1.5 times greater than ambient do
11 not result in AOT40, SUM06 or W126 values that are some constant multiple of the
12 ambient values of those indices. Depending on the fraction of hourly values that are
13 above the threshold or heavily weighted, the same average yearly exposure will result in
14 different exposure values when using thresholded or weighted metrics. In some years,
15 elevated exposures in FACE experiments experience many more values above the
16 threshold, or more heavily weighted than the ambient exposures; thus in those years, the
17 distance between ambient and elevated exposure values increases relative to other years.
18 As a consequence, the number of exposure levels in multi-year experiments is twice the
19 number of years. In the case of SoyFACE for the period between 2002 and 2008, ambient
20 exposure in the highest year was approximately equal to elevated exposure in the lowest
21 year, with 14 levels of O₃ exposure evenly distributed from lowest to highest. The
22 particular conditions of the Aspen FACE experiment resulted in 12 exposure levels
23 between 1998 and 2003, but they were not as evenly distributed between minimum and
24 maximum over the 6-year period.

25 There are necessary differences in the modeling of exposure-response in annual plants
26 such as soybean, and in perennial plants such as aspen trees, when exposure takes place
27 over multiple years. In annual plants, responses recorded at the end of the life cycle,
28 i.e., yearly, are analyzed in relationship to that year's exposure. Yield of soybeans is
29 affected by exposure during the year the crop was growing, and a new crop is planted
30 every year. Thus an exposure-response relationship can be modeled from yearly
31 responses matched to yearly exposures, with those exposure-response data points having
32 been generated in separate years. For perennial organisms, which are not harvested yearly
33 and continue to grow from year to year, such pairing of exposure and response cannot be
34 done without accounting for time. Not only does the size of the organism at the beginning
35 of each year of exposure increase, but size is also dependent on the exposure from
36 previous years. Therefore the relationship of response and exposure must be analyzed
37 either one year at a time, or by standardizing the response as a yearly increment relative
38 to size at the beginning of each year. Furthermore, the relevant measurement of exposure
39 is cumulative, or cumulative yearly average exposure, starting in the year exposure was

1 initiated, up to the end of the year of interest. When analyzing the growth of trees over
2 several years, it would be evidently incorrect to pair the exposure level in every discrete
3 year with absolute size of the trees that year, and posit a direct relationship between them,
4 without taking increasing age into consideration. In the Aspen FACE experiment, for
5 example, one could not establish an exposure-response relationship by matching
6 12 yearly exposures and 12 yearly tree sizes, while disregarding age as if size did not also
7 depend on it. This is the basis of the 2007 study of Aspen FACE data by [Percy et al.](#)
8 ([2007](#)), which compares the size of trees of various ages as if they were all the same age,
9 and was therefore not informative.

9.6.3.1 Comparison of NCLAN-Based Prediction and SoyFACE Data

10 For this ISA, EPA conducted a comparison between yield of soybean as predicted by the
11 composite function three-step process (Section [9.6.2](#)) using NCLAN data, and
12 observations of yield in SoyFACE. The median composite function for relative yield was
13 derived for the 11 NCLAN soybean Weibull functions for non-droughted studies, and
14 comparisons between the predictions of the median composite and SoyFACE
15 observations were conducted as follows.

16 For the years 2007 and 2008, SoyFACE yield data were available for 7 and 6 genotypes,
17 respectively. The EPA used those data to compare the relative change in yield observed
18 in SoyFACE in a given year between ambient O₃ and elevated O₃, versus the relative
19 change in yield predicted by the NCLAN-based median composite function between
20 those same two values of O₃ exposure. The two parameter median composite function for
21 relative yield of soybean based on NCLAN data was used to predict yield response at the
22 two values of exposure observed in SoyFACE in each year, and the change between yield
23 under ambient and elevated was compared to the change observed in SoyFACE for the
24 relevant year ([Table 9-12](#)). This approach results in a direct comparison of predicted
25 versus observed change in yield. Because the value of relative response between any two
26 values of O₃ exposure is independent of the intercept α , this comparison does not require
27 prediction of the absolute values of the responses.

28 Since comparisons of absolute values might be of interest, the predictive functions were
29 also scaled to the observed data: SoyFACE data were used to compute an intercept α
30 while the shape and scale parameters (β and η) were held at their value in the NCLAN
31 predictive model. This method gives a comparison of prediction and observation that
32 takes all the observed information into account to provide the best possible estimate of
33 the intercept, and thus the best possible scaling (

1 Table 9-13 and [Figure 9-18](#)). For the comparison of NCLAN and SoyFACE, this
 2 validation was possible for 2007 and 2008, where data for 7 and 6 soybean genotypes,
 3 respectively, were available. The median composite function for relative yield was
 4 derived for the 11 NCLAN soybean Weibull functions for nondroughted studies, and the
 5 values of median yield under ambient exposure at SoyFACE in 2007 and 2008 were used
 6 to obtain an estimate of the intercept α for the NCLAN median function in each of the
 7 two years. [Table 9-12](#) presents the results of ambient/elevated relative yield comparisons
 8 between the NCLAN-derived predictions and SoyFACE observations.

9 Table 9-13 and [Figure 9-18](#) present the results of comparisons between NCLAN-derived
 10 predictions and SoyFACE observations of yield, with the predictive function scaled to
 11 provide absolute yield values.

Table 9-12 Comparison between change in yield observed in the SoyFACE experiment between elevated and ambient ozone, and change predicted at the same values of ozone by the median composite function for NCLAN.

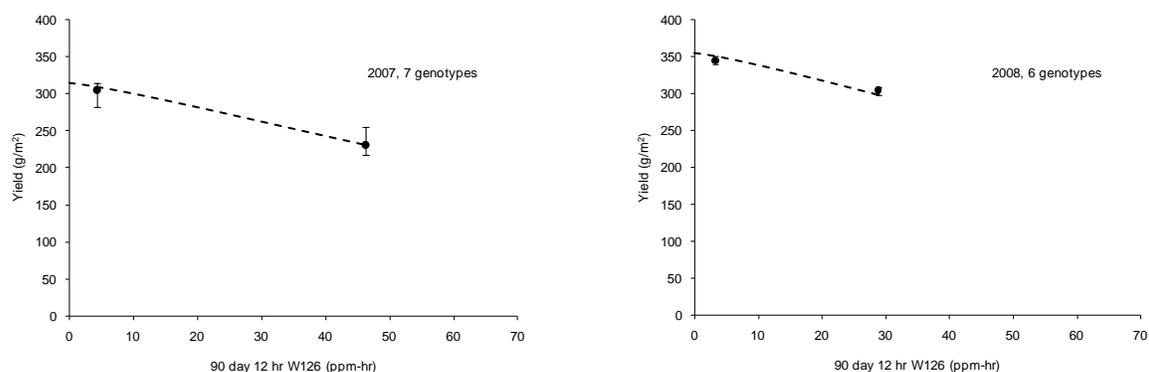
| Year | 90-day 12-h W126 (ppm-h) observed at SoyFACE | | Yield in Elevated O ₃ Relative to Ambient O ₃ (%) | |
|------|--|----------|---|---------------------|
| | Ambient | Elevated | Predicted by NCLAN ^a | Observed at SoyFACE |
| 2007 | 4.39 | 46.23 | 75 | 76 |
| 2008 | 3.23 | 28.79 | 85 | 88 |

^aTwo-parameter relative yield model.

Table 9-13 Comparison between yield observed in the SoyFACE experiment and yield predicted at the same values of ozone by the median composite function for NCLAN.

| Year | 90-day 12-h W126 (ppm-h) observed at SoyFACE | | Yield predicted by NCLAN ^a (g/m ²) | | Yield observed at SoyFACE (g/m ²) | |
|------|--|----------|---|----------|---|----------|
| | Ambient | Elevated | Ambient | Elevated | Ambient | Elevated |
| 2007 | 4.39 | 46.23 | 309.2 | 230.6 | 305.2 | 230.6 |
| 2008 | 3.23 | 28.79 | 350.3 | 298.2 | 344.8 | 304.4 |

^aThree-parameter absolute yield model with intercept scaled to SoyFACE data.

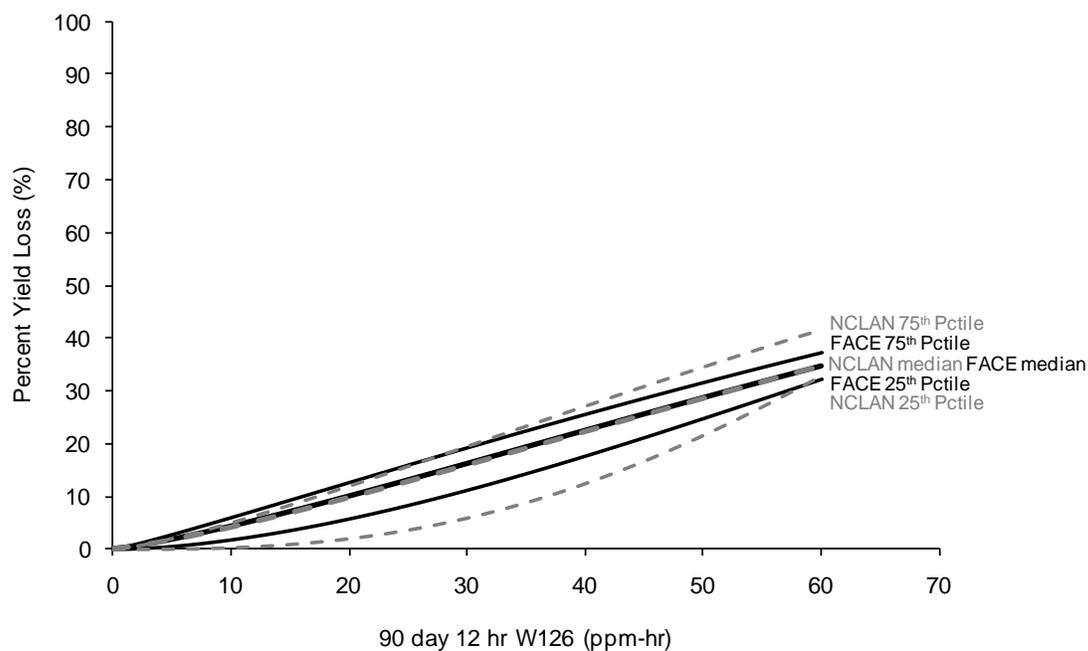


Note: Black dots are the median of 7 or 6 soybean genotypes in SoyFACE (2007, 2008); bars are Inter-Quartile Range for genotypes; dashed line is median composite model for 11 studies in NCLAN.

Source of data: [Betzelberger et al. \(2010\)](#); [Morgan et al. \(2006\)](#); [Lee and Hogsett \(1996\)](#).

Figure 9-18 Comparison of yield observed in SoyFACE experiment in a given year with yield predicted by the median composite function based on NCLAN.

1 Finally, a composite function for the 25th, 50th, and 75th percentiles was developed from
 2 SoyFACE annual yield data, and compared to the NCLAN-based function. The process
 3 described in Section [9.6.2](#) was applied to SoyFACE data for individual genotypes,
 4 aggregated over the years during which each was grown; one genotype from 2003 to
 5 2007, and six genotypes in 2007 and 2008. First, the three parameter Weibull model
 6 described in Section [9.6.2](#) was estimated using nonlinear regression on exposure-yield
 7 data for each genotype separately, over the years for which data were available, totaling
 8 seven curves. The 25th, 50th, and 75th percentiles of the predicted values for the two
 9 parameter relative yield curves were then identified at every integer of W126 between 0
 10 and 60, and a two-parameter Weibull model estimated by regression for the three
 11 quartiles. The comparison between these composite functions for the quartiles of relative
 12 yield loss in SoyFACE and the corresponding composite functions for NCLAN is
 13 presented in [Figure 9-19](#).



Source of data: [Betzelberger et al. \(2010\)](#); [Morgan et al. \(2006\)](#); [Lee and Hogsett \(1996\)](#).

Figure 9-19 Comparison of composite functions for the quartiles of 7 curves for 7 genotypes of soybean grown in the SoyFACE experiment, and for the quartiles of 11 curves for 5 genotypes of soybean grown in the NCLAN project.

1 As seen in
 2 Table 9-13 and [Table 9-14](#), and in [Table 9-18](#), the agreement between predictions based
 3 on NCLAN data and SoyFACE observations was notably close in single-year
 4 comparisons. Together with the very high agreement between median composite models
 5 for NCLAN and SoyFACE ([Figure 9-19](#)), it provides very strong mutual confirmation of
 6 those two projects' results with respect to the response of yield of soybeans to O₃
 7 exposure. It is readily apparent from these results that the methodology described in
 8 Section [9.6.2](#) for obtaining predictions of yield or yield loss from NCLAN data is
 9 strongly validated by SoyFACE results. As described in Section [9.2](#), the exposure
 10 technologies used in the two projects were in sharp contrast, specifically with respect to
 11 the balance each achieved between control of potential interacting factors or confounders,
 12 and fidelity to natural conditions. The comparisons that EPA conducted therefore
 13 demonstrate that the methodology used in developing the composite functions is resistant
 14 to the influence of nuisance variables and that predictions are reliable. They may also

1 suggest that the aspects in which the two exposure technologies differ have less influence
2 on exposure-response than initially supposed. These results are also in agreement with
3 comparative studies reviewed in Section [9.2.6](#).

9.6.3.2 Comparison of NHEERL/WED-Based Prediction of Tree Biomass Response and Aspen FACE Data

4 EPA also conducted two comparisons between prediction of above-ground biomass loss
5 based on NHEERL/WED results and observations from Aspen FACE. The median
6 composite function was developed from NHEERL/WED data for 11 studies that used
7 wild-type seedlings of aspen as well as four clonally propagated genotypes. All plants
8 were grown in OTCs for one growing season before being destructively harvested. Aspen
9 FACE data were from clonally propagated trees of five genotypes grown from 1998 to
10 2003, with above-ground biomass calculated using allometric equations derived from
11 data for trees harvested destructively in 2000 and 2002 ([King et al., 2005](#)).

12 The two parameter median composite function for relative biomass was used to predict
13 biomass response under the observed elevated exposure, relative to its value under
14 observed ambient exposure, for each separate year of Aspen FACE. EPA first compared
15 Aspen FACE observations of the change in biomass between ambient and elevated
16 exposure with the corresponding prediction at the same values of exposure. Comparisons
17 between observed and predicted absolute biomass values were then conducted for each
18 year by scaling the predictive function to yearly Aspen FACE data as described for
19 soybean data in Section [9.6.3.1](#). In all cases, yearly 90 day 12-hour W126 values for
20 Aspen FACE were computed as the cumulative average from the year of planting up to
21 the year of interest. A comparison of composite functions between NHEERL/WED and
22 Aspen FACE, similar to the one performed for NCLAN and SoyFACE, was not possible:
23 as discussed in the introduction to Section [9.6](#), the pairing of 12 exposure values from
24 separate years and 12 values of biomass cannot be the basis for a model of exposure-
25 response, because the trees continued growing for the six-year period of exposure.
26 Because the same trees were used for the entire duration, and continued to grow, data
27 could not be aggregated over years. [Table 9-14](#) presents the results of ambient/elevated
28 relative biomass comparisons between the NHEERL/WED-derived predictions and
29 Aspen FACE observations.

30 [Table 9-15](#) and [Figure 9-20](#) present the results of the comparison between
31 NHEERL/WED-derived predictions and Aspen FACE observations for absolute biomass,
32 using Aspen FACE data to scale the NHEERL/WED-derived composite function.

Table 9-14 Comparison between change in above-ground biomass elevated and ambient ozone in Aspen FACE experiment in 6 year, and change predicted at the same values of ozone by the median composite function for NHEERL/WED.

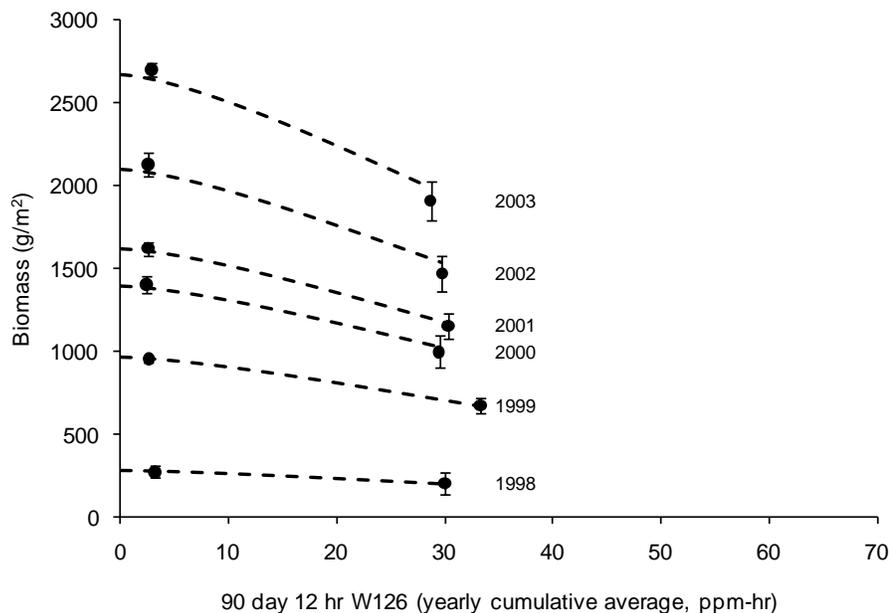
| Year | 90-day 12-h W126 (ppm-h) Cumulative Average observed at Aspen FACE | | Above-Ground Biomass in Elevated O ₃ relative To Ambient O ₃ (%) | |
|------|---|----------|---|------------------------|
| | Ambient | Elevated | Predicted by NHEERL/WED ^a | Observed at Aspen FACE |
| 1998 | 3.19 | 30.08 | 74 | 75 |
| 1999 | 2.61 | 33.85 | 70 | 70 |
| 2000 | 2.43 | 30.16 | 74 | 71 |
| 2001 | 2.55 | 31.00 | 73 | 71 |
| 2002 | 2.51 | 30.27 | 74 | 69 |
| 2003 | 2.86 | 29.12 | 75 | 71 |

^aTwo-parameter relative biomass model

Table 9-15 Comparison between above-ground biomass observed in Aspen FACE experiment in 6 year and biomass predicted by the median composite function based on NHEERL/WED.

| Year | 90 day 12-h W126 (ppm-h) Cumulative Average observed at Aspen FACE | | Biomass Predicted by NHEERL/WED ^a (g/m ²) | | Biomass Observed at Aspen FACE (g/m ²) | |
|------|--|----------|---|----------|---|----------|
| | Ambient | Elevated | Ambient | Elevated | Ambient | Elevated |
| 1998 | 3.19 | 30.08 | 276.0 | 203.2 | 274.7 | 204.9 |
| 1999 | 2.61 | 33.85 | 958.7 | 668.3 | 955.3 | 673.3 |
| 2000 | 2.43 | 30.16 | 1382.4 | 1022.8 | 1400.3 | 998.6 |
| 2001 | 2.55 | 31.00 | 1607.0 | 1173.7 | 1620.7 | 1154.9 |
| 2002 | 2.51 | 30.27 | 2079.0 | 1532.1 | 2125.9 | 1468.4 |
| 2003 | 2.86 | 29.12 | 2640.1 | 1981.2 | 2695.2 | 1907.8 |

^aThree-parameter absolute biomass model with intercept scaled to Aspen FACE data.



Note: Black dots are aspen biomass/m² for 3 FACE rings filled with an assemblage of 5 clonal genotypes of aspen at Aspen FACE; bars are SE for 3 rings; dashed line is median composite model for 4 clonal genotypes and wild-type seedlings in 11 NHEERL/WED 1-year OTC studies.

Source of data: [King et al. \(2005\)](#); [Lee and Hogsett \(1996\)](#).

Figure 9-20 Comparison between above-ground biomass observed in Aspen FACE experiment in 6 year and biomass predicted by the median composite function based on NHEERL/WED.

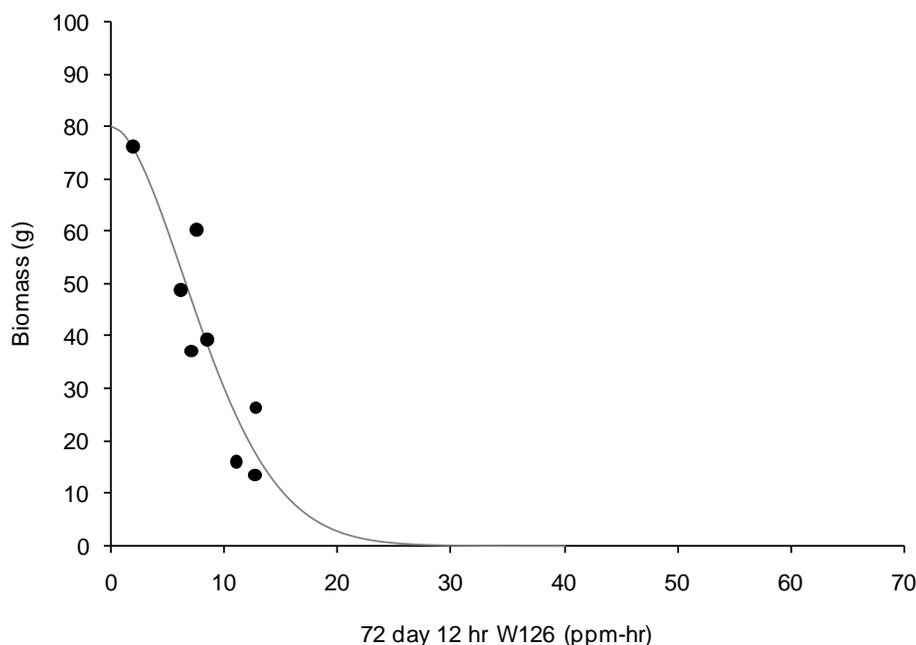
1 As in the comparisons between NCLAN and SoyFACE, the agreement between
 2 predictions based on NHEERL/WED data and Aspen FACE observations was very close.
 3 The results of the two projects strongly reinforce each other with respect to the response
 4 of aspen biomass to O₃ exposure. The methodology used for obtaining the median
 5 composite function is shown to be capable of deriving a predictive model despite
 6 potential confounders, and despite the added measurement error that is expected from
 7 calculating biomass using allometric equations. In addition, the function based on
 8 one year of growth was shown to be applicable to subsequent years.

9 The results of experiments that used different exposure methodologies, different
 10 genotypes, locations, and durations converged to the same values of response to O₃
 11 exposure for each of two very dissimilar plant species, and predictions based on the
 12 earlier experiments were validated by the data from current ones. However, in these
 13 comparisons, the process used in establishing predictive functions involved aggregating
 14 data over variables such as time, locations, and genotypes, and the use of a robust statistic

1 (quartiles) for that aggregation. The validating data, from SoyFACE and Aspen FACE,
2 were in turn aggregated over the same variables. The accuracy of predictions is not
3 expected to be conserved for individual values of those variables over which aggregation
4 occurred. For example, the predicted values for soybean, based on data for five
5 genotypes, are not expected to be valid for each genotype separately. As shown in the
6 validation, however, aggregation that occurred over different values of the same variable
7 did not affect accuracy: composite functions based on one set of genotypes were
8 predictive for another set, as long as medians were used for both sets. A study of
9 cottonwood (*Populus deltoides*) conducted using a naturally occurring gradient of O₃
10 exposure ([Gregg et al., 2006, 2003](#)) may provide an illustration of the response of an
11 individual species whose response is far from the median response for an aggregation of
12 species.

9.6.3.3 Exposure-Response in a Gradient Study

13 [Gregg et al. \(2003\)](#) grew saplings of one clonally propagated genotype of cottonwood
14 (*Populus deltoides*) in seven locations within New York City and in the surrounding
15 region between July and September in 1992, 1993 and 1994, and harvested them 72 days
16 after planting. Owing to regional gradients of atmospheric O₃ concentration, the
17 experiment yielded eight levels of exposure ([Figure 9-21](#)), and the authors were able to
18 rule out environmental variables other than O₃ to account for the large differences in
19 biomass observed after one season of growth. The deficit in growth increased
20 substantially faster with increasing O₃ exposure than has been observed in aspen, another
21 species of the same genus (*Populus tremuloides*, [Section 9.6.3.2](#)). Using a three
22 parameter Weibull model ([Figure 9-21](#)), the biomass of cottonwood at a W126 exposure
23 of 15 ppm-h, relative to biomass at 5 ppm-h, is estimated to be 0.18 (18% of growth at
24 5 ppm-h). The relative biomass of trembling aspen within the same 5-15 ppm-h range of
25 exposure is estimated to be 0.92, using the median composite model for aspen whose
26 very close agreement with Aspen FACE data was shown in [Section 9.6.3.2](#). Using a
27 median composite function for all deciduous trees in the NHEERL/WED project (6
28 species in 21 studies) also gives predictions that are very distant from the cottonwood
29 response observed in this experiment. For all deciduous tree species in NHEERL/WED,
30 biomass at a W126 exposure of 15 ppm-h, relative to biomass at 5 ppm-h, was estimated
31 to be 0.87.



Note: Line represents the three-parameter Weibull model.

Source: Modified with permission of Nature Publishing Group ([Gregg et al., 2003](#)).

Figure 9-21 Above-ground biomass for one genotype of cottonwood grown in seven locations for one season in 3 years.

1 As shown in Section [9.6.2](#), the median models available for trembling aspen and soybean
 2 have verifiable predictive ability for those particular species. This suggests that the
 3 corresponding NCLAN- and NHEERL/WED-based models for multiple crop and tree
 4 species can provide reliable estimates of losses for similar assortments of species.
 5 However, their predictive ability would likely be poor for individual species not tested.

6 The cottonwood data of [Gregg et al. \(2003\)](#) show an extremely severe response to O₃.
 7 They are consistent with the expectation that among species and genotypes, some are
 8 likely to be substantially more sensitive than a median measure, such as the estimate
 9 produced by NHEERL/WED ([Figure 9-16](#)), but the sensitivity of this particular species
 10 has not been studied elsewhere.

11 An alternative hypothesis for the difference between the response of cottonwood in this
 12 experiment and deciduous tree species in NHEERL/WED, or the difference between the
 13 response of cottonwood and aspen in NHEERL/WED and Aspen FACE, could be the
 14 presence of confounding factors in the environments where the experiment was
 15 conducted. However, variability in temperature, moisture, soil fertility, and atmospheric

deposition of N were all ruled out by [Gregg et al. \(2003\)](#) as contributing to the observed response to O₃. In addition, this hypothesis would imply that the unrecognized confounder(s) were either absent from both OTC and FACE studies, or had the same value in both. This is not impossible, but the hypothesis that cottonwood is very sensitive to O₃ exposure is more parsimonious, and sufficient.

9.6.3.4 Meta-analyses of growth and yield studies

Since the 2006 O₃ AQCD, five studies have used meta-analytic methods to integrate results from experimental studies of crops or tree species relevant to the U.S. It is possible to obtain exposure-response data for growth and yield from those meta-analyses, but because all of them provided summary measurements of O₃ exposure as hourly averages of various lengths of exposures, comparisons with exposure-response results where exposure is expressed as W126 are problematic. [Table 9-16](#) summarizes the characteristics of the five meta-analyses. They all included studies conducted in the U.S. and other locations worldwide, and all of them expressed responses as comparative change between levels of exposure to O₃, with carbon filtered air (CF) among those levels. Using hourly average concentration to summarize exposure, CF rarely equates with absence of O₃, although it almost always near zero when exposure is summarized as W126, SUM06, or AOT40.

Table 9-16 Meta-analyses of growth or yield studies published since 2005.

| Study | Number of articles included | Years of publication surveyed | Crop, species or genera | Response | Number of O ₃ levels | Duration of exposure |
|---|--|-------------------------------|--|----------------------|---------------------------------|----------------------|
| Ainsworth (2008) | 12 | 1980-2007 | Rice | Yield | 2 | unreported |
| Feng et al. (2008b) | 53 | 1980-2007 | Wheat | Yield | 5 | >10 days |
| Feng and Kobayashi (2009) | All crops together : 81 | 1980-2007 | Potato, barley, wheat, rice, bean, soybean | Yield | 3 | >10 days |
| Grantz et al. (2006) | 16 | 1992-2004 | 34 Herbaceous dicots 21 Herbaceous monocots 5 Tree species | Relative Growth Rate | 2 | 2-24 weeks |
| Wittig et al. (2009) | All responses:263 Articles that included biomass:unreported | 1970-2006 | 4 Gymnosperm tree genera 11 Angiosperm tree genera | Total biomass | 4 | >7 days |

1 The only effect of O₃ exposure on yield of rice reported in [Ainsworth \(2008\)](#) was a
2 decrease of 14% with exposure increasing from CF to 62 ppb average concentration.
3 [Feng et al. \(2008b\)](#) were able to separate exposure of wheat into four classes with average
4 concentrations of 42, 69, 97, and 153 ppb, in data where O₃ was the only treatment. Mean
5 responses relative to CF were yield decreases of 17, 25, 49, and 61% respectively. [Feng](#)
6 [et al. \(2008b\)](#) observed that wheat yield losses were smaller under conditions of drought,
7 and that Spring wheat and Winter wheat appeared similarly affected. However, mean
8 exposure in studies of Winter wheat was substantially higher than in studies of Spring
9 wheat (86 versus 64 ppb), which suggests that the yield of Spring wheat was in fact more
10 severely affected, since yield was approximately the same, even though Spring wheat was
11 exposed to lower concentrations. Exposures of the six crops considered in [Feng and](#)
12 [Kobayashi \(2009\)](#) were classified into two ranges, each compared to CF air. In the lower
13 range of exposure (41-49 ppb), potato studies had the highest average exposure (45 ppb)
14 and wheat and rice the lowest (41 ppb). In the higher range (51-75 ppb), wheat studies
15 had the highest average exposure (65 ppb), and potato, barley and rice the lowest
16 (63 ppb). In other words, across the studies included, all crops were exposed to very
17 similar levels of O₃. At approximately 42 ppb, the yield of potato, barley, wheat, rice,
18 bean, and soybean declined by 5.3, 8.9, 9.7, 17.5, 19, and 7.7% respectively, relative to
19 CF air. At approximately 64 ppb O₃, declines were 11.9, 12.5, 21.1, 37.5, 41.4, and
20 21.6%. [Grantz et al. \(2006\)](#) reported Relative Growth Rate (RGR) rather than growth,
21 and did not report O₃ exposure values in a way that would allow calculation of mean
22 exposure for each of the three categories of plants for which RGR changes are reported.
23 All studies used only two levels of exposure, with CF air as the lower one, and most used
24 elevated exposure in the range of 40 to 70 ppb. Decline in RGR was 8.2% for the 34
25 herbaceous dicots, 4.5% for the 21 herbaceous monocots, and 17.9% for the 5 tree
26 species. Finally, [Wittig et al. \(2009\)](#) divided the studies analyzed into three classes of
27 comparisons: CF versus ambient, CF versus elevated, and ambient versus elevated, but
28 reported comparisons between three average levels of exposure besides CF: 40 ppb,
29 64 ppb, and 97 ppb. Corresponding decreases in total biomass relative to CF were 7, 17,
30 and 17%.

31 These meta-analyses provide very strong confirmation of EPA's conclusions from
32 previous O₃ AQCDs: compared to lower levels of ambient O₃, current levels in many
33 locations are having a substantial detrimental effect on the growth and yield of a wide
34 variety of crops and natural vegetation. They also confirm strongly that decreases in
35 growth and yield continue at exposure levels higher than current ambient levels.
36 However, direct comparisons with the predictions of exposure-response models that use
37 concentration-weighted cumulative metrics are difficult.

9.6.3.5 Additional exposure-response data

1 The studies summarized in [Table 9-17](#) and [Table 9-18](#) contain growth or yield exposure-
2 response data at too few levels of exposure for exposure-response models, and/or used
3 metrics other than W126. These tables update Tables AX9-16 through AX9-19 of the
4 2006 O₃ AQCD.

9.6.4 Summary

5 None of the information on effects of O₃ on vegetation published since the 2006 O₃
6 AQCD has modified the assessment of quantitative exposure-response relationships that
7 was presented in that document. This assessment updates the 2006 exposure-response
8 models by computing them using the W126 metric, cumulated over 90 days. Almost all
9 of the experimental research on the effects of O₃ on growth or yield of plants published
10 since 2006 used only two levels of exposure. In addition, hourly O₃ concentration data
11 that would allow calculations of exposure using the W126 metric are generally
12 unavailable. However, two long-term experiments, one with a crop species (soybean),
13 one with a tree species (aspen), have produced data that can be used to validate the
14 exposure-response models presented in the 2006 O₃ AQCD, and methodology used to
15 derive them.

16 Quantitative characterization of exposure-response in the 2006 O₃ AQCD was based on
17 experimental data generated for that purpose by the National Crop Loss Assessment
18 Network (NCLAN) and EPA National Health and Environmental Effects Research
19 Laboratory, Western Ecology Division (NHEERL-WED) projects, using OTCs to expose
20 crops and trees seedling to O₃. In recent years, yield and growth results for two of the
21 species that had provided extensive exposure-response information in those projects have
22 become available from studies that used FACE technology, which is intended to provide
23 conditions much closer to natural environments ([Pregitzer et al., 2008](#); [Morgan et al.,
24 2006](#); [Morgan et al., 2004](#); [Dickson et al., 2000](#)). The robust methods that were used
25 previously with exposure measured as SUM06 were applied to the NCLAN and
26 NHEERL-WED data with exposure measured as W126, in order to derive single-species
27 median models for soybean and aspen from studies involving different genotypes, years,
28 and locations. The resulting models were used to predict the change in yield of soybean
29 and biomass of aspen between the two levels of exposure reported in recent FACE
30 experiments. Results from these new experiments were exceptionally close to predictions
31 from the models. The accuracy of model predictions for two widely different plant
32 species provides support for the validity of the corresponding multiple-species models for
33 crops and trees in the NCLAN and NHEERL-WED projects. However, variability among

species in those projects indicates that the range of sensitivity is likely quite wide. This was confirmed by a recent experiment with cottonwood in a naturally occurring gradient of exposure (Gregg et al., 2006), which established the occurrence of species with responses substantially more severe under currently existing conditions than are predicted by the median model for multiple species.

Results from several meta-analyses have provided approximate values for responses of yield of soybean, wheat, rice and other crops under broad categories of exposure, relative to charcoal-filtered air (Ainsworth, 2008; Feng et al., 2008b; Morgan et al., 2003).

Likewise, Feng and Kobayashi (2009) have summarized yield data for six crop species under various broad comparative exposure categories, while Wittig et al. (2009) reviewed 263 studies that reported effects on tree biomass. However, these analyses have proved difficult to compare with exposure-response models, especially given that exposure was not expressed in the same W126 metric.

Table 9-17 Summary of studies of effects of ozone exposure on growth and yield of agricultural crops.

| Species Facility Location | Exposure Duration | O ₃ Exposure (Additional Treatment) | Response Measured | Percent Change from CF (Percent Change from Ambient) | Reference |
|---|-------------------|---|---------------------------------------|--|--|
| Alfalfa (<i>Medicago sativa</i>) OTC; 0.27m ³ pots Federico, Italy | 2 yr, 2005, 2006 | AOT40: CF 0 ppm-h 13.9 ppm-h (2005), 10.1 ppm-h (2006) (NaCl: 0.29, 0.65, 0.83, 1.06 deciSiemens/meter) | Total shoot yield | n.s. (N/A) | Maggio et al. (2009) |
| Bean (<i>Phaseolus vulgaris</i> l. cv Borlotto) OTC; ground-planted Curno, Italy | 3 months, 2006 | Seasonal AOT40: CF (0.5 ppm-h); ambient (4.6 ppm-h) (N/A) | # Seeds per plant; 100-seed weight | -33 (N/A) n.s. (N/A) | Gerosa et al. (2009) |
| Big Blue Stem (<i>Andropogon gerardii</i>) OTC Alabama | 4 months, 2003 | 12-h avg: CF (14 ppb), Ambient (29 ppb), Elevated (71 ppb) (N/A) | Final harvest biomass; RVF | n.s. (n.s.) -7 (-7) | Lewis et al. (2006) |
| <i>Brassica napus</i> cv. Westar Growth chambers Finland | 17-26 days | 8-h avg: CF (0 ppb), 100 ppb (Bt/non-Bt; herbivory) | Shoot biomass | -30.70 (N/A) | Himanen et al. (2009b) |
| Corn (<i>Zea mays</i> cv. Chambord) OTC France | 33 days | AOT40 ppm-h: 1.1; 1.3; 4.9; 7.2; 9.3; 12.8 (N/A) | Total above-ground biomass | N/A (Highest treatment caused -26% change) | Leitao et al. (2007a) |

| Species Facility Location | Exposure Duration | O ₃ Exposure (Additional Treatment) | Response Measured | Percent Change from CF (Percent Change from Ambient) | Reference |
|---|--|--|--|--|--|
| Cotton cv. Pima OTC; 9-L pots San Joaquin Valley, CA | 8 weeks | 12-h avg: 12.8 ± 0.6; 79.9 ± 6.3; 122.7 ± 9.7 (N/A) | Above-ground biomass | -76 (n.s.) | Grant and Shrestha (2006) |
| Eastern Gamagrass (<i>Tripsacum dactyloides</i>) OTC Alabama | 4 months, 2003 | 12-h avg: CF (14ppb), Ambient (29 ppb), Elevated (71 ppb) (N/A) | Final harvest biomass; RVF | +68 (+42); -17 (-12) | Lewis et al. (2006) |
| Grapevine (<i>Vitis vinifera</i>) OTC Austria | 3 yr, May-Oct | AOT40 ppm-h: CF (0), Ambient (7-20), Elevated. 1 (20-30), Elevated. 2 (38-48) | Total fruit yield/ Sugar yield | -20 to -80 in different yr (-20 to -90 in different yr) | Soja et al. (2004) |
| Mustard (<i>Brassica campestris</i>) Chambers; 7.5-cm pots | 10 days | CF & 67.8 ppb for 7 h (N/A) | Seeds/plant | n.s. (N/A) | Black et al. (2007) |
| Oilseed Rape (<i>Brassica napus</i>) OTC Yangtze Delta, China | 39 days | Daily avg: 100 ppb, one with diurnal variation and one with constant concentration (N/A) | Biomass and pods per plant | Diurnal variability reduced both biomass and pod number more than constant fumigation (N/A) | Wang et al. (2008) |
| Peanut (<i>Arachis hypogaea</i>) OTC Raleigh, NC | 3 yr | 12-h avg: CF (22 ppb), Ambient (46 ppb), Elevated (75ppb) (CO ₂ : 375 ppm; 548 ppm; 730 ppm) | Yield (seed weight, g/m) | -33 (-8) | Burkey et al. (2007) |
| <i>Poa pratensis</i> OTC Braunschweig, Germany | 2000-2002: 4-5 weeks in the Spring | 8-h avg: CF+25 (21.7), NF+50 (73.1) (Competition) | Total biomass (g DW/pot) | N/A (n.s.) | Bender et al. (2006) |
| Potato (<i>Solanum tuberosum</i>) OTC; CHIP 6 northern European locations | 1988,1999. Emergence to harvest | AOT40:CF (0); Ambient (0.27-5.19); NF (0.002-2.93) NF+ (3.10-24.78 (N/A) | Tuber yield averaged across 5 field-sites; Tuber starch content regressed against [O ₃] report sig. ± slope with increasing [O ₃] | N/A (-27% -+27%, most comparisons n.s.) Linear regression slope = -0.0098) | Vandermeiren et al. (2005) |
| Rice (<i>Oryza sativa</i>) OTC Raleigh, NC | 1997-1998, June- September | 12-h mean ppb: CF (27.5), Elevated (74.8) (CO ₂) | Total biomass; Seed yield | -25(N/A) -13 to 20 (N/A) | Reid and Fiscus (2008) |

| Species Facility Location | Exposure Duration | O ₃ Exposure (Additional Treatment) | Response Measured | Percent Change from CF (Percent Change from Ambient) | Reference |
|---|----------------------------|---|---|--|---|
| Rice (<i>Oryza sativa</i>) 20 Asian cultivars OTC Gunma Prefecture, Japan | 2008 growing season | Daily avg (ppb): CF (2), 0.8×ambient (23); 1 ×ambient (28); 1.5×ambient (42); 2×ambient (57) (Cultivar comparisons) | Yield | From n.s. to -30 across all cultivars | Sawada and Kohno (2009) |
| Seminatural grass FACE Le Mouret, Switzerland | 5 yr | Seasonal AOT40: Ambient (0.1-7.2 ppm-h); Elevated. (1.8-24.1 ppm-h) (N/A) | Relative annual yield | N/A (2×faster decrease in yield/yr) | Volk et al. (2006) |
| Soybean OTC; CRA Bari, Italy | 2003-2005 growing seasons | Seasonal AOT40 ppm-h: CF (0), Ambient (3.4), High (9.0) (Drought) | Yield | -46 (-9) | Bou Jaoudé et al. (2008b) |
| Soybean (<i>Glycine max</i> cv. 93B15) SoyFACE Urbana, IL | 2002, 2003 growing seasons | 8-h avg: Ambient (62 & 50 ppb), Elevated (75 & 63 ppb) (N/A) | Yield | N/A (-15 in 2002; -25 in 2003) | Morgan et al. (2006) |
| Soybean (<i>Glycine max</i> cv. Essex) Chambers; 21 L Raleigh, NC | 2×3 months | 12-h avg: CF (28), Elevated (79), Elevated flux (112) (CO ₂ : 365 & 700) | Seed mass per plant | -30 (N/A) | Booker and Fiscus (2005) |
| Soybean (<i>Glycine max</i> cv. Essex) OTCs; 21-L pots Raleigh, NC | 2×3 months | 12-h avg: CF (18); Elevated (72) (CO ₂ : 367 & 718) | Seed mass per plant | -34 (N/A) | Booker et al. (2004b) |
| Soybean (<i>Glycine max</i> cv. Tracaja) Chambers; pots Brazil | 20 days | 12-h avg: CF & 30 ppb (N/A) | Biomass | -18 (N/A) | Bulbovas et al. (2007) |
| Soybean (<i>Glycine max</i>) 10 cultivars SoyFACE Urbana, IL | 2007 & 2008 | 8-h avg: Ambient (46.3 & 37.9), Elevated (82.5 & 61.3) (Cultivar comparisons) | Yield | N/A (-17.20) | Betzberger et al. (2010) |
| Spring Wheat (<i>Triticum aestivum</i> cv. Minaret; Satu; Drabant; Dragon) OTCs Belgium, Finland, & Sweden | 1990-2006 | Seasonal AOT40s ranged from 0 to 16 ppm-h (N/A) | Seed protein content; 1,000-seed weight regressed across all experiments | N/A (significant negative correlation) N/A (sig negative correlation) | Piikki et al. (2008b) |
| Strawberry (<i>Fragaria x ananassa</i> Duch. Cv Korona & Elsanta) Growth chambers Bonn, Germany | 2 months | 8-h avg: CF (0 ppb) & Elevated (78 ppb) (N/A) | Fruit yield (weight/plant) | -16 (N/A) | Keutgen et al. (2005) |

| Species Facility Location | Exposure Duration | O ₃ Exposure (Additional Treatment) | Response Measured | Percent Change from CF (Percent Change from Ambient) | Reference |
|--|-------------------------|---|----------------------------|---|--|
| Sugarbeet (<i>Beta vulgaris</i> cv. Patriot) OTC Belgium | 2003, 2004; 5 months | 8-h avg: Ambient (36 ppb); Elevated (62 ppb) (N/A) | Sugar yield | N/A (-9) | De Temmerman et al. (2007) |
| Sugarcane (<i>Saccharum spp</i>) CSTR San Joaquin Valley, CA | 2007; 11-13 weeks. | 12-h avg: CF (4 ppb); Ambient (58); Elevated (147) (N/A) | Total biomass (g/plant) | -40 (-30) | Grantz and Vu (2009) |
| Sweet Potato Growth chambers Bonn, Germany | 4 weeks | 8-h avg: CF (0 ppb), Ambient (<40 ppb) Elevated (255 ppb) (N/A) | Tuber weight | -14 (-11.5) | Keutgen et al. (2008) |
| Tomato (<i>Lycopersicon esculentum</i>) OTC Valencia, Spain | 133 days in 1998 | 8-h mean ppb: CF 16.3, NF 30.1, NF+ 83.2 (Various cultivars; early & late harvest) | Yield | n.s. (n.s.) | Dalstein and Vas (2005) |
| <i>Trifolium Subterraneum</i> OTC; 2.5-L pots Madrid, Spain | 29 days | 12-h avg: CF (<7.9 ± 6.3); Ambient (34.4 ± 10.8); Elevated (56.4 ± 22.3) (N: 5, 15 & 30 kg/ha) | Above-ground biomass | -45 (-35) | Sanz et al. (2005) |
| Watermelon (<i>Citrullus lanatus</i>) OTC Valencia, Spain | 2000, 2001. 90 days | AOT40: CF (0 ppm-h) Ambient (5.7 ppm-h), Elevated (34.1 ppm-h) (N:0, 14.0 & 29.6 g/pot) | total fruit yield (kg) | n.s. (54) | Calatayud et al. (2006) |
| Yellow Nutsedge OTC; 9-L pots San Joaquin Valley, CA | 8 weeks | 12-h avg: 12.8 ± 0.6; 79.9 ± 6.3; 122.7 ± 9.7 (N/A) | above-ground biomass | n.s. (n.s.) | Grantz and Shrestha (2006) |

In studies where variables other than O₃ were included in the experimental design, response to O₃ is only provided for the control level of those variables.

Table 9-18 Summary of studies of effects of ozone exposure on growth of natural vegetation.

| Species Facility Location | Exposure Duration | O ₃ Exposure (Additional Treatment) | Response Measured | Response | Reference |
|---|--|--|---|--|---|
| Yellow nutsedge (<i>Cyperus esculentus</i>) CSTR San Joaquin Valley, CA | 53 days in 2008 | 12-h mean ppb: CF (4); CF+ (60); CF2+ (115) | Above-ground biomass; tubers (g/plant) | ns; CF(4.1) CF+(3.9) CF2+(2.7) | Grantz et al. (2010a) |
| 35 herbaceous species OTC Corvallis, OR | 1999-2002, May-August | 4-yr avg; yearly W126 ppm-h: CF (0), CF+ (21), CF 2+ (49.5) | Total community above-ground biomass (35 species) after 4 years | CF (459 g/m ²), CF+ (457 g/m ²), CF2+ (398 g/m ²) | Pfleeger et al. (2010) |
| Highbush blackberry (<i>Rubus argutus</i>) OTC Auburn, AL | 2004, May-August | 12-h mean ppb: CF (21.7), Ambient (32.3), Elevated (73.3) | Vegetative regrowth after pruning | CF (75.1 g/plant), Ambient (76.4 g/plant), Elevated (73.1 g/plant) | Ditchkoff et al. (2009) |
| Horseweed (<i>Coryza canadensis</i>) CSTR San Joaquin Valley, CA | 2005, 2 runs, 28 days each (July-Aug, Sept) | W126 ppm-h: CF(0), CF+ (11), CF 2+ (30) (Glyphosate resistance) | Total biomass (g/plant) | Glyphosate sensitive: CF (0.354) CF+ (0.197) CF2+ (0.106) Glyphosate resistant: CF(0.510) CF+ (0.313) CF2+ (0.143) | Grantz et al. (2008) |
| Red Oak (<i>Quercus rubrum</i>) Forest sites Look Rock & Twin Creeks Forests, TN | 2001-2003, April-October | AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2001 in year 2002;2003) | -42.8%; +1% | McLaughlin et al. (2007a) |
| Pine species Forest sites Look Rock Forest, TN | 2001-2003, April-October | AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2001 in year 2002;2003) | -62.5%; -2.9% | McLaughlin et al. (2007a) |

| Species Facility Location | Exposure Duration | O ₃ Exposure (Additional Treatment) | Response Measured | Response | Reference |
|--|-----------------------------|--|---|------------|---|
| Hickory species Forest sites Look Rock Forest, TN | 2001-2003, April-October | AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2001 in year 2002;2003) | -14%; +30% | McLaughlin et al. (2007a) |
| Chestnut Oak (<i>Quercus prinus</i>) Forest sites Look Rock Forest, TN | 2001-2003, April-October | AOT60: 2001 (11.5), 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2001 in year 2002;2003) | +44%; +55% | McLaughlin et al. (2007a) |
| Black Cherry (<i>Prunus rigida</i>) Forest sites Twin Creeks Forest, TN | 2002-2003, April-October | AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2003 in year 2002) | -75% | McLaughlin et al. (2007a) |
| Shortleaf pine (<i>Pinus echinata</i>) Forest sites Twin Creeks Forest, TN | 2002-2003, April-October | AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2003 in year 2002) | -16.8% | McLaughlin et al. (2007a) |
| Hemlock (<i>Tsuga canadensis</i>) Forest sites Twin Creeks Forest, TN | 2002-2003, April-October | AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2003 in year 2002) | -21.9% | McLaughlin et al. (2007a) |
| Red Maple (<i>Acer rubrum</i>) Forest sites Twin Creeks Forest, TN | 2002-2003, April-October | AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2003 in year 2002) | -59.6% | McLaughlin et al. (2007a) |

| Species Facility Location | Exposure Duration | O ₃ Exposure (Additional Treatment) | Response Measured | Response | Reference |
|--|-----------------------------|---|---|---|---|
| Yellow Poplar (<i>Liriodendron tulipifera</i>) Forest sites Look Rock, Oak Ridge, & Twin Creeks Forest, TN | 2002-2003, April-October | AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2001 in years 2002; 2003) | -45.9%; -15.25% | McLaughlin et al. (2007a) |
| Sugar Maple (<i>Acer saccharum</i>) Forest sites Twin Creeks Forest, TN | 2002-2003, April-October | AOT60: 2002 (24.0), 2003 (11.7) (Observational study with multiple environmental variables) | Annual circumference increment (change relative to 2003 in year 2002) | -63.8% | McLaughlin et al. (2007a) |
| Trembling aspen (<i>Populus tremuloides</i>), 5 genotypes Aspen FACE Rhineland, WI | 1998-2004, May-October | Cumulative avg 90-day 12-h W126. Ambient 3.1 ppm-h Elevated: 27.2 ppm-h (Competition with birch, maple) | main stem volume after 7 years | Ambient: 6.22 dm ³ ; Elevated: 4.73 dm ³ | Kubiske et al. (2006) |
| Hybrid Poplar (<i>Populus trichocarpa</i> x <i>Populus deltoides</i>) OTC Seattle, WA | 2003, 3 months | Daily mean (µg/g): CF(<9), Elevated (85- 128) | Total biomass | CF to elevated: -12.9% | Woo and Hincley (2005) |

In studies where variables other than O₃ were included in the experimental design, response to O₃ is only provided for the control level of those variables.

9.7 Summary and Conclusions

1 Based on the evidence presented in Chapter 9 and summarized here, O₃ is causally related
2 or likely to be causally related to effects observed on vegetation and ecosystems. The
3 evidence for these effects spans the entire continuum of biological organization, from the
4 cellular and subcellular level to the whole plant, and up to ecosystem-level processes, and
5 includes evidence for effects at lower levels of organization, leading to effects at higher
6 levels. Given the current state of knowledge, exposure indices that cumulate and
7 differentially weight the higher hourly average concentrations and also include the mid-
8 level values are the most appropriate for use in developing response functions and
9 comparing studies. The framework for causal determinations (see Preamble) has been
10 applied to the body of scientific evidence to examine effects attributed to O₃ exposure
11 collectively and the determinations are presented in [Table 9-19](#).

Table 9-19 Summary of ozone causal determinations for vegetation and ecosystem effects

| Vegetation and Ecosystem Effects | Conclusions from 2006 O₃ AQCD | Conclusions from 2011 3rd Draft ISA |
|--|--|--|
| Visible Foliar Injury Effects on Vegetation | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause impaired aesthetic quality of many native plants and trees by increasing foliar injury. | Causal Relationship |
| Reduced Vegetation Growth | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause decreased growth and biomass accumulation in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees. | Causal Relationship |
| Reduced Productivity in Terrestrial Ecosystems | There is evidence that O ₃ is an important stressor of ecosystems and that the effects of O ₃ on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity. | Causal Relationship |
| Reduced Carbon (C) Sequestration in Terrestrial Ecosystems | Limited studies from previous review | Likely to be a Causal Relationship |
| Reduced Yield and Quality of Agricultural Crops | Data published since the 1996 O ₃ AQCD strengthen previous conclusions that there is strong evidence that current ambient O ₃ concentrations cause decreased yield and/or nutritive quality in a large number of agronomic and forage crops. | Causal Relationship |
| Alteration of Terrestrial Ecosystem Water Cycling | Ecosystem water quantity may be affected by O ₃ exposure at the landscape level. | Likely to be a Causal Relationship |
| Alteration of Below-ground Biogeochemical Cycles | Ozone-sensitive species have well known responses to O ₃ exposure, including altered C allocation to below-ground tissues, and altered rates of leaf and root production, turnover, and decomposition. These shifts can affect overall C and N loss from the ecosystem in terms of respired C, and leached aqueous dissolved organic and inorganic C and N. | Causal Relationship |
| Alteration of Terrestrial Community Composition | Ozone may be affecting above- and below -ground community composition through impacts on both growth and reproduction. Significant changes in plant community composition resulting directly from O ₃ exposure have been demonstrated. | Likely to be a Causal Relationship |

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10 THE ROLE OF TROPOSPHERIC OZONE IN CLIMATE CHANGE AND UV-B EFFECTS

10.1 Introduction

1 Atmospheric O₃ plays an important role in the Earth's energy budget by interacting with
2 incoming solar radiation and outgoing infrared radiation. Over mid-latitudes,
3 approximately 90% of the total atmospheric O₃ column is located in the stratosphere ([Kar
4 et al., 2010](#); [Crist et al., 1994](#)). Therefore, tropospheric O₃ makes up a relatively small
5 portion (~10%) of the total column of O₃ over mid-latitudes, but it does play an important
6 role in the overall radiation budget. The next section (Section [10.2](#)) briefly describes the
7 physics of the earth's radiation budget, providing background material for the subsequent
8 two sections assessing how perturbations in tropospheric O₃ might affect (1) climate
9 through its role as a greenhouse gas (Section [10.3](#)), and (2) health, ecology and welfare
10 through its role in shielding the earth's surface from solar ultraviolet radiation
11 (Section [10.4](#)). The concluding section in this chapter (Section [10.5](#)) includes a summary
12 of effects assessed in this chapter along with their associated causal determinations.

10.2 Physics of the Earth's Radiation Budget

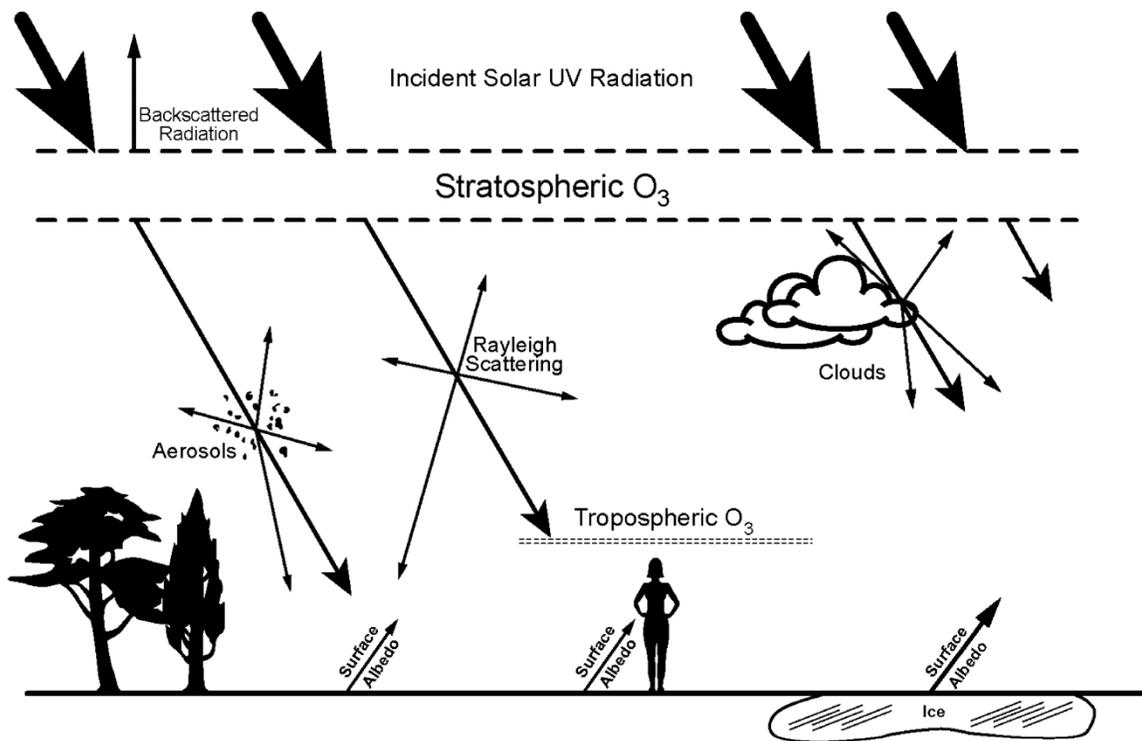
13 Radiant energy from the sun enters the atmosphere in a range of wavelengths, but peaks
14 strongly in the visible (400-750 nm) part of the spectrum. Longer wavelength infrared
15 (750 nm-1 mm) and shorter wavelength ultraviolet (100-400 nm) radiation are also
16 present in the solar electromagnetic spectrum. Since the energy possessed by a photon is
17 inversely proportional to its wavelength, infrared (IR) radiation carries the least energy
18 per photon, and ultraviolet (UV) radiation carries the most energy per photon. UV
19 radiation is further subdivided into classes based on wavelength: UV-A refers to
20 wavelengths from 400-315 nm; UV-B from 315-280 nm; and UV-C from 280-100 nm.
21 By the same argument above describing the relationship between photon wavelength and
22 energy, UV-A radiation is the least energetic and UV-C is the most energetic band in the
23 UV spectrum.

24 The wavelength of radiation also determines how the photons interact with the complex
25 mixture of gases, clouds, and particles present in the atmosphere (see [Figure 10-1](#)). UV-A
26 radiation can be scattered but is not absorbed to any meaningful degree by atmospheric
27 gases including O₃. UV-B radiation is absorbed and scattered in part within the
28 atmosphere. UV-C is almost entirely blocked by the Earth's upper atmosphere, where it

1 participates in photoionization and photodissociation processes including absorption by
2 stratospheric O₃.

3 Since UV-A radiation is less energetic and does not interact with O₃ in the troposphere or
4 the stratosphere and UV-C radiation is almost entirely blocked by stratospheric O₃, UV-B
5 radiation is the most important band to consider in relation to tropospheric O₃ shielding.
6 Furthermore, tropospheric O₃ plays a “disproportionate” role in absorbing UV-B
7 radiation compared with stratospheric O₃ on a molecule per molecule basis ([Balis et al.,
8 2002](#); [Zerefos et al., 2002](#); [Crist et al., 1994](#); [Bruhl and Crutzen, 1989](#)). This effect results
9 from the higher atmospheric pressure present in the troposphere, resulting in higher
10 concentrations of gas molecules present that can absorb or scatter radiation. For this
11 reason, the troposphere is referred to as a “multiple scattering” regime for UV absorption,
12 compared to the “single scattering” regime in the stratosphere. Thus, careful
13 quantification of atmospheric absorbers and scatterers, along with a well-resolved
14 description of the physics of these interactions, is necessary for predicting the effects of
15 tropospheric O₃ on UV-B flux at the surface.

16 Solar flux at all wavelengths has a temporal dependence, while radiative scattering and
17 absorption have strong wavelength, path length, and gas/particle concentration
18 dependencies. These combine to create nonlinear effects on UV flux at the Earth’s
19 surface. Chapter 10 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) describes in detail several
20 key factors that influence the spatiotemporal distribution of ground-level UV radiation
21 flux, including: (1) long-term solar activity including sunspot cycle; (2) solar rotation; (3)
22 the position of the Earth in its orbit around the sun; (4) atmospheric absorption and
23 scattering of UV radiation by gas molecules and aerosol particles; (5) absorption and
24 scattering by stratospheric and tropospheric clouds; and (6) surface albedo. The
25 efficiencies of absorption and scattering are highly dependent on the concentration of the
26 scattering medium, particle size (for aerosols and clouds), and the altitude at which these
27 processes are occurring. These properties are sensitive to meteorology, which introduces
28 additional elements of spatial and temporal dependency in ground-level UV radiation
29 flux.



Source: 2006 O₃ AQCD ([U.S. EPA, 2006b](#)).

Figure 10-1 Diagram of the factors that determine human exposure to ultraviolet radiation.

1 About 30% of incoming solar radiation is directly reflected back to space, mainly by
 2 clouds or surfaces with high albedo (reflectivity), such as snow, ice, and desert sand.
 3 Radiation that does penetrate to the Earth's surface and is absorbed can be re-emitted in
 4 the longwave (infrared) portion of the spectrum; the rest goes into evaporating water or
 5 soil moisture or emerges as sensible heat. The troposphere is opaque to the outgoing
 6 longwave radiation. Polyatomic gases such as water vapor, CO₂, CH₄, and O₃ absorb and
 7 re-emit the radiation upwelling from the Earth's surface, reducing the efficiency with
 8 which that energy returns to space. In effect, these gases act as a blanket warming the
 9 Earth's surface. This phenomenon, known as the "Greenhouse Effect," was first
 10 quantified in the 19th century ([Arrhenius, 1896](#)), and gives rise to the term "greenhouse
 11 gas." The most important greenhouse gas is water vapor.

10.3 Effects of Tropospheric Ozone on Climate

10.3.1 Background

1 As a result of its interaction with incoming solar radiation and outgoing longwave
2 radiation, tropospheric O₃ plays a major role in determining climate, and increases in its
3 abundance may contribute to climate change ([IPCC, 2007c](#)). Models estimate that the
4 global average concentration of O₃ in the troposphere has increased 30-70% since the
5 preindustrial era ([Gauss et al., 2006](#)), while observations indicate that in some regions
6 tropospheric O₃ may have increased by factors as great as 4 or 5 ([Marengo et al., 1994](#);
7 [Staelin et al., 1994](#)). These increases are tied to the rise in emissions of O₃ precursors
8 from human activity, mainly fossil fuel consumption and agricultural processes.

9 The effect on climate of the tropospheric O₃ change since preindustrial times has been
10 estimated to be about 25-40% of the anthropogenic CO₂ effect and about 75% of the
11 anthropogenic CH₄ effect ([IPCC, 2007c](#)), ranking it third in importance behind these two
12 major greenhouse gases. In the 21st century, as the Earth's population continues to grow
13 and energy technology spreads to developing countries, a further rise in the global
14 concentration of tropospheric O₃ is likely, with associated consequences for human health
15 and ecosystems relating to climate change.

16 To examine the science of a changing climate and to provide balanced and rigorous
17 information to policy makers, the World Meteorological Organization (WMO) and the
18 United Nations Environment Programme (UNEP) formed the Intergovernmental Panel on
19 Climate Change (IPCC) in 1988. The IPCC supports the work of the Conference of
20 Parties (COP) to the United Nations Framework Convention on Climate Change
21 (UNFCCC). The IPCC periodically brings together climate scientists from member
22 countries of WMO and the United Nations to review knowledge of the physical climate
23 system, past and future climate change, and evidence of human-induced climate change.
24 IPCC climate assessment reports are issued every five to seven years.

25 This section draws in part on the fourth IPCC Assessment Report (AR4) ([IPCC, 2007c](#)),
26 as well as other peer-reviewed published research. Section [10.3.2](#) reviews evidence of
27 climate change in the recent past and projections of future climate change. It also offers a
28 brief comparison of tropospheric O₃ relative to other greenhouse gases. Section [10.3.3](#)
29 describes factors that influence the magnitude of tropospheric O₃ effects on climate.
30 Section [10.3.4](#) considers the competing effects of O₃ precursors on climate. Finally,
31 Section [10.3.5](#) and Section [10.3.6](#) describe the effects of changing tropospheric O₃
32 concentrations on past and future climate. Downstream effects resulting from climate
33 change, such as ecosystem responses, are outside the scope of this assessment, which

1 focuses rather on the effects of changes in tropospheric O₃ concentrations on radiative
2 forcing and climate.

10.3.2 Climate Change Evidence and the Influence of Tropospheric Ozone

10.3.2.1 Climate Change in the Recent Past

3 From the end of the Last Ice Age 12,000 years ago until the mid-1800s, observations
4 from ice cores show that concentrations of the long-lived greenhouse gases CO₂, CH₄,
5 and N₂O have been relatively stable. Unlike these greenhouse gases, O₃ is not preserved
6 in ice, and no record of it before the late 1800s exists. Models, however, suggest that it,
7 too, has remained relatively constant during this time period ([Thompson et al., 1993](#);
8 [Thompson, 1992](#)). The stable mix of these greenhouse gases in the atmosphere, together
9 with water vapor, has kept the global mean temperature of the Earth close to 15°C.
10 Without the presence of greenhouse gases in the atmosphere, the Earth's global mean
11 temperature would be about 30°C cooler, or -15°C.

12 Since the start of the Industrial Revolution, human activity has led to observable
13 increases of greenhouse gases in the atmosphere, mainly through fossil fuel combustion.
14 According to the IPCC AR4 ([IPCC, 2007c](#)), there is now “very high confidence” that the
15 net effect of anthropogenic greenhouse gas emissions since 1750 has led to warming, and
16 it is “very likely” that human activity contributed to the 0.76°C rise in global mean
17 temperature observed over the last century. The increase of tropospheric O₃ may have
18 contributed 0.1-0.3°C warming to the global climate during this time period ([Hansen et](#)
19 [al., 2005](#); [Mickley et al., 2004](#)). Global cooling due to anthropogenic aerosols ([IPCC,](#)
20 [2007c](#)) has likely masked the full warming effect of the anthropogenic greenhouse gases
21 on a global scale.

10.3.2.2 Projections of Future Climate Change

22 The IPCC AR4 projects a warming of ~0.2°C per decade for the remainder of the 21st
23 century ([IPCC, 2007c](#)). Even at constant concentrations of greenhouse gases in the
24 atmosphere, temperatures are expected to increase by about 0.1°C per decade, due to the
25 slow response of oceans to the warming applied so far. It is likely that the Earth will
26 experience longer and more frequent heat waves in the 21st century, together with more
27 frequent droughts and/or heavy precipitation events in some regions, due to perturbations
28 in the hydrological cycle that result from changing temperatures. Sea levels could

1 increase by 0.3-0.8 meters by 2300 due to thermal expansion of the oceans. The extent of
2 Arctic sea ice is expected to decline, and contraction of the Greenland ice sheet could
3 further contribute to the sea level rise ([IPCC, 2007c](#)).

4 Projections of future climate change are all associated with some degree of uncertainty. A
5 major uncertainty involves future trends in the anthropogenic emissions of greenhouse
6 gases or their precursors. For the IPCC AR4 climate projections, a set of distinct
7 “storylines” or emission pathways was developed ([IPCC, 2000](#)). Each storyline took into
8 account factors such as population growth, mix of energy technologies, and the sharing of
9 technology between developed and developing nations, and each resulted in a different
10 scenario for anthropogenic emissions. When these trends in emissions are applied to
11 models, these scenarios yield a broad range of possible climate trajectories for the 21st
12 century.

13 A second factor bringing large uncertainty to model projections of future climate is the
14 representation of climate and, especially, climate feedbacks. A rise in surface
15 temperatures would perturb a suite of other processes in the earth-atmosphere-ocean
16 system, which may in turn either amplify the temperature increase (positive feedback) or
17 diminish it (negative feedback). One important feedback involves the increase of water
18 vapor content of the atmosphere that would accompany higher temperatures ([Bony et al.,
19 2006](#)). Water vapor is a potent greenhouse gas; accounting for the water vapor feedback
20 may increase the climate sensitivity to a doubling of CO₂ by nearly a factor of two ([Held
21 and Soden, 2000](#)). The ice-albedo feedback is also strongly positive; a decline in snow
22 cover and sea ice extent would diminish the Earth’s albedo, allowing more solar energy
23 to be retained at the surface ([Holland and Bitz, 2003](#); [Rind et al., 1995](#)). A final example
24 of a climate feedback involves the effects of changing cloud cover in a warming
25 atmosphere. Models disagree on the magnitude and even the sign of this feedback on
26 surface temperatures ([Soden and Held, 2006](#)).

10.3.2.3 Metrics of Potential Climate Change

27 Two metrics frequently used to estimate the potential climate effect of some perturbation
28 such as a change in greenhouse gas concentration are: (1) radiative forcing; and (2) global
29 warming potential (GWP). These metrics differ in a fundamental way as described below.

30 Radiative forcing is a change in the radiative balance at a particular level of the
31 atmosphere or at the surface when a perturbation is introduced in the earth-atmosphere-
32 ocean system. In the global mean, radiative forcing of greenhouse gases at the tropopause
33 (top of the troposphere) is roughly proportional to the surface temperature response
34 ([Hansen et al., 2005](#); [NRC, 2005](#)). It thus provides a useful metric for policymakers for

1 assessing the response of the earth's surface temperature to a given change in the
2 concentration of a greenhouse gas. Positive values of radiative forcing indicate warming
3 in a test case relative to the control; negative values indicate cooling. The units of
4 radiative forcing are energy flux per area, or W/m^2 .

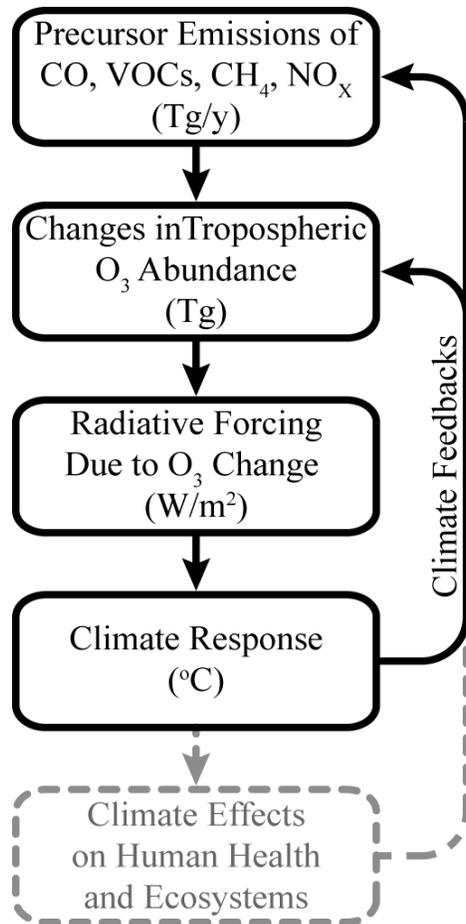
5 Radiative forcing requires just a few model years to calculate, and it shows consistency
6 from model to model. However, radiative forcing does not take into account the climate
7 feedbacks that could amplify or dampen the actual surface temperature response,
8 depending on region. Quantifying the change in surface temperature requires a climate
9 simulation in which all important feedbacks are accounted for. As some of these
10 processes are not well understood, the surface temperature response to a given radiative
11 forcing can be highly uncertain and can vary greatly among models and even from region
12 to region within the same model.

13 GWP indicates the integrated radiative forcing over a specified period (usually 100 years)
14 from a unit mass pulse emission of a greenhouse gas or its precursor, and is reported as
15 the magnitude of this radiative forcing relative to that of CO_2 . GWP is most useful for
16 comparing the potential climate effects of long-lived gases, such as N_2O or CH_4 . Since
17 tropospheric O_3 has a lifetime on the order of weeks to months, GWP is not seen as a
18 valuable metric for quantifying the importance of O_3 on climate ([Forster et al., 2007](#)).
19 Thus, this assessment focuses on radiative forcing as the metric of climate influence
20 resulting from changes in tropospheric O_3 .

10.3.2.4 Tropospheric Ozone as a Greenhouse Gas

21 Tropospheric O_3 differs in important ways from other greenhouse gases. It is not emitted
22 directly, but is produced through photochemical oxidation of CO , CH_4 , and nonmethane
23 volatile organic compounds (VOCs) in the presence of nitrogen oxide radicals
24 ($NO_x = NO + NO_2$; see Chapter 3, Section 3.2 for further details on the chemistry of O_3
25 formation). It is also supplied by vertical transport from the stratosphere. The lifetime of
26 O_3 in the troposphere is typically a few weeks, resulting in an inhomogeneous
27 distribution that varies seasonally; the distribution of the long-lived greenhouse gases like
28 CO_2 and CH_4 are much more uniform. The longwave radiative forcing by O_3 is mainly
29 due to absorption in the $9.6 \mu m$ window, where absorption by water vapor is weak. It is
30 therefore less sensitive to local humidity than the radiative forcing by CO_2 or CH_4 , for
31 which there is much more overlap with the water absorption bands ([Lenoble, 1993](#)). And
32 unlike other major greenhouse gases, O_3 absorbs in the shortwave as well as the
33 longwave part of the spectrum.

1 [Figure 10-2](#) shows the main steps involved in the influence of tropospheric O₃ on climate.
2 Emissions of O₃ precursors including CO, VOCs, CH₄, and NO_x lead to production of
3 tropospheric O₃. A change in the abundance of tropospheric O₃ perturbs the radiative
4 balance of the atmosphere, an effect quantified by the radiative forcing metric. The earth-
5 atmosphere-ocean system responds to the radiative forcing with a climate response,
6 typically expressed as a change in surface temperature. Finally, the climate response
7 causes downstream climate-related health and ecosystem effects, such as redistribution of
8 diseases or ecosystem characteristics due to temperature changes. Feedbacks from both
9 the climate response and downstream effects can, in turn, affect the abundance of
10 tropospheric O₃ and O₃ precursors through multiple mechanisms. Direct feedbacks are
11 discussed further in Section [10.3.3.4](#); the downstream climate effects and their feedbacks
12 are extremely complex and outside the scope of this assessment.

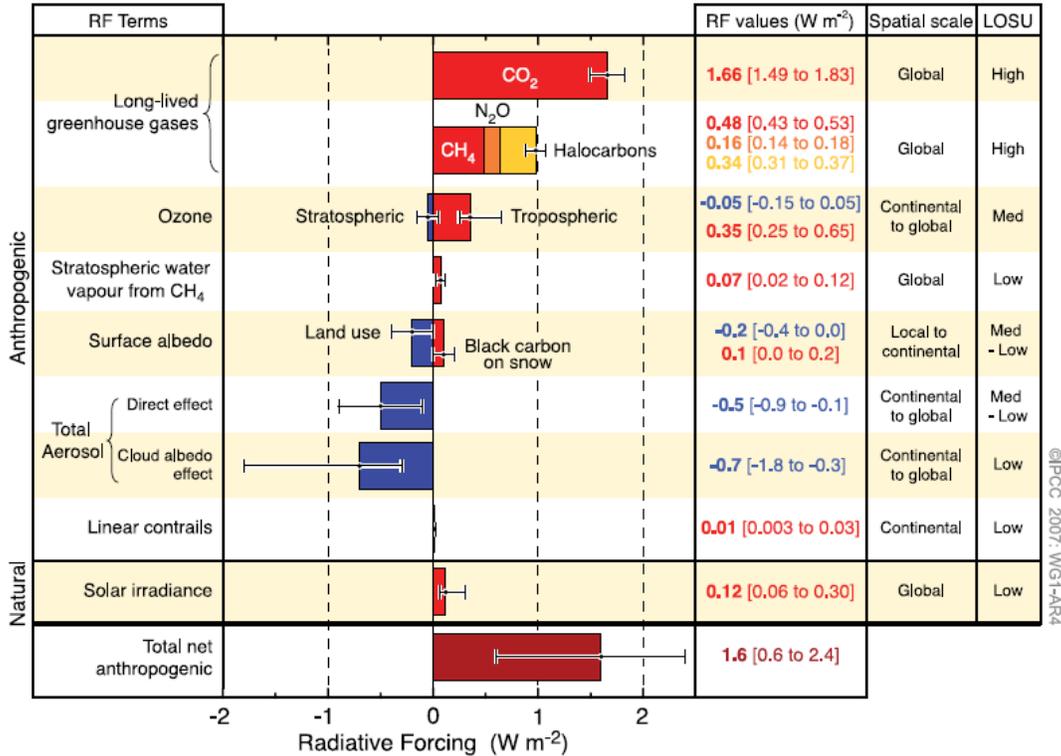


Note: Figure includes the relationship between precursor emissions, changes in tropospheric ozone abundance, radiative forcing, climate response, and climate effects. Units shown are those typical for each quantity illustrated. Feedbacks from both the climate response and climate effects can, in turn, affect the abundance of tropospheric ozone and ozone precursors through multiple feedback mechanisms. Climate effects and their feedbacks are deemphasized in the figure since these downstream effects are extremely complex and outside the scope of this assessment.

Figure 10-2 Schematic illustrating the effects of tropospheric ozone on climate.

1 The [IPCC \(2007c\)](#) reported a radiative forcing of 0.35 W/m^2 for the change in
 2 tropospheric O_3 since the preindustrial era, ranking it third in importance after the
 3 greenhouse gases CO_2 (1.66 W/m^2) and CH_4 (0.48 W/m^2). [Figure 10-3](#) shows the global
 4 average radiative forcing estimates and uncertainty ranges in 2005 for anthropogenic
 5 CO_2 , CH_4 , O_3 and other important agents and mechanisms. The error bars encompassing
 6 the tropospheric O_3 radiative forcing estimate in the figure range from 0.25 to 0.65 W/m^2 ,
 7 making it relatively more uncertain than the long-lived greenhouse gases.

RADIATIVE FORCING COMPONENTS



Note: Figure shows the typical geographical extent (spatial scale) of the radiative forcing and the assessed level of scientific understanding (LOSU). The net anthropogenic radiative forcing and its range are also shown. These require summing asymmetric uncertainty estimates from the component terms, and cannot be obtained by simple addition. Additional radiative forcing factors not included here are considered to have a very low LOSU.

Source: Reprinted with permission of Cambridge University Press (IPCC, 2007c).

Figure 10-3 Global average radiative forcing (RF) estimates and uncertainty ranges in 2005 for anthropogenic CO₂, CH₄, ozone and other important agents and mechanisms.

10.3.3 Factors that Influence the Effect of Tropospheric O₃ on Climate

1 This section describes the main factors that influence the magnitude of the climate
 2 response to changes in tropospheric O₃. They include: (1) trends in the concentration of
 3 tropospheric O₃; (2) the effect of surface albedo on O₃ radiative forcing; (3) the effect of
 4 vertical distribution on O₃ radiative forcing; (4) feedback factors that can alter the climate
 5 response to O₃ radiative forcing; and (5) the indirect effects of tropospheric O₃ on the
 6 carbon cycle. Trends in stratospheric O₃ may also affect temperatures at the Earth's
 7 surface, but aside from issues relating to stratospheric-tropospheric exchange discussed in
 8 Chapter 3, Section 3.4.1.1, stratospheric O₃ assessment is beyond the scope of this
 9 document.

10.3.3.1 Trends in the Concentration of Tropospheric Ozone

1 To first order, the effect of tropospheric O₃ on global surface temperature is proportional
2 to the change in tropospheric O₃ concentration. The earth's surface temperatures are most
3 sensitive to O₃ perturbations in the mid to upper troposphere. This section therefore
4 focuses mainly on observed O₃ trends in the free troposphere or in regions far from O₃
5 sources, where a change in O₃ concentrations may indicate change throughout the
6 troposphere. Data from ozonesondes, mountaintops, and remote surface sites are
7 discussed, as well as satellite data.

Observed Trends in Ozone since the Preindustrial Era

8 Measurements of O₃ at two European mountain sites dating from the late 1800s to early
9 1900s show values at about 10 ppb, about one-fifth the values observed today at similar
10 sites ([Pavelin et al., 1999](#); [Marenco et al., 1994](#)). The accuracy of these early
11 measurements is questionable however, in part because they exhibit O₃ concentrations
12 equivalent to or only a couple of parts per billion greater than those observed at nearby
13 low-altitude sites during the same time period ([Mickley et al., 2001](#); [Volz and Kley,
14 1988](#)). A larger vertical gradient in tropospheric O₃ would be expected because of its
15 stratospheric source and its longer lifetime aloft. In another study, [Staehelin et al. \(1994\)](#)
16 revisited observations made in the Swiss mountains during the 1950s and found a
17 doubling in O₃ concentrations from that era to 1989-1991.

18 Routine observations of O₃ in the troposphere began in the 1970s with the use of balloon-
19 borne ozonesondes, but even this record is sparse. Trends from ozonesondes have been
20 highly variable and dependent on region ([Logan et al., 1999](#)). Over most sites in the U.S.,
21 ozonesondes reveal little trend. Over Canada, observations show a decline in O₃ between
22 1980 and 1990, then a rebound in the following decade ([Tarasick et al., 2005](#)).

23 Ozonesondes over Europe give a mixed picture. European ozonesondes showed increases
24 in the 1970s and 1980s, with smaller increases or even declines since then ([Oltmans et
25 al., 2006](#); [Logan et al., 1999](#)). Over Japan, O₃ in the lower troposphere increased about
26 0.2-0.4 ppb/year during the 1990s ([Naja and Akimoto, 2004](#)).

27 Ground-based measurements in remote regions provide a record of tropospheric O₃, but
28 like ozonesonde data are sparse before the 1970s. Springtime O₃ observations from
29 several mountain sites in the western U.S. show a positive trend of about of 0.5-
30 0.7 ppb/year since the 1980s ([Cooper et al., 2010](#); [Jaffe et al., 2003](#)). Ship-borne O₃
31 measurements for the time period 1977 to 2002 indicate increases of 0.1-0.7 ppb/year
32 over much of the Atlantic south of 40°N, but no appreciable change north of 40°N
33 ([Lelieveld et al., 2004](#)). The lack of trend for the North Atlantic would seem at odds with

1 O₃ observations at Mace Head (53°N) on the west coast of Ireland, which show a
2 significant positive trend of about 0.5 ppb/year from 1987 to 2003 ([Simmonds et al.,
3 2004](#)). Over Japan, O₃ at a remote mountain site has increased 1 ppb/year from 1998 to
4 2003 ([Tanimoto, 2009](#)), a rate more than double that recorded by ozonesondes in the
5 lower troposphere over Japan during the 1990s ([Naja and Akimoto, 2004](#)). At Zugspitze,
6 a mountain site in Germany, O₃ increased by 12% per decade during the 1970s and
7 1980s, consistent with European ozonesondes ([Oltmans et al., 2006](#)). Since then, O₃
8 continues to increase at Zugspitze, but more slowly. What little data exist for the
9 Southern Hemisphere point to measurable increases in tropospheric O₃ in recent decades,
10 as much as ~15% at Cape Grim in the 1989-2004 time period ([Oltmans et al., 2006](#)).

11 The satellite record is now approaching a length that can be useful for diagnosing trends
12 in the total tropospheric O₃ column (details on the use of satellites to measure
13 tropospheric O₃ are covered in Chapter 3, Section 3.5.5.5). In contrast to the surface data
14 from ships, tropospheric O₃ columns from the Total Ozone Mapping Spectrometer
15 (TOMS) show no trend over the tropical Atlantic for the period 1980-1990 ([Thompson
16 and Hudson, 1999](#)). Over the Pacific, a longer, 25 year record of TOMS data again
17 reveals no trend over the tropics, but shows increases in tropospheric column O₃ of about
18 2-3 Dobson Units (DU)¹ at mid-latitudes in both hemispheres ([Ziemke et al., 2005](#)).

19 Interpreting these recent trends in tropospheric O₃ is challenging. The first difficulty is
20 reconciling apparently contradictory trends in the observations, e.g., over tropical oceans.
21 A second difficulty is that the O₃ trends depend on several factors, not all of which can be
22 well characterized. These factors include (1) trends in emissions of O₃ precursors,
23 (2) variation in the stratospheric source of O₃, (3) changes in solar radiation resulting
24 from stratospheric O₃ depletion, and (4) trends in tropospheric temperatures ([Fusco and
25 Logan, 2003](#)). Recent positive trends in the western U.S. and over Japan are consistent
26 with the rapid increase in emissions of O₃ precursors from mainland Asia and transport of
27 pollution across the Pacific ([Cooper et al., 2010](#); [Tanimoto, 2009](#)). The satellite trends
28 over the northern mid-latitudes are consistent with this picture as well ([Ziemke et al.,
29 2005](#)). Increases in tropospheric O₃ in the Southern Hemisphere are also likely due to
30 increased anthropogenic NO_x emissions, especially from biomass burning ([Fishman et
31 al., 1991](#)). Recent declines in summertime O₃ over Europe can be partly explained by
32 decreases in O₃ precursor emissions there ([Jonson et al., 2005](#)), while springtime
33 increases at some European sites are likely linked to changes in stratospheric dynamics
34 ([Ordonez et al., 2007](#)). Over Canada, [Fusco and Logan \(2003\)](#) found that O₃ depletion in

¹ The Dobson Unit is a typical unit of measure for the total O₃ in a vertical column above the Earth's surface. One DU is equivalent to the amount of O₃ that would exist in a 1 μm (10⁻⁵ m) thick layer of pure O₃ at standard temperature (0°C) and pressure (1 atm), and corresponds to a column of O₃ containing 2.69 × 10²⁰ molecules/m². A typical value for the amount of ozone in a column of the Earth's atmosphere, although highly variable, is 300 DU and approximately 10% (30 DU) of that exists in the troposphere at mid latitudes.

1 the lowermost stratosphere may have reduced the stratospheric flux of O₃ into the
2 troposphere by as much as 30% from the early 1970s to the mid 1990s, consistent with
3 the trends in ozonesondes there.

Calculation of Ozone Trends for the Recent Past

4 Simulations of trends in tropospheric O₃ provide a means for testing current knowledge
5 of O₃ processes and predicting with greater confidence trends in future O₃ concentrations.
6 Time-dependent emission inventories of O₃ precursors have also been developed for
7 1850-2000 ([Lamarque et al., 2010](#)) and for 1890-1990 ([VanAardenne et al., 2001](#)). These
8 inventories allow for the calculation of changing O₃ concentration over time.

9 One recent multi-model study calculated an increase in the O₃ concentration since
10 preindustrial times of 8-14 DU, or about 30-70% ([Gauss et al., 2006](#)). The large spread in
11 modeled estimates reveals the limitations in knowledge of processes in the pristine
12 atmosphere. Models typically overestimate the late nineteenth and early twentieth century
13 observations available in surface air and at mountain sites by 50-100% ([Lamarque et al.,
14 2005](#); [Shindell et al., 2003](#); [Mickley et al., 2001](#); [Kiehl et al., 1999](#)). Reconciling the
15 differences between models and measurements will require more accurate simulation of
16 the natural sources of O₃ ([Mickley et al., 2001](#)) and/or implementation of novel sinks
17 such as bromine radicals, which may reduce background O₃ in the pristine atmosphere by
18 as much as 30% ([Yang et al., 2005c](#)).

19 For the more recent past (since 1970), application of time-dependent emissions reveals an
20 equatorward shift in the distribution of tropospheric O₃ in the Northern Hemisphere due
21 to the industrialization of societies at low-latitudes ([Lamarque et al., 2005](#); [Berntsen et
22 al., 2000](#)). By constraining a model with historical (1950s-2000) observations, [Shindell
23 and Faluvegi \(2002\)](#) calculated a large increase of 8.2 DU in tropospheric O₃ over
24 polluted continental regions since 1950. This trend is not captured in standard chemistry
25 models, but is consistent with the change in tropospheric O₃ since preindustrial times
26 implied by the observations from the late 1800s ([Pavelin et al., 1999](#); [Marenco et al.,
27 1994](#)).

10.3.3.2 The Effect of Surface Albedo on Ozone Radiative Forcing

28 The Earth's surface albedo plays a role in O₃ radiative forcing. Through most of the
29 troposphere, absorption of incoming shortwave solar radiation by O₃ is small relative to
30 its absorption of outgoing longwave terrestrial radiation. However, over surfaces
31 characterized by high albedo (e.g., over snow, ice, or desert sand), incoming radiation is

1 more likely to be reflected than over darker surfaces, and the probability that O₃ will
2 absorb shortwave solar radiation is therefore larger. In other words, energy that would
3 otherwise return to space may instead be retained in the atmosphere. Several studies have
4 shown that transport of O₃ to the Arctic from mid-latitudes leads to radiative forcing
5 estimates greater than 1.0 W/m² in the region, especially in summer ([Shindell et al., 2006](#);
6 [Liao et al., 2004b](#); [Mickley et al., 1999](#)). Both the high surface albedo of the Arctic and
7 the large solar zenith angles there (which increase the path length of incoming sunlight)
8 lead to strong shortwave forcing in the region. Because the Arctic is especially sensitive
9 to radiative forcing through the ice-albedo feedback, the large contribution in the
10 shortwave solar spectrum to the total radiative forcing in the region may be important.

10.3.3.3 The Effect of Vertical Distribution on Ozone Radiative Forcing

11 In the absence of feedbacks, O₃ increments near the tropopause produce the largest
12 increases in surface temperature ([Lacis et al., 1990](#); [Wang et al., 1980](#)). This is a result of
13 the colder temperature of the tropopause relative to the rest of the troposphere and
14 stratosphere. Since radiation emitted by the atmosphere is approximately proportional to
15 the fourth power of its temperature¹, the colder the added O₃ is relative to the earth's
16 surface, the weaker the radiation emitted and the greater the "trapping" of longwave
17 radiation in the troposphere.

10.3.3.4 Feedback Factors that Alter the Climate Response to Changes in Ozone Radiative Forcing

18 Estimates of radiative forcing provide a first-order assessment of the effect of
19 tropospheric O₃ on climate. In the atmosphere, climate feedbacks and transport of heat
20 alter the sensitivity of Earth's surface temperature to addition of tropospheric O₃.
21 Assessment of the full climate response to increases in tropospheric O₃ requires use of a
22 climate model to simulate these interactions.

23 Due to its short lifetime, O₃ is heterogeneously distributed through the troposphere. Sharp
24 horizontal gradients exist in the radiative forcing of O₃, with the greatest radiative forcing
25 since preindustrial times occurring over the northern mid-latitudes (more on this in
26 Section [10.3.5](#) and Section [10.3.6](#)). If climate feedbacks are particularly powerful, they
27 may obscure or even erase the correlation between regional radiative forcing and climate

¹ As described by the Stefan-Boltzmann law, an ideal blackbody--which the atmosphere approximates--absorbs at all wavelengths and re-radiates proportional to the fourth power of its temperature.

1 response ([Harvey, 2004](#); [Boer and Yu, 2003](#)). The transport of heat through the
2 atmosphere, though not technically a feedback, may also weaken the correlation between
3 forcing and climate response. Several model studies have reported that the horizontal
4 pattern of surface temperature response from 2000-2100 trends in predicted short-lived
5 species (including O₃) closely matches the pattern from the trends in the long-lived
6 greenhouse gases over the same time period ([Levy et al., 2008](#); [Shindell et al., 2008](#);
7 [Shindell et al., 2007](#)). This correspondence occurs even though the patterns of radiative
8 forcing for the short-lived and long-lived species differ substantially. In a separate paper,
9 [Shindell et al. \(2007\)](#) found that Arctic temperatures are especially sensitive to the mid-
10 latitude radiative forcing from tropospheric O₃.

11 Other studies have found that the signature of warming due to tropospheric O₃ does show
12 some consistency with the O₃ radiative forcing. For example, [Mickley et al. \(2004\)](#)
13 examined the change in O₃ since preindustrial times and found greater warming in the
14 Northern Hemisphere than in the Southern Hemisphere (+0.4°C versus +0.2°C), as well
15 as higher surface temperatures downwind of Europe and Asia and over the North
16 American interior in summer. For an array of short-lived species including O₃, [Shindell
17 and Faluvegi \(2009\)](#) found that radiative forcing applied over northern mid-latitudes yield
18 more localized responses due to local cloud, water vapor, and albedo feedbacks than
19 radiative forcing applied over the tropics.

20 Climate feedbacks can also alter the sensitivity of surface temperature to the vertical
21 distribution of tropospheric O₃. The previous section (Section [10.3.3.3](#)) described the
22 greater effect of O₃ added to the upper troposphere (near the tropopause) on radiative
23 forcing, relative to additions in the mid- to lower troposphere. However, warming
24 induced by increased O₃ in the upper troposphere could stabilize the atmosphere to some
25 extent, limiting the transport of heat to the Earth's surface and mitigating the effect of the
26 added O₃ on surface temperature ([Joshi et al., 2003](#); [Christiansen, 1999](#)). [Hansen et al.
27 \(1997\)](#) determined that allowing cloud feedbacks in a climate model meant that O₃
28 enhancements in the mid-troposphere had the greatest effect on surface temperature.

29 Finally, climate feedbacks can amplify or diminish the climate response of one
30 greenhouse gas relative to another. For example, [Mickley et al. \(2004\)](#) found a greater
31 temperature response to CO₂ radiative forcing than to an O₃ radiative forcing of similar
32 global mean magnitude, due in part to the relatively weak ice-albedo feedback for O₃.
33 Since CO₂ absorbs in the same bands as water vapor, CO₂ radiative forcing saturates in
34 the middle troposphere and is also shifted toward the drier poles. A poleward shift in
35 radiative forcing amplifies the ice-albedo feedback in the case of CO₂, and the greater
36 mid-troposphere radiative forcing allows for greater surface temperature response,
37 relative to that for O₃.

10.3.3.5 Indirect Effects of Tropospheric Ozone on the Carbon Cycle

1 A proposed indirect effect of tropospheric O₃ on climate involves the carbon cycle. By
2 directly damaging plant life in ways discussed in Chapter 9, increases in tropospheric O₃
3 may depress the land-carbon sink of CO₂, leading to accumulation of CO₂ in the
4 atmosphere and ultimately warming of the Earth's surface. [Sitch et al. \(2007\)](#) calculated
5 that this indirect warming effect of O₃ on climate has about the same magnitude as the O₃
6 direct effect. Their results suggest a doubled sensitivity of surface temperatures to O₃
7 radiative forcing, compared to current model estimates.

10.3.4 Competing Effects of Ozone Precursors on Climate

8 Changes in O₃ precursors can affect the radiative balance of the atmosphere through
9 multiple (and sometimes competing) mechanisms. For example, the O₃ precursor CH₄ is
10 itself a powerful greenhouse gas. O₃ and its other precursors also exert a strong control on
11 the oxidizing capacity of the troposphere, and so can affect the lifetime of gases such as
12 CH₄ ([Derwent et al., 2001](#)). For example, an increase in CO or VOCs would lead to a
13 decrease in hydroxyl (OH) concentrations. Since OH is a major sink for CH₄, a decline in
14 OH would lengthen the CH₄ lifetime, enhance the CH₄ concentration, and amplify
15 surface warming. A rise in NO_x emissions, on the other hand, could lead to an increase in
16 OH in certain locations, shortening the CH₄ lifetime and causing surface cooling
17 ([Fuglestedt et al., 1999](#)). O₃ can itself generate OH through (1) photolysis leading to
18 excited oxygen atoms followed by reaction with water vapor and (2) reaction with HO₂.

19 [Figure 10-4](#) shows the radiative forcing associated with a suite of anthropogenic
20 emissions, including O₃ precursors ([IPCC, 2007b](#)). The emission-based radiative forcing
21 for CH₄, which includes the CH₄ effect on O₃ production, is +0.9 W/m², or nearly double
22 that of the CH₄ abundance-based radiative forcing shown in [Figure 10-3](#). [Figure 10-4](#) also
23 shows a warming from anthropogenic CO and VOC emissions of +0.27 W/m² and a net
24 cooling of -0.21 W/m² for NO_x emissions. The net cooling for NO_x occurs mainly due to
25 the links between NO_x and CH₄. Consistent with these results, [Shindell and Faluvegi](#)
26 [\(2009\)](#) calculated positive (+0.25 W/m²) radiative forcing from the increase in
27 anthropogenic emissions of CO and VOCs since preindustrial times, as well as for CH₄
28 (+1 W/m²). In contrast, [Shindell and Faluvegi \(2009\)](#) found negative (-0.29 W/m²)
29 radiative forcing from anthropogenic emissions of NO_x. Other studies have found a near
30 cancellation of the positive O₃ radiative forcing and the negative CH₄ radiative forcing
31 that arise from an incremental increase in anthropogenic NO_x emissions ([Naik et al.,](#)
32 [2005](#); [Fiore et al., 2002](#); [Fuglestedt et al., 1999](#)). The net effect of aircraft NO_x on
33 climate is especially complex ([Isaksen et al., 2001](#); [Wild et al., 2001](#)). [Stevenson \(2004\)](#)

1 calculated that aircraft NO_x leads to short-term net warming via O₃ production in the cool
2 upper troposphere, but long-term net cooling because of CH₄ loss.

3 OH production from O₃ precursors can also affect regional sulfate air quality and climate
4 forcing by increasing gas-phase oxidation rates of SO₂. Using the A1B scenario in the
5 IPCC AR4, [Unger \(2006\)](#) reported that by 2030, enhanced OH from the A1B O₃
6 precursors may increase surface sulfate aerosol concentrations by up to 20% over India
7 and China, relative to the present-day, with a corresponding increase in radiative cooling
8 over these regions. In this way, O₃ precursors may impose an indirect cooling via sulfate
9 ([Unger, 2006](#)).

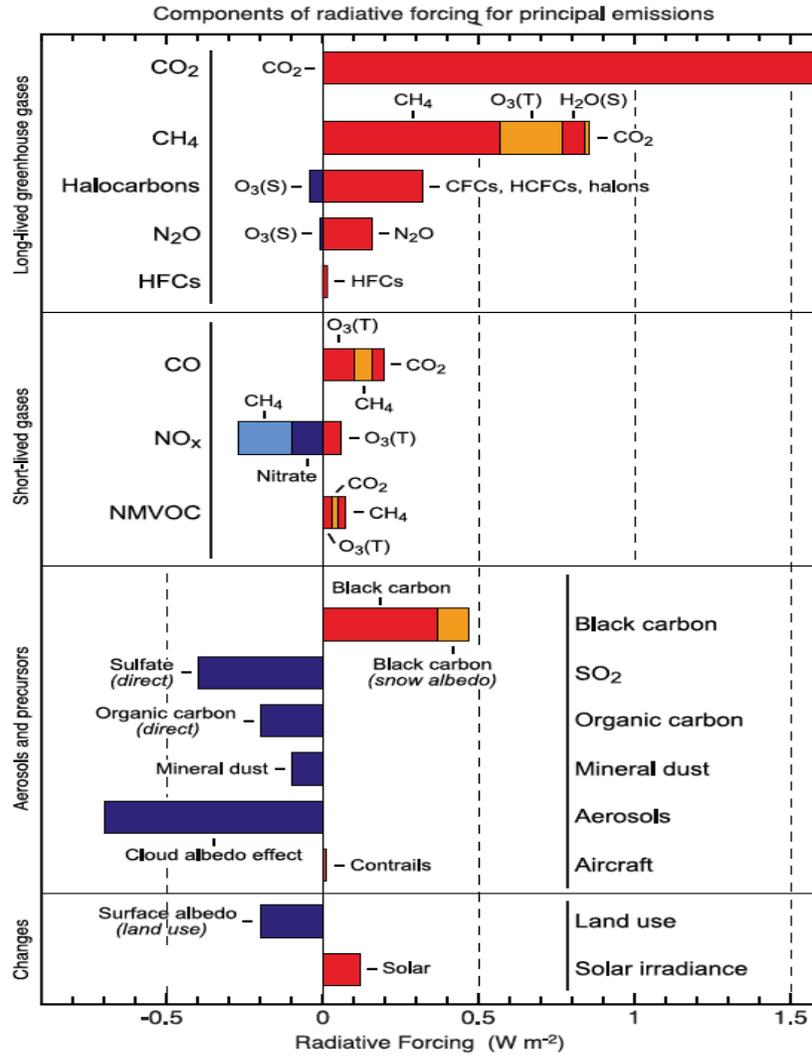
10 Taken together, these results point out the need for careful assessment of net radiative
11 forcing involving multiple pollutants in developing climate change policy ([Unger et al.,
12 2008](#)). Many studies point to CH₄ as a particularly attractive target for emissions control
13 since CH₄ is itself an important precursor of O₃ ([West et al., 2007](#); [Fiore et al., 2002](#)).
14 [Fiore et al. \(2002\)](#) found that reducing anthropogenic CH₄ emissions by 50% would lead
15 to a global negative (-0.37 W/m²) radiative forcing, mostly from CH₄. In later research,
16 [Fiore et al. \(2008\)](#) reported that CH₄ reductions would most strongly affect tropospheric
17 O₃ column amounts in regions of strong downwelling from the upper troposphere
18 (e.g., around 30°N) and in regions of NO_x-saturated conditions.

19 The magnitude of the radiative forcing from the change in tropospheric O₃ since the
20 preindustrial era is uncertain. This uncertainty derives in part from the scarcity of early
21 measurements and in part from limited knowledge regarding processes in the natural
22 atmosphere. As noted previously, the IPCC AR4 reports a radiative forcing of 0.35 W/m²
23 from the change in tropospheric O₃ since 1750 ([Forster et al., 2007](#)), ranking it third in
24 importance behind the greenhouse gases CO₂ and CH₄. The O₃ radiative forcing could, in
25 fact, be as large as 0.7 W/m², if reconstructions of preindustrial and mid-20th century O₃
26 based on the measurement record are valid ([Shindell and Faluvegi, 2002](#); [Mickley et al.,
27 2001](#)). In any event, [Unger et al. \(2010\)](#) showed that present-day O₃ radiative forcing can
28 be attributed to emissions from many economic sectors, including on-road vehicles,
29 household biofuel, power generation, and biomass burning. As much as one-third of the
30 radiative forcing from the 1890 to 1990 change in tropospheric O₃ could be due to
31 increased biomass burning ([Ito et al., 2007a](#)).

32 These calculated radiative forcing estimates can be compared to those obtained from
33 satellite data. Using data from TOMS, [Worden et al. \(2008\)](#) estimated a reduction in
34 clear-sky outgoing longwave radiation of 0.48 W/m² by O₃ in the upper troposphere over
35 oceans in 2006. This radiative forcing includes contributions from both anthropogenic
36 and natural O₃. Assuming that the concentration of O₃ has roughly doubled since
37 preindustrial times ([Gauss et al., 2006](#)), the total O₃ radiative forcing estimated with

1
2

TOMS is consistent with that obtained from models estimating just the anthropogenic contribution.



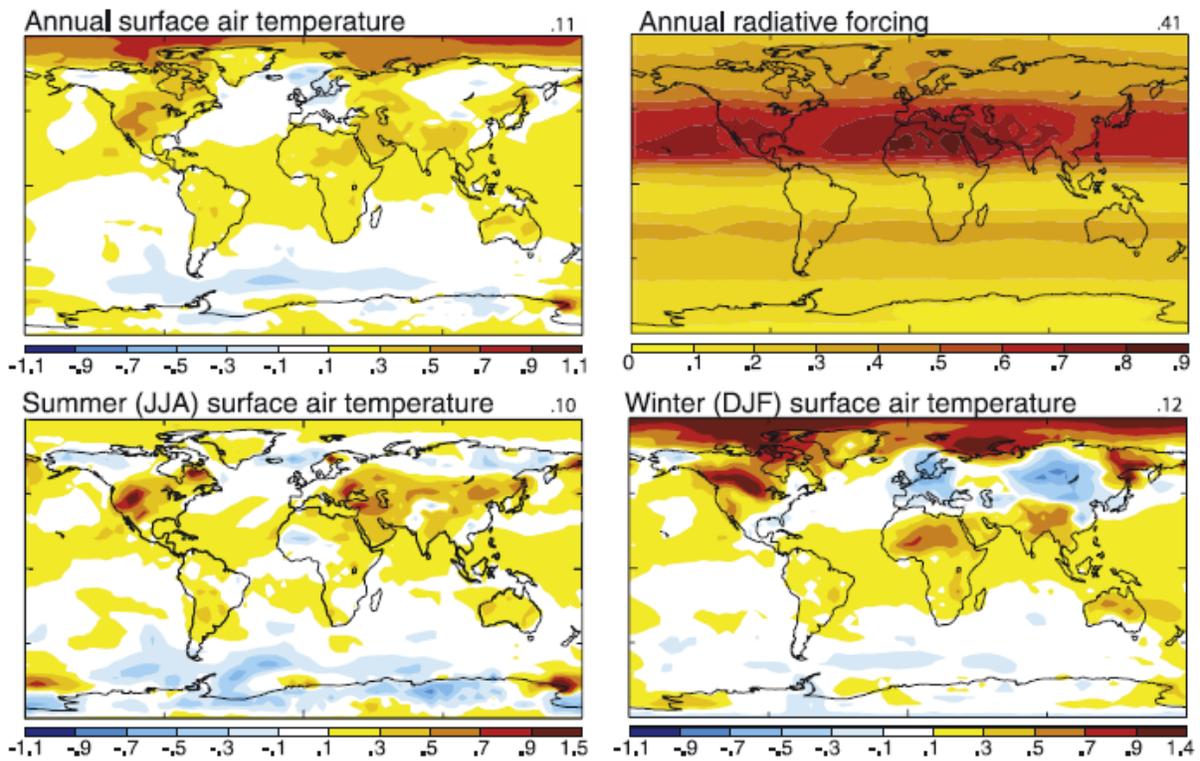
Note: Values represent radiative forcing in 2005 due to emissions and changes since 1750. (S) and (T) next to gas species represent stratospheric and tropospheric changes, respectively. Source: Reprinted with permission of Cambridge University Press ([IPCC, 2007b](#)).

Figure 10-4 Components of radiative forcing for emissions of principal gases, aerosols, aerosol precursors, and other changes.

10.3.5 Calculating Radiative Forcing and Climate Response to Past Trends in Tropospheric Ozone

1 Calculation of the climate response to the O₃ radiative forcing is challenging due to
2 complexity of feedbacks, as mentioned in Section [10.3.2.2](#) and Section [10.3.3.4](#). In their
3 modeling study, [Mickley et al. \(2004\)](#) reported a global mean increase of 0.28°C since
4 preindustrial times, with values as large as 0.8°C in continental interiors. For the time
5 period since 1870, [Hansen et al. \(2005\)](#) estimated a much smaller increase in global mean
6 surface temperature (0.11°C), but they implemented 1880s anthropogenic emissions in
7 their base simulation and also took into account trends in both stratospheric and
8 tropospheric O₃. The modeled decline of lower stratospheric O₃, especially over polar
9 regions, cooled surface temperatures in this study, counteracting the warming effect of
10 increasing tropospheric O₃.

11 [Figure 10-5](#) shows the [Hansen et al. \(2005\)](#) results as reported in [Shindell et al. \(2006\)](#). In
12 that figure, summertime O₃ has the largest radiative effect over the continental interiors
13 of the Northern Hemisphere. [Shindell et al. \(2006\)](#) estimated that the change in
14 tropospheric O₃ over the 20th century could have contributed about 0.3°C to annual mean
15 Arctic warming and as much as 0.4-0.5°C during winter and spring. Over eastern China,
16 [Chang et al. \(2009\)](#) calculated a surface temperature increase of 0.4°C to the 1970-2000
17 change in tropospheric O₃. It is not clear, however, to what degree regional changes in O₃
18 concentration influenced this response, as opposed to more global changes.



Note: Figure includes the input radiative forcing (W/m^2), as computed by the NASA GISS chemistry-climate model. Values are surface temperature trends for the annual average (top left), June–August (bottom left), and December–February (bottom right) and annual average tropopause instantaneous radiative forcing from 1880 to 1990 (top right). Temperature trends greater than about $0.1^{\circ}C$ are significant over the oceans, while values greater than $0.3^{\circ}C$ are typically significant over land, except for northern middle and high latitudes during winter where values in excess of about $0.5^{\circ}C$ are significant. Values in the top right corner give area-weighted global averages in the same units as the plots.

Source: Reprinted with permission of American Geophysical Union ([Shindell et al., 2006](#)).

Figure 10-5 Ensemble average 1900-2000 radiative forcing and surface temperature trends ($^{\circ}C$ per century) in response to tropospheric ozone changes.

10.3.6 Calculating Radiative Forcing and Climate Response to Future Trends in Tropospheric Ozone

- 1 Future trends in tropospheric O_3 concentrations depend in large part on what pathways in
- 2 energy technology the world's societies will follow in coming decades. The trends in O_3
- 3 will also depend on the changes in a suite of climate-sensitive factors, such as the water
- 4 vapor content of the atmosphere. This section describes the following issues:
- 5 (1) projected trends in the anthropogenic emissions of O_3 precursors; (2) the effects of
- 6 these emissions on the tropospheric O_3 concentrations; (3) the effects of changing climate

1 on tropospheric O₃; and (4) radiative forcing and climate response to 21st century trends
2 in tropospheric O₃.

10.3.6.1 Emissions of Anthropogenic Ozone Precursors Across the 21st Century

3 The IPCC SRES effort devised scenarios for short-lived O₃ precursors as well as the
4 well-mixed greenhouse gases including NO_x, CO, and VOCs ([IPCC, 2000](#)). Using the
5 IMAGE socioeconomic model, [Streets et al. \(2004\)](#) provided speciation for NO_x and
6 VOCs and allocated the trends in emissions over 17 regions and 8 economic sectors for
7 the 2000-2050 time period. The worst-case IPCC scenario, A2, features continued
8 dependence on fossil fuels, rapid population growth, and little sharing of technology
9 between developed and developing nations. By 2100 in this scenario, global NO_x, CO
10 and CH₄ emissions increase by a factor of 3.5, 2.6, and 2.9, respectively, relative to 2000
11 ([IPCC, 2000](#)). Most of these increases in emissions occur over developing countries. For
12 example over Asia, NO_x emissions in the A2 scenario increase by more than a factor of
13 four by 2100. The more moderate A1B scenario has global NO_x and CO emissions
14 increasing by 25% and 90%, respectively by 2100, but global CH₄ emissions decreasing
15 by 10%. In the B1 scenario, with its emphasis on clean and efficient technologies, global
16 emissions of NO_x, CO, and CH₄ all decrease by 2100 relative to the present day (-40%,
17 -60%, and -30%, respectively).

18 Other emissions scenarios have been recently developed to describe trends in the short-
19 term (up to 2030). The Current Legislation (CLE) scenario provides trends consistent
20 with existing air quality regulations; the Maximum Feasible Reduction (MFR) scenario
21 seeks to reduce emissions of O₃ precursors to the maximum extent possible. Emission
22 source changes relative to the present day for CLE, MFR, and A2 are given in [Stevenson
23 et al. \(2006\)](#).

24 For the Fifth Assessment Report (IPCC AR5), a new set of climate futures has been
25 developed: the Representative Concentration Pathways (RCPs) ([Moss et al., 2010](#)). The
26 RCPs will explore for the first time approaches to climate change mitigation. The RCPs
27 are designed to achieve radiative forcing targets of 2.6, 4.5, 6.0 and 8.5 W/m² by 2100,
28 and have been designated RCP 2.6, RCP 4.5, RCP 6.0, and RCP 8.5, respectively (RCP
29 2.6 is also known as RCP3-PD.) The trends in O₃ precursors for the RCP scenarios were
30 determined by climate policies implicit in each scenario and by plausible assumptions
31 regarding future air quality regulations. These scenarios were chosen to map the wide
32 range of climate outcomes presented in the literature and represent only four of many
33 possible scenarios that would lead to the specific radiative forcing targets; a wide range

1 of socioeconomic conditions could be consistent with each forcing pathway ([Moss et al.,](#)
2 [2010](#)). Therefore, they should not be interpreted as forecasts of future conditions, but
3 rather as plausible climate and socio-economic futures.

4 Plots and comparisons of the RCP trends are available on the RCP website ([RCP, 2009](#)).
5 In all RCPs, global anthropogenic NO_x emissions decline 30-50% during the 21st century,
6 though RCP 8.5 shows a peak during the 2020s at a value ~15% greater than that of
7 2000. Global anthropogenic VOC and CO emissions are relatively flat during the 2000-
8 2050 time range, and then decline by 30-50% by the end of the century. For CH₄, global
9 mean emission trends for the four RCP projections differ substantially across the 21st
10 century, with RCP 8.5 showing a tripling of emissions by 2100, and RCP 2.6 showing the
11 emissions cut by half in this time range. RCP 4.5 and 6.0 show a peak in CH₄ emissions
12 in the middle of the century before dropping by the end of the century to just below 2000
13 emission levels. All these global trends, however, contain some regional variation. For
14 example, Asian emissions of both NO_x and VOCs show large increases in the near term
15 (2030s to 2050s).

10.3.6.2 Impact of 21st Century Trends in Emissions on Tropospheric Ozone

16 Due to its short lifetime, tropospheric O₃ will respond readily to changes in
17 anthropogenic emissions of its precursors. As shown in [Table 10-1](#), a recent multi-model
18 study found increases in the tropospheric O₃ concentration of 15% and 6% for the IPCC
19 A2 and CLE scenarios respectively for the 2000-2030 time period, and a decrease for the
20 MFR scenario of 5% ([Stevenson et al., 2006](#)). These results indicate that the growth in
21 tropospheric O₃ between 2000 and 2030 could be reduced or even reversed, depending on
22 emission controls. For the relatively moderate A1B emissions scenario over the 2000-
23 2050 time period, [Wu et al. \(2008a\)](#) calculated a change in O₃ concentration of about
24 20%.

25 As noted above, the RCP scenarios show large variations in their future projections of
26 global mean CH₄ emissions, but mainly declines in the emissions of the other O₃
27 precursors across the 21st century. In one of the first efforts to assess the effect of these
28 emission trends on global O₃ abundances, [Lamarque et al. \(2011\)](#) found that the large
29 CH₄ increase in the RCP 8.5 scenario would drive a 15% enhancement of the
30 tropospheric O₃ burden by 2100, relative to the present-day, leading to a global mean
31 radiative forcing of +0.2 W/m². By contrast, the global O₃ burden would decrease in the
32 other three RCPs, with declines in forcing ranging from -0.07 to -0.2 W/m².

Table 10-1 2000-2030 changes in anthropogenic emissions, and CH₄ and tropospheric ozone concentrations, and the associated tropospheric ozone forcing for three scenarios.

| Scenario | IPCC A2 ^a | Current Legislation (CLE) ^a | Maximum Feasible Reduction (MFR) ^a |
|---|----------------------|--|---|
| Percent change in NO _x emissions | +96% | +18% | -53% |
| Percent change in CO emissions | +62% | -16% | -53% |
| Percent change in CH ₄ concentration | +23% | +19% | 0% |
| Percent change in tropospheric O ₃ concentration | +15% | +6% | -5% |
| Radiative forcing due to O ₃ change ^b (W/m ²) | 0.3 | 0.18 | -0.05 |

^aValues are ensemble means.

^bIncludes radiative forcing due to corresponding CH₄ change.

Source: Adapted from [Stevenson et al. \(2006\)](#).

10.3.6.3 Impact of 21st Century Climate on Tropospheric Ozone

1 For the time period from the 1800s to the present-day, most of the increase in the
 2 concentration of tropospheric O₃ can be traced to changing emissions. Model studies
 3 show that climate change so far has likely had little effect on the tropospheric O₃ ([e.g.,
 4 Grenfell et al., 2001](#)). In the future, however, climate change is expected to bring large
 5 changes in a suite of variables that could affect O₃ production, loss, and transport. For
 6 example, increased water vapor in a warming atmosphere is expected to enhance OH
 7 concentrations, which in remote, NO_x-poor regions will accelerate O₃ loss rates ([Johnson
 8 et al., 1999](#)).

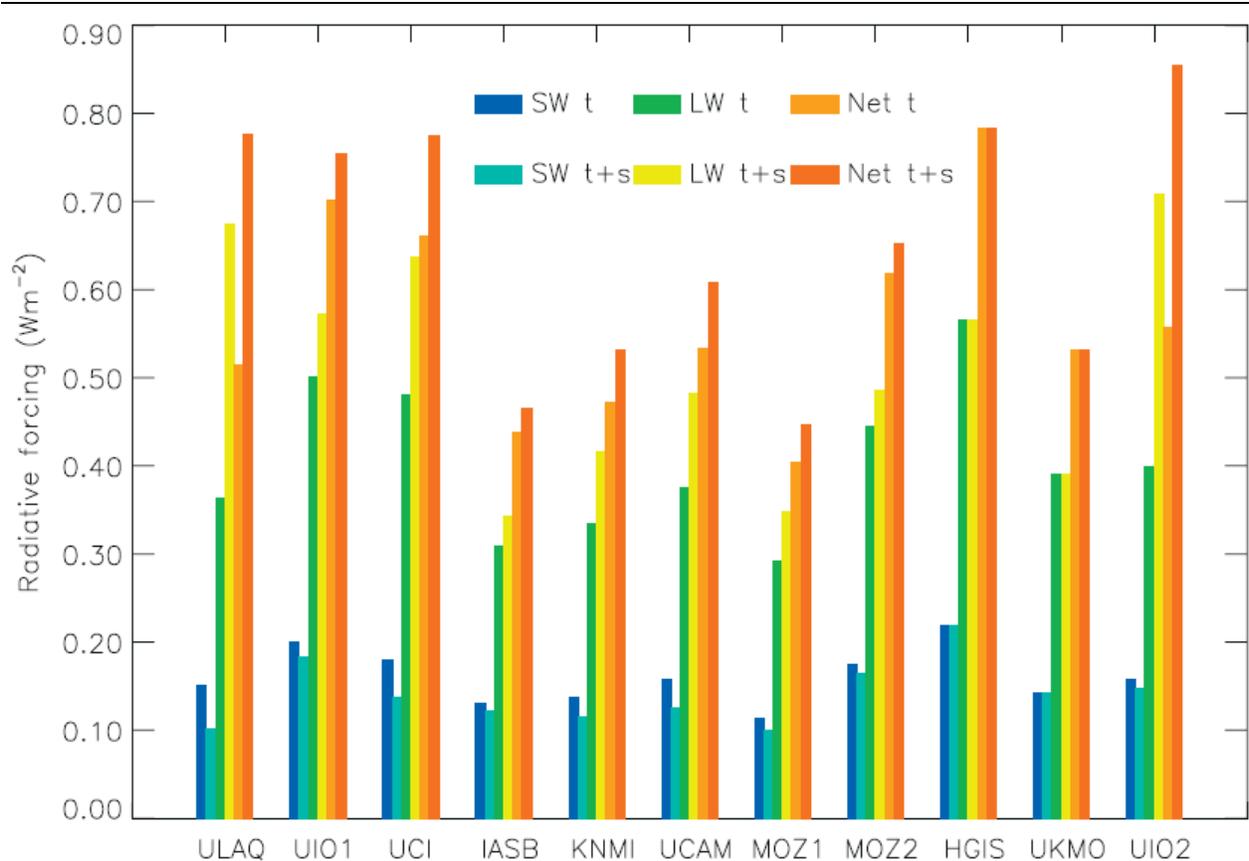
9 In the 2050s A1B climate, [Wu et al. \(2008b\)](#) calculated a 5 ppb decrease in surface O₃
 10 over oceans. A rise in temperatures will also likely promote emissions of isoprene, an
 11 important biogenic precursor of O₃. Model studies have calculated 21st-century increases
 12 in isoprene emissions ranging from 25-50%, depending on climate scenario and time
 13 horizon ([Wu et al., 2008a and references therein](#)). These studies however did not take
 14 into account the effects of changing climate and CO₂ concentration on vegetation extent,
 15 which could have large consequences for biogenic emissions ([Heald et al., 2008](#);
 16 [Sanderson et al., 2003](#)). In any event, enhanced isoprene emissions will increase O₃
 17 concentrations in VOC-limited regions, but decrease O₃ in NO_x-limited regions ([Wu et
 18 al., 2008a](#); [Pyle et al., 2007](#); [Sanderson et al., 2003](#)). Convection frequencies and
 19 lightning flash rates will also likely change in a changing climate, with consequences for
 20 lightning NO_x emissions and O₃ concentrations in the upper troposphere ([Sinha and
 21 Toumi, 1997](#); [Price and Rind, 1994](#)). While [Wu et al. \(2008a\)](#) calculated an increase in
 22 lightning NO_x by 2050 due to enhanced deep convection, [Jacobson and Streets \(2009\)](#)

1 projected a decrease in lightning NO_x due to a declining cloud ice in their future
2 atmosphere. Finally, changes in transport processes will almost certainly accompany
3 global climate change. For the 2050 A1B climate, [Wu et al. \(2008b\)](#) showed that
4 flattening of the meridional temperature gradient in a warming world would lead to
5 slower intercontinental transport of tropospheric O₃. For the A2 climate in 2100, [Zeng
6 and Pyle \(2003\)](#) projected an 80% increase in the flux of stratospheric O₃ into the
7 troposphere, relative to the present-day.

8 Taken together, these climate-driven processes could have appreciable effects on the
9 concentration and distribution of tropospheric O₃. As shown in [Wu et al. \(2008b\)](#), model
10 projections of the change in O₃ concentration due solely to future climate change range
11 from -12% to +3%, depending on the model, scenario, and time horizon.

10.3.6.4 Radiative Forcing and Climate Response from 21st Century Trends in Tropospheric Ozone

12 In the near term (2000-2030), [Stevenson et al. \(2006\)](#) estimated an O₃ forcing of near zero
13 for MFR, 0.18 W/m² for CLE, and +0.3 W/m² for the A2 scenario ([Table 10-1](#)). [Menon et
14 al. \(2008\)](#), following the moderate A1B scenario, calculated a radiative forcing of
15 0.12 W/m² from the 2000-2030 change in tropospheric O₃, about the same as that derived
16 by [Stevenson et al. \(2006\)](#) for the CLE scenario. Over the longer term (2000 to 2100) for
17 the A1B scenario, [Gauss et al. \(2003\)](#) reported large positive radiative forcing (0.40 to
18 0.78 W/m²) due to the change in tropospheric O₃, as shown in [Figure 10-6](#). Normalized
19 radiative forcing for these model calculations fell within a relatively narrow range, 0.032
20 to 0.040 W/m² DU, indicating that the largest uncertainty lies in the model-calculated
21 changes in O₃ concentration. Applying the A2 scenario, [Chen et al. \(2007b\)](#) estimated a
22 global mean radiative forcing of 0.65 W/m² from tropospheric O₃ by 2100, consistent
23 with the [Gauss et al. \(2003\)](#) results. These studies took into account only the effect of
24 changing emissions on tropospheric O₃. In their calculations of the 2000-2100 radiative
25 forcing from O₃ in the A2 scenario, [Liao et al. \(2006\)](#) found that inclusion of climate
26 effects on tropospheric O₃ reduced their radiative forcing estimate by 20%.



Note: Shown are the components of radiative forcing in W/m^2 . SW = shortwave component; LW = longwave component; Net = total forcing; t = tropospheric ozone changes only; and t + s = both tropospheric and stratospheric changes.

Source: Reprinted from [Gauss et al. \(2003\)](#), American Geophysical Union.

Figure 10-6 Global mean radiative forcing estimates calculated by a set of models for the 2000-2100 change in tropospheric ozone.

1 Several studies have included tropospheric O_3 in their investigations of the response in
 2 the future atmosphere to a suite of short-lived species (e.g., [Levy et al., 2008](#); [Shindell et
 3 al., 2008](#); [Shindell et al., 2007](#)). Few studies, however, have calculated the climate
 4 response to changes in tropospheric O_3 alone in the future atmosphere. For the A2
 5 atmosphere, [Chen et al. \(2007b\)](#) estimated a global mean surface temperature increase of
 6 $+0.34^\circ C$ by 2100 in response to the change in O_3 . The largest temperature increases in
 7 this study, as much as $5^\circ C$, occurred over the populous regions of Asia and the Middle
 8 East and downwind of biomass burning regions in South Africa and South America.

10.4 UV-B Related Effects and Tropospheric Ozone

10.4.1 Background

1 UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to
2 break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on
3 living organisms and materials. Atmospheric O₃ plays a crucial role in reducing exposure
4 to solar UV radiation at the Earth's surface. Stratospheric O₃ is responsible for the
5 majority of this shielding effect, as approximately 90% of total atmospheric O₃ is located
6 there over mid-latitudes ([Kar et al., 2010](#); [Crist et al., 1994](#)). Investigation of the
7 supplemental shielding of UV-B radiation provided by tropospheric O₃ is necessary for
8 quantifying UV-B exposure and the incidence of related human health effects, ecosystem
9 effects, and materials damage. The role of tropospheric O₃ in shielding of UV-B radiation
10 is discussed in this section.

10.4.2 Human Exposure and Susceptibility to Ultraviolet Radiation

11 The factors that potentially influence UV radiation exposure were discussed in detail in
12 Chapter 10 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) and are summarized here. These
13 factors included outdoor activity, occupation, age, gender, geography, and protective
14 behavior. Outdoor activity and occupation both influenced the amount of time people
15 spend outdoors during daylight hours, the predominant factor for exposure to solar UV
16 radiation. Age and gender were found to be factors that influence human exposure to UV
17 radiation, particularly by influencing other factors of exposure such as outdoor activity
18 and risk behavior. Studies indicated that females generally spent less time outdoors and,
19 consequently, had lower UV radiation exposure on average compared to males.

20 Geography influences the degree of solar UV flux to the surface, and hence exposure to
21 UV radiation. Higher solar flux at lower latitudes increased the annual UV radiation dose
22 for people living in southern states relative to northern states. Altitude was also found to
23 influence personal exposure to UV radiation. Protective behaviors such as using
24 sunscreen, wearing protective clothing, and spending time in shaded areas were shown to
25 reduce exposure to UV radiation. Given these and other factors that potentially influence
26 UV radiation exposure, the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) listed the following
27 subpopulations potentially at risk for higher exposures to UV radiation:

- 28 ■ Individuals who engage in high-risk behavior (e.g., sunbathing);
- 29 ■ Individuals who participate in outdoor sports and activities;

- 1 ▪ Individuals who work outdoors with inadequate shade (e.g., farmers,
2 construction workers, etc.); and
- 3 ▪ Individuals living in geographic areas with higher solar flux including lower
4 latitudes (e.g., Honolulu, HI) and higher altitudes (e.g., Denver, CO).

5 The risks associated with all these factors are, of course, highly dependent on season and
6 region ([Slaney and Wengraitis, 2006](#)).

10.4.3 Human Health Effects due to UV-B Radiation

7 Chapter 10 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) covered in detail the human health
8 effects associated with solar UV-B radiation exposure. These effects include erythema,
9 skin cancer, ocular damage, and immune system suppression. These adverse effects,
10 along with protective effects of UV radiation through increased production of vitamin D
11 are summarized in this section. For additional details, the reader is referred to Chapter 10
12 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)) and references therein.

13 The most conspicuous and well-recognized acute response to UV radiation is erythema,
14 or the reddening of the skin. Erythema is likely caused by direct damage to DNA by UV
15 radiation. Many studies discussed in Chapter 10 of the 2006 O₃ AQCD ([U.S. EPA,
16 2006b](#)) found skin type to be a significant risk factor for erythema. Skin cancer is another
17 prevalent health effect associated with UV radiation. Exposure to UV radiation is
18 considered to be a major risk factor for all forms of skin cancer. Ocular damage from UV
19 radiation exposure includes effects on the cornea, lens, iris, and associated epithelial and
20 conjunctival tissues. The region of the eye affected by exposure to UV radiation depends
21 on the wavelength of the incident UV radiation. Depending on wavelength, common
22 health effects associated with UV radiation include photokeratitis (snow blindness; short
23 wavelengths) and cataracts (opacity of the lens; long wavelengths).

24 Experimental studies reviewed in Chapter 10 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#))
25 have shown that exposure to UV radiation may suppress local and systemic immune
26 responses to a variety of antigens. Results from human clinical studies suggest that
27 immune suppression induced by UV radiation may be a risk factor contributing to skin
28 cancer induction. There is also evidence that UV radiation has indirect involvement in
29 viral oncogenesis through the human papillomavirus, dermatomyositis, human
30 immunodeficiency virus and other forms of immunosuppression.

31 A potential health benefit of increased UV-B exposure relates to the production of
32 vitamin D in humans. Most humans depend on sun exposure to satisfy their requirements
33 for vitamin D. Vitamin D deficiency can cause metabolic bone disease among children

1 and adults, and also may increase the risk of many common chronic diseases, including
2 type I diabetes mellitus and rheumatoid arthritis. Substantial in vitro and toxicological
3 evidence also support a role for vitamin D activity against the incidence or progression of
4 various forms of cancer. In some studies, UV-B related production of vitamin D had
5 potential beneficial immunomodulatory effects on multiple sclerosis, insulin-dependent
6 diabetes mellitus, and rheumatoid arthritis. More details on UV-B protective studies are
7 provided in Chapter 10 of the 2006 O₃ AQCD ([U.S. EPA, 2006b](#)).

8 In establishing guidelines on limits of exposure to UV radiation, the International
9 commission on Non-ionizing Radiation Protection (ICNIRP) agreed that some low-level
10 exposure to UV radiation has health benefits ([ICNIRP, 2004](#)). However, the adverse
11 health effects of higher UV exposures necessitated the development of exposure limits
12 for UV radiation. The ICNIRP recognized the challenge in establishing exposure limits
13 that would achieve a realistic balance between beneficial and adverse health effects. As
14 concluded by [ICNIRP \(2004\)](#), “[t]he present understanding of injury mechanisms and
15 long-term effects of exposure to [UV radiation] is incomplete, and awaits further
16 research.”

10.4.4 Ecosystem and Materials Damage Effects Due to UV-B Radiation

17 A 2009 progress report on the environmental effects of O₃ depletion from the UNEP,
18 Environmental Effects Assessment Panel ([UNEP, 2009](#)) lists many ecosystem and
19 materials damage effects from UV-B radiation. An in-depth assessment of the global
20 ecosystem and materials damage effects from UV-B radiation per se is out of the scope of
21 this assessment. However, a brief summary of some mid-latitude effects is provided in
22 this section to provide context for UV-B related issues pertaining to tropospheric O₃. The
23 reader is referred to the UNEP report ([UNEP, 2009](#)) and references therein for further
24 details. All of these UV-B related ecosystem and materials effects can also be influenced
25 by climate change through temperature and other meteorological alterations, making
26 quantifiable predictions of UV-B effects difficult.

27 **Terrestrial ecosystem effects** from increased UV-B radiation include reduced plant
28 productivity and plant cover, changes in biodiversity, susceptibility to infection, and
29 increases in natural UV protective responses. In general, however, these effects are small
30 for moderate UV-B increases at mid-latitudes. A field study on wheat in southern Chile
31 found no substantial changes in crop yield with moderate increases in UV-B radiation
32 ([Calderini et al., 2008](#)). Similarly, field studies on silver birch (*Betula pendula*) in
33 Finland found no measurable effects in photosynthetic function with increases in UV-B
34 radiation ([Aphalo et al., 2009](#)). Subtle, but important, changes in habitat and biodiversity

1 have also been linked to increases in UV-B radiation ([Mazza et al., 2010](#); [Obara et al.,](#)
2 [2008](#); [Wahl, 2008](#)). Some plants have natural coping mechanisms for dealing with
3 changes in UV-B radiation ([Favory et al., 2009](#); [Jenkins, 2009](#); [Brown and Jenkins, 2008](#);
4 [Ioki et al., 2008](#)), but these defenses may have costs in terms of reduced growth ([Snell et](#)
5 [al., 2009](#); [Clarke and Robinson, 2008](#); [Semerdjieva et al., 2003](#); [Phoenix et al., 2000](#)).

6 **Aquatic ecosystem effects** from increased UV-B radiation include sensitivity in
7 growth, immune response, and behavioral patterns of aquatic organisms. One study
8 looking at coccolithophores, an abundant phytoplankton group, found a 25% reduction in
9 cellular growth with UV-B exposure ([Gao et al., 2009a](#)). Exposure to relevant levels of
10 UV-B radiation has been shown to modify immune response, blood chemistry, and
11 behavior in certain species of fish ([Markkula et al., 2009](#); [Holtby and Bothwell, 2008](#);
12 [Jokinen et al., 2008](#)). Adverse effects on growth and development from UV-B radiation
13 have also been observed for amphibians, sea urchins, mollusks, corals, and zooplankton
14 ([Garcia et al., 2009](#); [Romansic et al., 2009](#); [Croteau et al., 2008b](#); [Croteau et al., 2008a](#);
15 [Marquis et al., 2008](#); [Marquis and Miaud, 2008](#); [Oromi et al., 2008](#)). Increases in the flux
16 of UV-B radiation may also result in an increase in the catalysis of trace metals including
17 mercury, particularly in clear oligotrophic lakes with low levels of dissolved organic
18 carbon to stop the penetration of UV-B radiation ([Schindler et al., 1996](#)). This could then
19 alter the mobility of trace metals including the potential for increased mercury
20 volatilization and transport within and among ecosystems.

21 **Biogeochemical cycles**, particularly the carbon cycle, can also be influenced by
22 increased UV-B radiation. A study on high latitude wetlands found UV-induced increases
23 in CO₂ uptake through soil respiration ([Haapala et al., 2009](#)) while studies on arid
24 terrestrial ecosystems found evidence for UV-induced release of CO₂ through
25 photodegradation of above-ground plant litter ([Brandt et al., 2009](#); [Henry et al., 2008](#);
26 [Caldwell et al., 2007](#); [Zepp et al., 2007](#)). Changes in solar UV radiation may also have
27 effects on carbon cycling and CO₂ uptake in the oceans ([Brewer and Peltzer, 2009](#);
28 [Meador et al., 2009](#); [Fritz et al., 2008](#); [Zepp et al., 2008](#); [Hader et al., 2007](#)) as well as
29 release of dissolved organic matter from sediment and algae ([Mayer et al., 2009](#);
30 [Riggsbee et al., 2008](#)). Additional studies showing effects on these and additional
31 biogeochemical cycles including the water cycle and halocarbon cycle can be found in
32 the UNEP report ([UNEP, 2009](#)) and references therein.

33 **Materials damage** from increased UV-B radiation include UV-induced
34 photodegradation of wood ([Kataoka et al., 2007](#)) and plastics ([Pickett et al., 2008](#)). These
35 studies and others summarizing photo-resistant coatings and materials designed to reduce
36 photodegradation of materials are summarized in the UNEP report ([UNEP, 2009](#)) and
37 references therein.

10.4.5 UV-B Related Effects Associated with Changes in Tropospheric Ozone Concentrations

1 There are multiple complexities in attempting to quantify the relationship between
2 changes in tropospheric O₃ concentrations and UV-B exposure. The 2006 O₃ AQCD
3 ([U.S. EPA, 2006b](#)) described a handful of studies addressing this relationship, but none
4 reported quantifiable effects of tropospheric O₃ concentration fluctuations on UV-B
5 exposure at the surface. Further quantifying the relationship between UV-B exposure and
6 health or welfare effects is complicated by the uncertainties involved in the selection of
7 an action spectrum and appropriate characterization of dose (e.g., peak or cumulative
8 levels of exposure, timing of exposures, etc.) The lack of published studies that critically
9 examined these issues together--that is the incremental health or welfare effects
10 attributable specifically to UV-B changes resulting from changes in tropospheric O₃
11 concentrations--lead to the prior conclusion that the effect of changes in surface-level O₃
12 concentrations on UV-induced health outcomes could not be critically assessed within
13 reasonable uncertainty ([U.S. EPA, 2006b](#)).¹

14 A recent study by [Madronich et al. \(2011\)](#) used CMAQ to estimate UV radiation
15 response to changes in tropospheric O₃ under different control scenarios projected out to
16 2020. This study focused on southeastern U.S. and accounted for spatial and temporal
17 variation in tropospheric O₃ reductions, an important consideration since most controls
18 are focused on reducing O₃ in populated urban areas. The contrasting control strategies
19 considered in this study included a historical scenario designed to meet an 84 ppb 8-h
20 daily max standard and a reduced scenario designed to bring areas predicted to exceed a
21 similarly designed 70 ppb standard into attainment. A biologically effective irradiance
22 was estimated by multiplying the modeled UV irradiance by a sensitivity function (action
23 spectrum) for the induction of nonmelanoma skin cancer in mice corrected for human
24 skin transmission, then integrating over UV wavelengths. The average relative change in
25 skin cancer-weighted surface UV radiation between the two scenarios was 0.11 ± 0.03%
26 over June, July and August. Weighting by population, this estimate increased to
27 0.19 ± 0.06%. [Madronich et al. \(2011\)](#) report that their estimated UV radiation increment
28 is an order of magnitude less than that reported in an earlier study by [Lutter and Wolz](#)
29 ([1997](#)) with the main reason for the discrepancy coming from the unrealistic uniform
30 10 ppb reduction in O₃ assumed in the former study. [Madronich et al. \(2011\)](#) did not
31 attempt to link their predicted increase in UV radiation to a predicted increase in skin
32 cancer incidence, however, due to several remaining and substantial uncertainties.

¹ The reader is referred to the U.S. EPA 2003 Final Response to Court Remand ([U.S. EPA, 2003](#)) for detailed discussions of the data and scientific issues associated with the determination of public health benefits resulting from the attenuation of UV-B by surface-level O₃.

1 Quantitatively estimating human health and welfare effects directly attributed to changes
2 in UV-B penetration resulting from changes in ground-level O₃ concentrations will
3 require both (a) a solid understanding of the multiple factors that define the extent of
4 exposure to UV-B, and (b) well-defined and quantifiable links between UV-B exposure
5 and human disease and welfare effects. Detailed information does not exist regarding the
6 relevant type (e.g., peak or cumulative) and time period (e.g., developmental, lifetime, or
7 current) of exposure, wavelength dependency of biological responses, and
8 inter-individual variability in UV resistance.

9 Although the UV-B related health effects attributed to marginal reductions in
10 tropospheric or ground-level O₃ have not been directly assessed to date, they would be
11 expected to be small based on current information indicating a negligibly small effect of
12 potential future changes in tropospheric O₃ concentrations on ground-level UV-B
13 radiation. In conclusion, the effect of changes in surface-level O₃ concentrations on
14 UV-induced health and welfare outcomes cannot yet be critically assessed within
15 reasonable uncertainty.

10.5 Summary and Causal Determinations

10.5.1 Summary of the Effects of Tropospheric Ozone on Climate

16 Tropospheric O₃ is a major greenhouse gas, third in importance after CO₂ and CH₄. While
17 the developed world has successfully reduced emissions of O₃ precursors in recent
18 decades, many developing countries have experienced large increases in precursor
19 emissions and these trends are expected to continue, at least in the near term. Projections
20 of radiative forcing due to changing O₃ over the 21st century show wide variation, due in
21 large part to the uncertainty of future emissions of source gases. In the near-term (2000-
22 2030), projections of O₃ radiative forcing range from near zero to +0.3 W/m², depending
23 on the emissions scenario ([Stevenson et al., 2006](#)). Reduction of tropospheric O₃
24 concentrations could therefore provide an important means to slow climate change in
25 addition to the added benefit of improving surface air quality.

26 It is clear that increases in tropospheric O₃ lead to warming. However the precursors of
27 O₃ also have competing effects on the greenhouse gas CH₄, complicating emissions
28 reduction strategies. A decrease in CO or VOC emissions would enhance OH
29 concentrations, shortening the lifetime of CH₄, while a decrease in NO_x emissions could
30 depress OH concentrations in certain regions and lengthen the CH₄ lifetime.

1 Abatement of CH₄ emissions would likely provide the most straightforward means to
2 address climate change since CH₄ is itself an important precursor of background O₃
3 ([West et al., 2007](#); [West et al., 2006](#); [Fiore et al., 2002](#)). A reduction of CH₄ emissions
4 would also improve air quality on its own right. A set of global abatement measures
5 identified by [West and Fiore \(2005\)](#) could reduce CH₄ emissions by 10% at a cost
6 savings, decrease background O₃ by about 1 ppb in the Northern Hemisphere summer,
7 and lead to a global net cooling of 0.12 W/m². [West et al. \(2007\)](#) explored further the
8 benefits of CH₄ abatement, finding that a 20% reduction in global CH₄ emissions would
9 lead to greater cooling per unit reduction in surface O₃, compared to 20% reductions in
10 VOCs or CO.

11 Important uncertainties remain regarding the effect of tropospheric O₃ on future climate
12 change. To address these uncertainties, further research is needed to: (1) improve
13 knowledge of the natural atmosphere; (2) interpret observed trends of O₃ in the free
14 troposphere and remote regions; (3) improve understanding of the CH₄ budget, especially
15 emissions from wetlands and agricultural sources, (4) understand the relationship
16 between regional O₃ radiative forcing and regional climate change; and (5) determine the
17 optimal mix of emissions reductions that would act to limit future climate change.

18 The effect of the tropospheric O₃ change since preindustrial times on climate has been
19 estimated to be about 25-40% of anthropogenic CO₂ effect and about 75% of
20 anthropogenic CH₄ effect according to the IPCC. There are large uncertainties in the
21 radiative forcing estimate attributed to tropospheric O₃, making the effect of tropospheric
22 O₃ on climate more uncertain than the effect of the long-lived greenhouse gases. Overall,
23 the evidence supports **a causal relationship between changes in tropospheric O₃**
24 **concentrations and radiative forcing.**

25 Radiative forcing does not take into account the climate feedbacks that could amplify or
26 dampen the actual surface temperature response. Quantifying the change in surface
27 temperature requires a complex climate simulation in which all important feedbacks and
28 interactions are accounted for. As these processes are not well understood or easily
29 modeled, the surface temperature response to a given radiative forcing is highly uncertain
30 and can vary greatly among models and from region to region within the same model. In
31 light of these uncertainties, the evidence indicates that there **is likely to be a causal**
32 **relationship between changes in tropospheric O₃ concentrations and effects on**
33 **climate.**

10.5.2 Summary of UV-B Related Effects on Human Health, Ecosystems, and Materials Relating to Changes in Tropospheric Ozone Concentrations

1 UV radiation emitted from the Sun contains sufficient energy when it reaches the Earth to
2 break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on
3 living organisms and materials. Atmospheric O₃ plays a crucial role in reducing exposure
4 to solar UV radiation at the Earth's surface. Ozone in the stratosphere is responsible for
5 the majority of this shielding effect, as approximately 90% of total atmospheric O₃ is
6 located there over mid-latitudes. Ozone in the troposphere provides supplemental
7 shielding of radiation in the wavelength band from 280-315 nm, referred to as UV-B
8 radiation. UV-B radiation has important effects on human health and ecosystems, and is
9 associated with materials damage.

10 There is a lack of published studies that critically examine the incremental health or
11 welfare effects (adverse or beneficial) attributable specifically to changes in UV-B
12 exposure resulting from perturbations in tropospheric O₃ concentrations. While the
13 effects are expected to be small, they cannot yet be critically assessed within reasonable
14 uncertainty. Overall, the evidence **is inadequate to determine if a causal relationship**
15 **exists between changes in tropospheric O₃ concentrations and effects on health**
16 **and welfare related to UV-B shielding.**

10.5.3 Summary of Ozone Causal Determinations

17 The evidence reviewed in this chapter describes the recent findings regarding the climate
18 and UV-B related effects of changes in tropospheric O₃ concentrations. [Table 10-2](#)
19 provides an overview of the causal determinations for each of the categories evaluated.

Table 10-2 Summary of ozone causal determinations for climate and UV-B effects.

| Effects | Causal Determination |
|--|---|
| Radiative Forcing | Causal relationship |
| Climate Change | Likely to be a causal relationship |
| Health and Welfare Effects Related to UV-B Shielding | Inadequate to determine if a causal relationship exists |

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