

# Integrated Science Assessment for Ozone and Related Photochemical Oxidants

National Center for Environmental Assessment-RTP Division  
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# Ozone Project Team

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## Executive Direction

Dr. John Vandenberg (Director)—National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Debra Walsh (Deputy Director)—National Center for Environmental Assessment-RTP Division, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Mary Ross (Branch Chief)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Doug Johns (Acting Branch Chief)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

---

## Scientific Staff

Dr. James Brown (O<sub>3</sub> Team Leader)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Christal Bowman—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Barbara Buckley—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Ye Cao—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Allen Davis—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jean-Jacques Dubois—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Steven J. Dutton—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jeffrey Herrick—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Erin Hines—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Dennis Kotchmar—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Meredith Lassiter—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Lingli Liu—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Thomas Long—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Thomas Luben—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Qingyu Meng—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Kristopher Novak—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Elizabeth Oesterling Owens—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Molini Patel—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Joseph P. Pinto—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Joann Rice—on detail to the National Center for Environmental Assessment, Office of Research and Development, from the Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Jason Sacks—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Lisa Vinikoor-Imler—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

---

### **Technical Support Staff**

Mr. Kenneth J. Breito—Senior Environmental Employment Program, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Ellen Lorang—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. J. Sawyer Lucy—Student Services Authority, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Deborah Wales—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Richard N. Wilson—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Barbara Wright—Senior Environmental Employment Program, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

# Authors, Contributors, and Reviewers

---

## Authors

Dr. James Brown (O<sub>3</sub> Team Leader)—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Christal Bowman—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Barbara Buckley—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Maggie Clark—Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO

Dr. Jean-Jacques Dubois—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Steven J. Dutton—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Kelly Gillespie— Donald Danforth Plant Science Center, St. Louis, MO

Dr. Terry Gordon—Department of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. Jeffrey Herrick—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Erin Hines—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Kazuhiko Ito—Department of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. Dennis Kotchmar—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Meredith Lassiter—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Lingli Liu— Oak Ridge Institute for Science and Education, Postdoctoral Research Fellow to National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Thomas Long—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Thomas Luben—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Loretta J. Mickley—School of Engineering & Applied Sciences, Harvard University, Cambridge, MA

Dr. Kristopher Novak—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Elizabeth Oesterling Owens—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Molini Patel—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jennifer Peel—Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO

Dr. Joseph Pinto—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Joann Rice—on detail to the National Center for Environmental Assessment, Office of Research and Development, from the Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Jason Sacks—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. George Thurston—Department of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. Lisa Vinikoor-Imler—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Cosima Wiese—Department of Biology, Misericordia University, Dallas, PA

---

## **Contributors**

Mr. Brian Adams—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Halil Cakir—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Ye Cao—Oak Ridge Institute for Science and Education, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Allen Davis—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Mark Evangelista—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. E. Henry Lee—National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Corvallis, OR

Dr. Qingyu Meng—Oak Ridge Institute for Science and Education, Postdoctoral Research Fellow to National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. David Mintz—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Mark Schmidt—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Huiquin Wang, School of Engineering and Applied Science, Harvard University, Cambridge, MA

Mr. Benjamin Wells—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

---

## Reviewers

Dr. Christian Andersen—National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Corvallis, OR

Ms. Lea Anderson—Office of General Counsel, U.S. Environmental Protection Agency, Washington, D.C.

Dr. Robert Arnts—National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. John Balmes— Department of Medicine, University of California, San Francisco and School of Public Health, University of California, Berkeley, CA

Dr. Souad Benromdhane—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Fitzgerald Booker—USDA-ARS Plant Science Research Unit, Raleigh, NC

Dr. Philip Bromberg—School of Medicine, University of North Carolina, Chapel Hill, NC

Dr. Kent Burkey—USDA-ARS Plant Science Research Unit, Raleigh, NC

Dr. David DeMarini—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Russ Dickerson—Department of Atmospheric and Oceanic Science, University of Maryland, College Park, MD

Mr. Patrick Dolwick—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Aimen Farraj—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Arlene Fiore—NOAA/Geophysical Dynamics Laboratory, Princeton, NJ

Dr. Ian Gilmour—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Tara Greaver—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Gary Hatch—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Bryan Hubbel—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Karl Jensen—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Urmila Kodavanti—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Petros Koutrakis—Department of Environmental Health, Harvard School of Public Health, Boston, MA

Mr. John Langstaff—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Christopher Lau—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. Gary Lear—Office of Air and Radiation, U.S. Environmental Protection Agency, Office of Administration and Policy, Washington, DC

Dr. Morton Lippmann—Nelson Institute of Environmental Medicine, New York University, Tuxedo, NY

Dr. Karen Martin—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Connie Meacham—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Mr. David Mintz—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Pradeep Rajan—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. John Rogers—National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Vicki Sandiford—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Ms. Susan Stone—Office of Air Quality Planning and Standards, Office of Air and Radiation, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. John Vandenberg—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. James G. Wagner—Department of Pathobiology and Diagnostic Investigation, Michigan State University, East Lansing, MI

Ms. Debra Walsh—National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC

Dr. Jason West—Department of Environmental Sciences & Engineering, University of North Carolina, Chapel Hill, NC

# Clean Air Scientific Advisory Committee Ozone NAAQS Review Panel

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## Chair of the Environmental Protection Agency's Clean Air Scientific Advisory Committee

Dr. Jonathan M. Samet\*, Department of Preventive Medicine at the Keck School of Medicine, and Director of the Institute for Global Health at the University of Southern California, Los Angeles, CA

---

## Chair of the Ozone Review Panel

Dr. Jonathan M. Samet\*, Department of Preventive Medicine at the Keck School of Medicine, and Director of the Institute for Global Health at the University of Southern California, Los Angeles, CA

---

## Members

Dr. George A. Allen\*, Northeast States for Coordinated Air Use Management (NESCAUM), Boston, MA

Professor Ed Avol, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

Dr. John Bailar, The National Academies, Washington, D.C.

Dr. Michelle Bell, School of Forestry & Environmental Studies, Yale University, New Haven, CT

Dr. Joseph Brain\*, Department of Environmental Health, Harvard School of Public Health, Harvard University, Boston, MA

Dr. David Chock, Independent Consultant, Bloomfield Hills, MI

Dr. William Michael Foster, Division of Pulmonary, Allergy, and Critical Care Medicine, Duke University Medical Center, Durham, NC

Dr. H. Christopher Frey\*, Department of Civil, Construction and Environmental Engineering, College of Engineering, North Carolina State University, Raleigh, NC

Dr. Judith Graham, Independent Consultant, Pittsboro, NC

Dr. David Grantz, College of Natural and Agricultural Sciences, Air Pollution Research Center, University of California Riverside, Parlier, CA

Dr. Jack Harkema, Center for Integrated Toxicology, Michigan State University, East Lansing, MI

Dr. Daniel Jacob, Atmospheric Chemistry and Environmental Engineering, Harvard University, Cambridge, MA

Dr. Steven Kleeberger, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC

Dr. Frederick J. Miller, Independent Consultant, Cary, NC

Dr. Howard Neufeld, Department of Biology, Appalachian State University, Boone, NC

Dr. Armistead (Ted) Russell\*, Department of Civil and Environmental Engineering, Georgia Institute of Technology, Atlanta, GA

Dr. Helen Suh MacIntosh\*, Environmental Health, NORC at the University of Chicago, and the School of Public Health, Harvard University, Boston, MA

Dr. James Ultman, Department of Chemical Engineering, Pennsylvania State University, University Park, PA

Dr. Sverre Vedal, Department of Environmental and Occupational Health Sciences, School of Public Health and Community Medicine, University of Washington, Seattle, WA

Dr. Kathleen Weathers\*, Cary Institute of Ecosystem Studies, Millbrook, NY

Dr. Peter Woodbury, Department of Crop and Soil Sciences, Cornell University, Ithaca, NY

\* Members of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the EPA Administrator

---

**Science Advisory Board Staff**

Dr. Holly Stallworth, Designated Federal Officer, Environmental Protection Agency, Mail Code 1400R, 1300 Pennsylvania Avenue, NW, Washington, DC, 20004, Phone: 202-564-2073, Email: stallworth.holly@epa.gov

# Acronyms and Abbreviations

$\alpha$	alpha, ambient exposure factor
$\alpha$ -TOH	Alpha tocopherol
Å, A	Ångström, angstrom ( $10^{-10}$ meter)
AA	arachidonic acid; ambient air; atomic absorption; ascorbic acid
AADT	annual average daily traffic
AAS	atomic absorption (spectrophotometry, spectrometry, spectroscopy)
ABA	abscisic acid
ABI2	phospho-tyrosine-specific protein phosphatase
AC	air conditioning
ACC	1-aminocyclopropane-1-carboxylate
ACE	angiotensin converting enzyme
ACGIH	American Conference of Governmental Industrial Hygienists
ACh	acetylcholine
AChE	acetylcholinesterase
ACS	American Cancer Society; 1-aminocyclopropane-1-carboxylase synthase
ACS-CPS-II	ACS Cancer Prevention Study II
ADC	arginine decarboxylase
ADSS	aged and diluted sidestream cigarette smoke
AED	aerodynamic equivalent diameter
AER	air exchange rate
AEROCE	Atmospheric/Ocean Chemistry Experiment
AF	atrial fibrillation; absorption fraction; adsorbed fraction
AGL	above ground level
AH <sub>2</sub>	ascorbic acid
AHCs	aromatic hydrocarbons
A horizon	uppermost layer of soil (litter and humus)
AHR	airway(s) hyperresponsiveness, airway(s) hyperreactivity
AhR	aryl hydrocarbon receptor
AHSMOG	(California Seventh Day) Adventist Health and Smog (Study)
AirPE <sub>x</sub>	Air Pollution Exposure (model)
AirQUIS	Air Quality Information System (model, Norwegian Institute for Air Research [NILU])
AIRS	Aerometric Information Retrieval System; Atmospheric Infrared Sounder (instrument)

ALI	air liquid interface
AM	alveolar macrophage(s)
$A_{\max}$	maximum photosynthesis rate
ANF	atrial natriuretic factor
ANN	artificial neural network
ANOVA	analysis of variance
ANP	Acadia National Park
AOP2	antioxidant protein 2
AOS	allene oxide synthase
AOT40	seasonal sum of the difference between an hourly concentration at the threshold value of 40 ppb, minus the threshold value of 40 ppb
AOT60	seasonal sum of the difference between an hourly concentration at the threshold value of 60 ppb, minus the threshold value of 60 ppb
$AOT_x$	family of cumulative, cutoff concentration-based exposure indices
AP	alkaline phosphatase
AP-CIMS	Atmospheric Pressure Chemical Ionization Mass Spectrometer
APEX	Air Pollutants Exposure (model)
APHEA	Air Pollution on Health: a European Approach (study)
APHENA	Air Pollution and Health: A European and North American Approach
APX	ascorbate peroxidase
AQCD	Air Quality Criteria Document
AQS	(U.S. EPA) Air Quality System (database)
AR	Acoustic rhinometry
AR4	Fourth Assessment Report (AR4) from the IPCC
ARE	antioxidant response element
ARG	arginase
ARIC	Atherosclerosis Risk in Communities
$A_{\text{sat}}$	photosynthetic assimilation in saturating light
ASC	ascorbate
ASTM	American Society for Testing and Materials
ATLAS	atmospheric model (by Kurucz)
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase; adenosine triphosphate synthase
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Research

A/V	surface-to-volume ratio
AVG	1-aminoethoxyvinyl-glycine
avg	average
AZO	azoxystrobin
$\beta$	beta, beta coefficient, slope; log relative risk
$\beta_2$ -AR	beta-2-adrenergic receptor
BNP	$\beta$ -type natriuretic peptide
BAL	bronchoalveolar lavage; British anti-Lewisite (AKA dimercaprol)
BALF	bronchoalveolar lavage fluid
BALT	bronchus-associated lymphoid tissue(s)
B[a]P	benzo[a]pyrene
BC	black carbon
BCB	blue copper binding protein
BEIS	Biogenic Emissions Inventory System
BERLIOZ	Berlin Ozone Experiment
BHC	biogenic hydrocarbons
BLD	below limit of detection
BME	Bayesian Maximum Entropy (framework)
BMI	body mass index
BMZ	basement membrane zone
BP	blood pressure
bpm	breaths per minute
BrdU	bromodeoxyuridine
BS	black smoke
BSA	bovine serum albumin; body surface area
$B_{\text{scatter}}$	back scatter
bw	body weight
C	carbon; concentration
C3	plants that use only the Calvin cycle for fixing the carbon dioxide from the air
C3a	complement protein fragment
C4	plants that use the Hatch-Slack cycle for fixing the carbon dioxide from the air
CA	Conducting airways
Ca	calcium
$\text{Ca}^{2+}$	calcium ion
CAA	Clean Air Act

CAAA	Amendments to the Clean Air Act (1990)
Cab	chlorophyll a/b binding protein
CADS	Cincinnati Activity Diary Study
CAM	plants that use crassulacean acid metabolism for fixing the carbon dioxide from the air
CAP(s)	concentrated ambient particles
CAPMoN	Canadian Air and Precipitation Monitoring Network
CAR	centriacinar region
CARB	California Air Resources Board
CASAC	Clean Air Scientific Advisory Committee
CASTNET	Clean Air Status and Trends Network
CAT	catalase; computer-aided tomography
CB	carbon black
CBL	convective boundary layer
CBU	cumulative breath units
CBVD	cerebrovascular disease
% C/C	percent carbon of total carbon
CC16	Clara cell protein, Clara cell 16 protein
CCh	carbachol
CCSP	Climate Change Science Program; Clara cell secretory protein
CDC	Centers for Disease Control and Prevention
cDNA	complementary DNA
CDPHE	Colorado Department of Public Health and Environment
CDT	Central Daylight Time
C <sub>dyn</sub> , C <sub>dyn</sub>	dynamic lung compliance
CE	continuous exercise
CEC	controlled environment chambers
CEPEX	Central Equatorial Pacific Experiment
CF	charcoal-filtered
CFA	charcoal/Purafil-filtered air
CFCs	chlorinated fluorocarbons
CFD	computational fluid dynamics (modeling)
CFI	continuous forest inventory
CFR	Code of Federal Regulations; reference method
CG	cloud-to-ground (lightning flash)
CGRP	Calcitonin gene-related peptide
CH <sub>3</sub>	methyl group

CH <sub>4</sub>	methane
C <sub>2</sub> H <sub>4</sub>	ethene
C <sub>5</sub> H <sub>8</sub>	isoprene
C <sub>6</sub> H <sub>6</sub>	benzene
C <sub>10</sub> H <sub>16</sub>	terpene
CHAD	Consolidated Human Activity Database
ChAT	choline acetyl-transferase
CH <sub>3</sub> Br	methyl bromide
CH <sub>2</sub> =C(CH <sub>3</sub> )-CHO	methacrolein
CH <sub>3</sub> CCl <sub>3</sub>	Methyl chloroform
C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	toluene
CH <sub>3</sub> CHO	acetaldehyde
CH <sub>3</sub> CH(ONO <sub>2</sub> )CHO	2-nitratopropanol
CHCl <sub>3</sub>	chloroform
CH <sub>3</sub> Cl	Methyl chloride
CH <sub>3</sub> CN	acetonitrile
CH <sub>3</sub> -CO	acetyl
CH <sub>3</sub> -C(O)-CH=CH <sub>2</sub>	methyl vinyl ketone
CH <sub>3</sub> C(O)CH <sub>2</sub> ONO <sub>2</sub>	1-nitratopropanone
CH <sub>3</sub> CO <sub>3</sub> NO <sub>2</sub>	PAN, peroxyacetyl nitrate
CH <sub>3</sub> -C(O)O <sub>2</sub> , CH <sub>3</sub> -C(O)OO	acetyl peroxy radical; peroxyacetyl
C <sub>2</sub> H <sub>5</sub> -H; C <sub>2</sub> H <sub>6</sub>	ethane
CH <sub>2</sub> O	formaldehyde
CH <sub>3</sub> O	methoxy
CH <sub>3</sub> O <sub>2</sub> ·	methyl peroxy (radical)
CH <sub>3</sub> OH	methanol
CH <sub>3</sub> -O(O)CH <sub>3</sub>	acetone
CH <sub>3</sub> OOH	acetic acid; methyl hydroperoxide
CHD	coronary heart disease
CHF	congestive heart failure
CH <sub>3</sub> I	methyl iodide
CHIP	Effects of Elevated Carbon Dioxide and Ozone on Potato Tuber Quality in the European Multiple Site Experiment
CHO	Chinese hamster ovary cells
CI	confidence interval(s)
CIE	Commission Internationale de l'Eclairage (International Commission on Illumination)
CIMS	chemical ionization mass spectroscopy

CINC	cytokine-induced neutrophil chemoattractant
CIU	cumulative inhalation units
CL	chemiluminescence
Cl	chlorine
CLM	chemiluminescence method
CMAQ	Community Multi-scale Air Quality modeling system; Congestion Mitigation and Air Quality
CMBO	chloromethylbutenone
CMD	count median diameter
CMSA	consolidated metropolitan statistical area
CN	condensation nuclei
CO	carbon monoxide; Cardiac output
CO <sub>2</sub>	carbon dioxide
COD	coefficient of divergence; coefficient of determination
ConA	concanavalin A
COP	Conference of Parties
COPD	chronic obstructive pulmonary disease
C-R	concentration-response
CRKs	cysteine-rich RLKs, which are part of the receptor-like/Pelle kinase (RLKs) group
CRP	C-reactive protein
CS	corticosteroid
CSA	Combined Statistical Area
CSTR	continuous stirred tank reactor
CTL	cytotoxic T lymphocyte
CTM	chemical transport model
CU	cumulative uptake (coefficient of variation)
CUOt	The cumulative stomatal uptake of O <sub>3</sub> , using a constant O <sub>3</sub> uptake rate threshold of t nmol/m <sup>2</sup> /s
CV; c.v.; cv	Cultivar
CV	cardiovascular
C.V.	coefficient of variation
CVD	cardiovascular disease
CYP	cytochrome (e.g., CYP1A, CYP-2A6, CYP3A4, CYP450)
CYP 1A1	cytochrome P450 1A1
CyS	Protein cysteines
cyt	cytochrome
Δ, δ	delta, difference; change

2-D	two-dimensional
3-D	three-dimensional
d <sub>50</sub>	50 percent cut point or 50 percent diameter
D <sub>a</sub>	aerodynamic diameter
Da	Dalton
DA	dry airstream; dopamine; dopaminergic
DAHPS	3-deoxy-D-arabino-heptulosonate-7-phosphate synthase
DBP	diastolic blood pressure
DD	doubling dose
df	degrees of freedom
DG	diacylglycerol
DGDG	digalactosyldiacylglycerol
DHA	dehydroascorbate; docosahexaenoic acid
DHAR	dehydroascorbate reductase
DHBA	2,3-dihydroxybenzoic acid
DI	dry intrusion
DIAL	differential absorption lidar (system)
DLEM	Dynamic Land Ecosystem Model
DMPO	dimethylphosphoroxyl 1-oxide; 5,5-dimethyl-1-pyrroline N-oxide
DNA	deoxyribonucleic acid
DOAS	differential optical absorption spectroscopy
DOC	dissolved organic carbon
DOE	U.S. Department of Energy
DOPAC	3,4-dihydroxyphenylacetic acid
DPCC	1,2-dipalmitoyl-SN-glycero-3-phosphocholine
DR	disulfide reductase
DTPA	diethylene triamine pentaacetic acid
DU	Dobson units
ε	epsilon; convergence precision
EBC	exhaled breath condensate (fluid)
EC	elemental carbon
EC <sub>0.05%</sub>	0.05% excess risk in mortality
EC <sub>50</sub>	effect concentration for 50% of test population
ECG	electrocardiography; electrocardiogram
ECM	ectomycorrhizal fungi
ECOPHYS	whole-tree ecophysiological growth process model
EC-SOD	extracellular superoxide dismutase

ED	emergency department
EDMAS	Exposure and Dose Modeling and Analysis System
EDTA	ethylenediaminetetraacetic acid
EDU	ethylenediurea
EE	energy expenditure (average EE rate)
EEA(s)	Essential Ecological Attribute(s)
EEG	electroencephalogram; electroencephalographic
eGPx	extracellular glutathione peroxidase
EGTA	ethyleneglycoltetraacetic acid
EGU(s)	electricity generating unit(s)
EKG, ECG	electrocardiogram
ELF	epithelial lining fluid; extracellular lining fluid
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
ENA-78	epithelial cell-derived neutrophil-activating peptide 78
eNO	exhaled nitric oxide
eNOS	endothelial nitric oxide synthase
ENSO	El Niño-Southern Oscillation
EOFs	empirical orthogonal functions
EOTCP	European Open Top Chamber Programme
EPA	U.S. Environmental Protection Agency
EPEM	Event Probability Exposure Model
EPO	epoxyconazole
EPR	Electron Paramagnetic Resonance
EPRI	Electric Power Research Institute
ER	emergency room; excess risk
ERAQS	Eastern Regional Air Quality Study
ERD1	ethylene response
ESPACE-wheat	European Stress Physiology and Climate Experiment on the Effects of Carbon Dioxide and Oxygen on Spring Wheat
ESR	electron spin resonance (spectroscopy); EPR
EST	Eastern Standard Time
ET	ethylene; endotracheal
ETS	environmental tobacco smoke
EU	endotoxin units; European Union
EVR	equivalent ventilation rate
F	female

f, <i>f</i> , $f_B$	frequency of breathing
F344	Fischer 344 strain of rats
FA	filtered air; fatty acid; fractional absorption; absorbed fraction
FAA	Federal Aviation Administration
FACE	free-air CO <sub>2</sub> enrichment (system)
$f_B$	breathing frequency
FDA	Food and Drug Administration
FEF	forced expiratory flow
FEF <sub>25-75</sub>	forced expiratory flow between the times at which 25% and 75% of the vital capacity is reached
FEF <sub>x</sub>	forced expiratory flow after (x)% vital capacity (e.g., after 25, 50, or 75% vital capacity)
FEM	Federal equivalent method
FEV <sub>1</sub>	forced expiratory volume in 1 second
FFAs	free fatty acids
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FHM	Forest Health Monitoring
FIA	USDA Forest Inventory and Analysis Program
$F_{inf}$	infiltration factor
FIVC	forced inspiratory vital capacity
FLAG	Federal Land Managers' Air Quality Related Values Workgroup
FN; Fn	fibronectin
FP	fluticasone propionate
FPM	Forest Pest Management
FR	Federal Register; fixed-ratio operant conditioning; fixed ratio schedule
FRAP	ferric reducing ability of plasma
FRC	functional residual capacity
FRM	Federal reference method
FS	field stimulation
FTIR	Fourier Transform Infrared Spectroscopy
FVC	forced volume vital capacity
Fv/Fm	a measure of the maximum efficiency of Photosystem II
FVI	fruit and vegetable index
G	plants rooted in ground
GAM	generalized additive model(s)
GBS	group B streptococcus

GC	gas chromatography
GCE	Goddard Cumulus Ensemble (model)
GC-FID	gas chromatography-flame ionization detection
GCM(s)	general circulation model(s), global climate model
GC/MS	gas chromatography/mass spectrometry
GD	gestational day
GDP	guanosine diphosphate
GDT	glutathione-disulfide transhydrogenase
GEE	generalized estimating equations
GEOS	Goddard Earth Observing System
GEOS-1DAS	Goddard Earth Observing System Data Assimilation System
GEOS-Chem	Goddard Earth Observing System-Chemistry (model)
GHG	greenhouse gas
GLM(s)	generalized linear model(s)
GLMM(s)	generalized linear mixed model(s)
GLRAG	Great Lakes Regional Assessment Group
GLU	glutamate
GM-CSF	granulocyte macrophage colony-stimulating factor
GMD	Global Monitoring Division
GMT	Greenwich mean time
G6P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GPP	Gross Primary Production
GPx	glutathione peroxidase
GR	glutathione reductase
GRSM	Great Smoky Mountains National Park
GSFC	NASA Goddard Space Flight Center
GSH	glutathione; reduced glutathione
GSHPx, GPx	glutathione peroxidase
GSMNP	Great Smoky Mountains National Park
GSSG	oxidized glutathione; glutathione disulfide
GST	glutathione transferase; glutathione S-transferase
GSTM1	glutathione S-transferase polymorphism M1
GSTM1null	glutathione S-transferase $\mu$ -1 null (genotype)
GSTP1	glutathione S-transferase P 1
GSx	glutathione; glutathione-containing material
H; H <sup>+</sup> ; H <sup>•</sup>	atomic hydrogen, hydrogen ion; hydrogen radical

$^3\text{H}$	radiolabeled hydrogen; tritium
h	hour
$\text{H}_2$	molecular hydrogen
HA	hospital admission
ha	hectare
HC(s)	hydrocarbon(s)
HCFC(s)	hydrochlorofluorocarbon(s)
HCHO	formaldehyde
$\text{HCO}^\bullet$	formyl (radical)
$\text{H}_2\text{CO}$ , HCHO	formaldehyde
HDM	house dust mite
2HDM, 2ndHDM	second-highest daily maximum 1-h concentration
HDMA	house dust mite allergen
HEPA	high efficiency particle air (filter)
HERO	Health and Environmental Research Online, NCEA Database System
HF	hydrogen fluoride; hydrofluoride; Howland Forest site; (HRV signal) high-frequency power
HFCs	hydrofluorocarbons
Hg	mercury
HHP-C9	1-hydroxy-1-hydroperoxynonane
HIST	histamine
HLA	human leukocyte antigen
HMOX	Heme oxygenase
HMOX1	heme-oxygenase (decycling)-1
HNE	4-hydroxynonenal
$\text{HNO}_2$ , HONO	nitrous acid
$\text{HNO}_3$	nitric acid
$\text{HNO}_4$	pernitric acid
HO	hydroxyl; heme oxygenase
$\text{HO}^\bullet$	hydroxyl radical
$\text{HO}_2^\bullet$	hydroperoxyl; hydroperoxy radical; protonated superoxide
$\text{HO}_3^\bullet$	protonated ozone radical
$\text{H}_2\text{O}$	water
$\text{H}_3\text{O}^+$	Hydronium ion
$\text{H}_2\text{O}_2$	hydrogen peroxide
$\text{HOCH}_2\text{OOH}$	hydroxymethylhydroperoxide

HONO	nitrous acid
HO <sub>2</sub> NO <sub>2</sub>	peroxynitric acid
HOONO	pernitrous acid
HO <sub>x</sub>	hydrogen radical(s)
HPLC	high-pressure liquid chromatography
HPOT	13-hydroperoxide linolenic acid
HR	heart rate, hazard ratio; hypersensitive response
HR <sub>max</sub>	maximum heart rate
HRP	horseradish peroxidase
HRV	heart rate variability
hs-CRP	high-sensitivity C-reactive protein
H <sub>2</sub> SO <sub>4</sub>	sulfuric acid
5-HT	5-hydroxytryptamine
hν	Energy per photon of electromagnetic energy at frequency ν
HVAC	heating, ventilation, and air conditioning
Hz	hertz
I	iodine
I/O	indoor-outdoor ratio
IARC	International Agency for Research on Cancer
IAS	interalveolar septum
IBM	individual-based model or modeling
IC	inspiratory capacity; intracloud (lightning flash)
ICAM-1	intercellular adhesion molecule
ICAS	Inner City Asthma Study
ICD	implantable cardioverter defibrillator(s); International Classification of Diseases
ICD-9	International Classification of Disease 9th revision
ICD-10	International Classification of Disease 10th revision
ICEM	Indoor Chemistry and Exposure Model
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ICP Forests	International Cooperative Programme on Assessment of Air Pollution Effects on Forests
ICS	inhaled steroids
ID#	identification number
IDW	inverse-distance-weighted
IE	intermittent exercise
IFN	interferon (e.g., IFN-())
IFN-γ	interferon-gamma

Ig	immunoglobulin (e.g., IgE)
IgA	immunoglobulin A
IgE	immunoglobulin E
IGF <sub>1</sub>	insulin-like growth factor 1
IgG	immunoglobulin G
IgM	Immunoglobulin M fraction
IHD	ischemic heart disease
IL	interleukin
Ile	isoleucine
IL-x	interleukin-6, 8, etc.
i.m.	intramuscular (route)
IMPACT	Interactive Modeling Project for Atmospheric Chemistry and Transport
IMPROVE	Interagency Monitoring of Protected Visual Environment
IN	intranasal
INF	interferon
inh	inhalation
iNOS	inducible nitric oxide synthase
INTRASTAND	a stand-level model designed for hourly, daily and annual integration of forest carbon and water cycle fluxes
IL-1 $\beta$	Interleukin-1Beta
IOM	Institute of Medicine
i.p.	intraperitoneal (route)
IPCC	Intergovernmental Panel on Climate Change
IPCC-AR4	Intergovernmental Panel on Climate Change 4th Assessment Report
IPCC-TAR	Intergovernmental Panel on Climate Change Third Assessment Report
IPMMI	International Photolysis Frequency Measurement and Modeling Inter-comparison
IQR	interquartile range
IR	infrared
ISA	Integrated Science Assessment
ISCCP	International Satellite Cloud Climatology Project
ISO	International Standards Organization
8-iso-PGF	8-isoprostane
IT	intratracheal, intratracheally
IU	International Units
IUGR	intrauterine growth restriction

i.v.	intravenous (route)
IVF	in vitro fertilization
JA	jasmonic acid
J <sub>max</sub>	maximum rate of electron transport (for regeneration of RuBP)
J(NO <sub>2</sub> )	photolysis rate coefficient for NO <sub>2</sub>
J(O <sub>3</sub> )	photolysis rate coefficient for O <sub>3</sub>
JPL	Jet Propulsion Laboratory
J <sub>sat</sub>	saturating light
κ <sub>B</sub>	kappa B
k	dissociation rate; root:shoot allometric coefficient
K <sup>+</sup>	potassium ion
K <sub>a</sub>	intrinsic mass transfer coefficient/parameter
K <sub>g</sub>	mass transfer coefficient for gas phase
kHz	kilohertz
kJ	kilojoules
K <sub>l</sub>	mass transfer coefficient for liquid phase
km	kilometer
KM	particle optical reflectance
KO	knockout
K <sub>r</sub>	reaction rate constant
KROFEX	Krauzberg Ozone Fumigation Experiment
K <sub>TB</sub>	tracheobronchial region overall mass transfer coefficient
L, dL, mL, μL	Liter, deciLiter, milliLiter, microLiter
LAI	leaf area index
LBW	low birth weight
LC <sub>50</sub>	median lethal concentration
LCL	lower 95th% confidence limit
LDH	lactate dehydrogenase, lactic acid dehydrogenase
LDL	low-density lipoprotein
LF	(HRV signal) low-frequency power
LFHFR	low frequency/high frequency (ratio)
LFT	lower free troposphere
LI	labeling index
LIDAR	Light Detection and Ranging (remote sensing system)
LIF	laser-induced fluorescence
LINKAGES	individual-based model of forest succession
LIS	lateral intercellular space

LLJ	low-level jet
LM	light microscopy
Ln	Natural logarithm
LnRMSSD	natural log of RMSSD; measure of HRV
lnSDNN	natural log of the standard deviation of NN intervals in an EKG
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEL	lowest-observed-effect level
LOESS	locally weighted scatterplot smoothing
LOP	lipid ozonation products
LOWESS	locally weighted scatter plot smoother
LOX-1	Lipoxygenase; lectin-like oxidized low density lipoprotein receptor-1
LPS	lipopolysaccharide
LRS	lower respiratory symptoms
LRT	lower respiratory tract; lower airways; Long range transport
LST	local standard time
LT	leukotriene (e.g., LTB <sub>4</sub> , LTC <sub>4</sub> , LTD <sub>4</sub> , LTE <sub>4</sub> ); local time
LTA	lymphotoxin-alpha
LT- $\alpha$	lymphotoxin- $\alpha$
LUR	land use regression
LWC	liquid water content
$\mu$	mu, micro
$\mu\text{eq}$	microequivalent
$\mu\text{g}$	microgram
$\mu\text{g}/\text{m}^3$	micrograms per cubic meter
$\mu\text{m}$	micrometer, micron
M	male; maximum number of iterations; air molecule
M7	7-hour seasonal mean
M12	12-hour seasonal mean of O <sub>3</sub>
M, mM, $\mu\text{M}$ , nM, pM	Molar, milliMolar, microMolar, nanoMolar, picoMolar
m, cm, $\mu\text{m}$ , nm	meter(s), centimeter(s), micrometer/[micron](s), nanometer(s)
ma	moving average
mAOT	modified accumulated exposure over threshold
MAP	mitogen-activated protein; mean arterial pressure
MAPK	mitogen-activated protein kinase(s), MAP kinase
MAQSIP	Multiscale Air Quality Simulation Platform (model)

MARAT	Mid-Atlantic Regional Assessment Team
MARCO	Macrophage receptor with collagenous structure
max	maximum
MBL	marine boundary layer
MCCP	Mountain Cloud Chemistry Program
Mch; MCh	methacholine
MCM	master chemical mechanism
MCP	monocyte chemotactic protein
MDA	malondialdehyde
MDAR	monodehydroascorbate reductase
MDI	Mediterranean diet index
MDL	minimum detection level
MED	minimal erythema dose
MEF <sub>50%</sub>	maximal midexpiratory flow at 50% of forced vital capacity
MeJA	methyl jasmonate
MENTOR	Modeling Environment for Total Risk Studies
METs	metabolic equivalent unit(s) [of work]
MGDG	monogalactosyldiacylglycerol
MHC	major histocompatibility complex
MI	myocardial infarction, “heart attack”
MIESR	matrix isolation electron spin resonance (spectroscopy)
min	minute; minimum
MIP	macrophage inflammatory protein
mL	milliliter
MLN	mediastinal lymph node
Mm	megameter
MM Mt.	Mt. Mitchell site
MM5	National Center for Atmospheric Research/Penn State Mesoscale Model, version 5
MMAD	mass median aerodynamic diameter; mass median aerodynamic density
MMEF	maximal midexpiratory flow
mmHg	millimeters of mercury
MMMD	mean maximum mixing height depth
MnSOD	Manganese superoxide dismutase
mo	month
MOA(s)	mode(s) of Action

MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
MoOx	molybdenum oxides
MOSES	Met Office Surface Exchange Scheme
MOZAIC	Measurement of Ozone and Water Vapor by Airbus In-Service Aircraft
MPAN	peroxymethacryloyl nitrate; peroxy-methacrylic nitric anhydride
MPO	myeloperoxidase
MQL	Minimum quantification limit
MRI	magnetic resonance imaging; Midwest Research Institute; Meteorological Research Institute
mRNA	messenger RNA
MS	mass spectrometry; Mt. Moosilauke site
ms	millisecond
MS/MS	tandem mass spectrometry
MSA	Metropolitan Statistical Area; methane sulfonic acid
MSL	mean sea level
MT	million tons; metric ton
MT, Mt	metallothionein
MT1	mitochondria
Mtn	mountain
MV	methyl viologen
MW	molecular weight
N	nitrogen; North
<sup>13</sup> N	nitrogen-15, stable isotope of nitrogen
n, N	number; number of observations
N <sub>2</sub>	molecular nitrogen; nonreactive nitrogen
N100	number of hours ≥ 0.10 ppm
NA	noradrenaline
NA; N/A	not available
Na	sodium
Na <sup>+</sup>	sodium ion
NAAQS	National Ambient Air Quality Standards
NAD	nicotinamide adenine nucleotide
NADH	reduced nicotinamide adenine dinucleotide; nicotinamide adenine dinucleotide dehydrogenase
NADP	National Atmospheric Deposition Program
NADPH; NAD(P)H	reduced nicotinamide adenine dinucleotide phosphate

NADPH-CR	reduced nicotinamide adenine dinucleotide phosphatecytochrome c reductase
NaE	sodium erythorbate
Na-K-ATPase	sodium-potassium-dependent adenosine triphosphatase
NAMS	National Ambient Monitoring Stations
NAMS/SLAMS	National Ambient Monitoring Stations and State and Local Air Monitoring Stations
NAPAP	National Acid Precipitation Assessment Program
NAPBN	National Air Pollution Background Network
NARE	North Atlantic Regional Experiment
NARSTO	North American Regional Strategy for Atmospheric Ozone
NAS	National Academy of Sciences; Normative Aging Study
NASA	National Aeronautics and Space Administration
NBS	National Bureau of Standards
NBTH	3-methyl-2-benzothiazolinone acetone azine
NCEA	National Center for Environmental Assessment
NCEA-RTP	NCEA Division in Research Triangle Park, NC
NCHS	National Center for Health Statistics
NCICAS	National Cooperative Inner-City Asthma Study
NCLAN	National Crop Loss Assessment Network
NCore	National Core multi-pollutant monitoring network
NC-R	resistant clones of white clover
NC-S	sensitive clones of white clover
ND; n.d.	not detectable; not detected; no data
NDF	neutral detergent fiber
NEE	net ecosystem CO <sub>2</sub> exchange
NEI	National Emissions Inventory
NEM	National Ambient Air Quality Standards Exposure Model
NEP	Net Ecosystem Production
+NERAG	New England Regional Assessment Group
NERL	National Exposure Research Laboratory
NESCAUM	Northeast States for Coordinated Air Use Management
NF	National Forest; non-filtered
NF-κB	nuclear factor kappa B
NH	northern hemisphere
NH <sub>3</sub>	ammonia
NH <sub>4</sub> <sup>+</sup>	ammonium ion
NHANES	National Health and Nutrition Examination Survey

NHAPS	National Human Activity Pattern Survey
NHEERL/WED	EPA National Health and Environmental Effects Research Laboratory, Western Ecology Division
NH <sub>4</sub> HSO <sub>4</sub>	Ammonium bisulfate
(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> ; (NH <sub>4</sub> ) <sub>2</sub> HSO <sub>4</sub>	ammonium sulfate
NHIS	National Health Interview Survey
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NK	natural killer cells; neurokinin
NKT	Natural killer T cells
NL	nasal lavage
NLF	nasal lavage fluid
NM	National Monument
NMHC(s)	nonmethane hydrocarbon(s)
NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NMOC(s)	nonmethane organic compound(s)
NMVOCs	nonmethane volatile organic compounds
NN	normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
NNK	4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
nNOS	neuronal nitric oxide synthase (NOS)
NO	nitric oxide
NO <sub>2</sub>	nitrogen dioxide
NO <sub>3</sub> ; NO <sub>3</sub> <sup>•</sup>	nitrate, nitrate radical
NO <sub>3</sub> <sup>-</sup>	nitrate, nitrate ion
N <sub>2</sub> O	nitrous oxide
N <sub>2</sub> O <sub>5</sub>	dinitrogen pentoxide
NOAA	National Oceanic and Atmospheric Administration
NOAEL	no observed adverse effect level
NOS	nitric oxide synthase
NOS-1	neuronal nitric oxide synthase
NOS-2	inducible nitric oxide synthase; iNOS
NOS-3	endothelial nitric oxide synthase
NO <sub>x</sub>	nitrogen oxides, oxides of nitrogen (NO + NO <sub>2</sub> )
NO <sub>y</sub>	sum of NO <sub>x</sub> and NO <sub>z</sub> ; odd nitrogen species; total oxidized nitrogen
NO <sub>z</sub>	sum of all inorganic and organic reaction products of NO <sub>x</sub> (HONO, HNO <sub>3</sub> , HNO <sub>4</sub> , organic nitrates, particulate nitrate, nitro-PAHs, etc.)

NP	National Park
NPP	net primary production
NPS	National Park Service, U.S. Department of the Interior
NQO1	NAD(P)H-quinone oxidoreductase (genotype)
NQO1wt	NAD(P)H-quinone oxidoreductase wild type (genotype)
NR	not reported
Nr	reactive nitrogen
NRC	National Research Council
Nrf-2	nuclear factor erythroid 2-related factor 2
NS; n.s.	nonsignificant; non-smoker; national seashore; natural spline
NSAID	non-steroidal anti-inflammatory agent
NSBR	nonspecific bronchial responsiveness
NSF	National Science Foundation
NTE	nasal turbinate epithelial (cells)
NTN	National Trends Network
NTP	National Toxicology Program
NTRMs	NIST Traceable Reference Materials
NTS	nucleus of the solitary tract (in brainstem)
NWR	national wildlife refuge
NWS	National Weather Service
NZW	New Zealand white (rabbit)
O	oxygen; horizon forest floor
<sup>1</sup> O <sub>2</sub>	singlet oxygen
<sup>18</sup> O	oxygen-18, stable isotope of oxygen
O <sub>2</sub>	molecular oxygen
O <sub>2</sub> <sup>-</sup>	superoxide
O <sub>2</sub> <sup>•</sup>	superoxide radical
O <sub>3</sub>	ozone
<sup>18</sup> O <sub>3</sub>	(oxygen-18 labeled) ozone
O <sub>3</sub> <sup>*</sup>	electronically excited ozone
OAQPS	Office of Air Quality Planning and Standards
OAR	Office of Air and Radiation
OBM	observationally based methods
OC	organic carbon
OD	outer diameter; optical density
O( <sup>1</sup> D)	electronically excited oxygen atom
OH, OH <sup>•</sup>	hydroxyl group, hydroxyl radical

8-OHdG	8-hydroxy-2'-deoxyguanosine
OLS	ordinary least squares
OMI	Ozone Monitoring Instrument
O( <sup>3</sup> P)	ground-state oxygen atom
OPE	ozone production efficiency
OPECs	Outdoor Plant Environment Chambers
OR	odds ratio
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
OTC	open-top chamber
OVA	ovalbumin
O <sub>x</sub>	odd oxygen species; total oxidants
OxComp	oxidative capacity of the atmosphere
Φ	Phi; calculated efficiency
ΦPSII-max	maximum photochemical effective quantum yield of PSII
P	pressure in atmospheres; plants grown in pots
p	probability value
P <sub>90</sub>	90th percentile of the absolute difference in concentrations
P450	cytochrome P450
PAD	peripheral arterial disease; pollutant applied dose
PAF	platelet-activating factor; paroxysmal atrial fibrillation
PAH(s)	polycyclic aromatic hydrocarbon(s)
PAL	phenylalanine ammonia lyase
PAMS	Photochemical Assessment Monitoring Stations network
PAN	peroxyacetyl nitrate; peroxyacetic nitric anhydride
PaO <sub>2</sub>	arterial oxygen pressure
PAR	photosynthetically active radiation; proximal alveolar region
P <sub>atm</sub>	Pressure in atmospheres
<i>p</i> -ATP	<i>para</i> -acetamidophenol
PBL	planetary boundary layer; peripheral blood lymphocytes
PBM	population-based model or modeling
PBN	C-phenyl N-tert-butyl nitrone
PBPK	physiologically based pharmacokinetic (model)
PBS	phosphate buffered saline
PC	phosphatidylcholine
PC <sub>20</sub>	provocative concentration that produces a 20% decrease in forced expiratory volume in 1 second

PC <sub>20</sub> FEV <sub>1</sub>	provocative concentration that produces a 20% decrease in FEV <sub>1</sub>
PC <sub>50</sub>	provocative concentration that produces a 50% decrease in forced expiratory volume in 1 second
PCA	principal component analysis
PC-ALF	1-palmitoyl-2-(9-oxonononoyl)- <i>sn</i> -glycero-3-phosphocholine
PCD	programmed cell death
PCI	picryl chloride
pCNEM	Canadian version of National Ambient Air Quality Standards Exposure Model
PCO <sub>2</sub>	Average partial pressure of O <sub>2</sub> in lung capillaries
pCO <sub>2</sub>	partial pressure of carbon dioxide
PCR	polymerase chain reaction
PCR-DGGE	PCR–denaturing gradient gel electrophoresis
PD <sub>100</sub>	provocative dose that produces a 100% increase in sRAW
PD <sub>100</sub> SRaw	provocative dose that produces a 100% increase in SRaw
PD <sub>20</sub> ; PD <sub>20</sub> FEV <sub>1</sub>	provocative dose that produces a 20% decrease in FEV <sub>1</sub>
PE	post exposure, phosphatidylethanolamine
PEF	peak expiratory flow
PEF <sub>0.75</sub>	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)
P <sub>enh</sub>	enhanced pause
PEPc	phosphoenolpyruvate carboxylase
PFD	photosynthetic flux density
PG	prostaglandin (e.g., PGE <sub>2</sub> , PGF <sub>2</sub> ); phosphatidylglycerol
6PGD	6-phosphogluconate dehydrogenase
PGHS-2	prostaglandin endoperoxide G/H synthase 2
PGP	protein gene product (e.g., PGP9.5)
PGSM	Plant Growth Stress Model
pH	relative acidity; Log of the reciprocal of the hydrogen ion concentration
PHA	phytohemagglutinin A
PI	phosphatidylinositol; probability interval; posterior interval
PIF	peak inspiratory flow
PK	pharmacokinetics

pKa	dissociation constant
PLFA	Phospholipid fatty acid
PM	particulate matter
PM <sub>0.1</sub>	particulate matter with a nominal mobility diameter less than or equal to 0.1 µm (referred to as ultrafine PM)
PM <sub>1</sub>	particulate matter with a nominal aerodynamic diameter less than or equal to 1 µm
PM <sub>2.5</sub>	particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm (a surrogate for fine PM)
PM <sub>10-2.5</sub>	particulate matter with a nominal aerodynamic diameter greater than 2.5 µm and less than or equal to 10 µm (a surrogate for thoracic coarse particulate matter or the coarse fraction of PM <sub>10</sub> ). Concentration may be measured or calculated as the difference between measured PM <sub>10</sub> and measured PM <sub>2.5</sub> concentrations.
PM <sub>x-y</sub>	particulate matter with a nominal diameter greater than x µm and less than y µm where x and y are the numeric mean aerodynamic or mobility diameters (µm).
PM <sub>10</sub>	particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm
PM <sub>13</sub>	particulate matter with a nominal aerodynamic diameter less than or equal to 13 µm
PM <sub>15</sub>	particulate matter with a nominal aerodynamic diameter less than or equal to 15 µm
PM <sub>x</sub>	particulate matter of a specific size range. X refers to the diameter at which the sampler collects 50% of the particles and rejects 50% of the particles. Collection efficiency increases for particles with smaller diameters and decreases for particles with larger diameters. The variation of collection efficiency with size is given by a collection efficiency curve. The definition of PM <sub>x</sub> is frequently abbreviated as “particles with a nominal aerodynamic diameter less than or equal to x µm. See 40 CFR 58.1 for a full definition.
PM-CAM <sub>x</sub>	Comprehensive Air Quality Model with extensions and with particulate matter chemistry
PMN(s)	polymorphonuclear leukocyte(s)
PMT	photomultiplier tube
PND	post natal day
pNEM	probabilistic National Exposure Model
PnET	Photosynthetic EvapoTranspiration model
PNN	proportion of interval differences of successive normal-beat intervals in EKG
PNN <sub>50</sub>	proportion of interval differences of successive normal-beat intervals greater than 50 ms in EKG
POC	particulate organic carbon
POD	peroxidase
polyADPR	poly(adenosinediphosphate-ribose)

ppb	parts per billion
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.
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
PQH <sub>2</sub>	plastoquinone
PR	pathogenesis-related (protein)
PR-1	promoter region 1
PRB	policy-relevant background
PRYL	predicted relative yield (biomass) loss
PS	penalized spline
PS II	Photosystem II: enzyme that uses light to obtain electrons from water (for photosynthesis).
PSA	picryl sulfonic acid
PSC	polar stratospheric clouds
PTB	preterm birth
PTR-MS	proton-transfer-reaction mass spectroscopy
PU, PUL	pulmonary
PUFA(s)	polyunsaturated fatty acid(s)
PV	potential vorticity
PVCD	peripheral vascular and cerebrovascular disease
PVD	peripheral vascular disease
PVOCs	photochemical volatile organic compounds
PWM	pokeweed mitogen
Pxase	peroxidase
QCE	quasi continuous exercise
q <sub>NP</sub>	non-photochemical quenching
qP	photochemical quenching
QRS	A complex of three distinct electrocardiogram waves which represent the beginning of ventricular contraction
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

r	Pearson correlation coefficient
R, r	correlation coefficient
$r^2$	correlation coefficient
$R^2$	multiple regression correlation coefficient
$R^2, r^2$	coefficient of determination
RACM	Regional Atmospheric Chemistry Mechanism
RADM	Regional Acid Deposition Model
rALP	recombinant antileukoprotease
RAMS	Regional Atmospheric Modeling System
RANTES	regulated upon activation, normal T cell expressed and secreted (cells)
$R_{aw}$ , Raw	airway resistance
RB	respiratory bronchiole
RBC(s)	red blood cell(s); erythrocyte(s)
<i>rbcL</i>	Rubisco large subunit
<i>rbcS</i>	Rubisco small subunit
rcd1	Arabidopsis mutant radical induced cell death
R'C(O)-O <sub>2</sub>	acyl peroxy
RDBMS	Relational Database Management Systems
Re	Reynolds number
REHEX	Regional Human Exposure Model
RER	rough endoplasmic reticulum; Respiratory exchange ratio
RF	radiative forcing
RGR	Relative growth rate
RH	relative humidity
RIOPA	Relationship of Indoor, Outdoor, and Personal Air (study)
$R_L$	total pulmonary resistance
RLKs	receptor-like/Pelle kinase group
RMR	resting metabolic rate
rMSSD	root mean squared differences between adjacent normal-to-normal heartbeat intervals
Rn	nasal resistance
RNA	ribonucleic acid
RO <sub>2</sub>	organic peroxy; organic peroxy
ROG	reactive organic gases
ROI	reactive oxygen intermediate/superoxide anion
RONO <sub>2</sub>	organic nitrate
ROOH	organic peroxides

ROONO <sub>2</sub> , RO <sub>2</sub> NO <sub>2</sub>	peroxy nitrate
ROS	reactive oxygen species
RR	normal-to-normal (NN or RR) time interval between each QRS complex in the EKG; ribonucleotide reductase; risk ratio; relative risk
RRMS	relatively remote monitoring sites
RT	respiratory tract
R <sub>T</sub>	transepithelial resistance
RTL <sub>F</sub>	respiratory tract lining fluid
RuBisCO; Rubisco	ribulose-1,5-bisphosphate carboxylase/oxygenase
RuBP	ribulose bisphosphate
σ	sigma, standard deviation
σ <sub>g</sub>	sigma-g; geometric standard deviation
S	smoker; sulfur; South
s	second
SA	salicylic acid
SAB	Science Advisory Board
SAC	<i>Staphylococcus aureus</i> Cowan 1 strain
SAG21	senescence
SAI	Systems Applications International
SAMD	<i>S</i> -adenosyl methionine decarboxylase
S <sub>a</sub> O <sub>2</sub>	oxygen saturation of arterial blood
SAPALDIA	Study of Air Pollution and Lung Diseases in Adults
SAR	systemic acquired resistance
SAROAD	Storage and Retrieval of Aerometric Data (U.S. Environmental Protection Agency centralized database; superseded by Aerometric Information Retrieval System [AIRS])
SAW <sub>grp</sub>	small airway function group
SBP	systolic blood pressure
SBUV	Solar Backscatter Ultraviolet Spectrometer
SC	stratum corneum
Sc	scandium
s.c.	subcutaneous
SCAQS	Southern California Air Quality Study
SCE(s)	sister chromatid exchange(s)
SD	standard deviation; Sprague-Dawley rat
SDNN	standard deviation normal-to-normal (NN or RR) time interval between each QRS complex in the EKG
SE	standard error

SEBAS	Social Environment and Biomarkers of Aging Study
SEM	simultaneously extracted metal; standard error of the mean; scanning electron microscopy
SES	socioeconomic status
SF <sub>6</sub>	sulfur hexafluoride (tracer gas)
SGA	small for gestational age
SGaw	specific airway conductance
SH	Shenandoah National Park site
SHEDS	Stochastic Human Exposure and Dose Simulation
SHEN	Shenandoah National Park
sICAM-1	soluble intercellular adhesion molecule
SIDS	sudden infant death syndrome
SIGMOID	sigmoid weighted summed concentration
SINIC	Simple Nitrogen Cycle model
SIPK	salicylic acid (SA) induced protein kinase
SK	shikimate kinase
SLA	specific leaf area
SLAMS	State and Local Air Monitoring Stations
SMD	soil moisture deficit
SME	soybean oil methyl ester
SNAAQs	Secondary National Ambient Air Quality Standards
SNP(s)	single-nucleotide polymorphism
SO <sub>2</sub>	sulfur dioxide
SO <sub>4</sub> <sup>2-</sup>	sulfate
SOA	secondary organic aerosol
SOD	superoxide dismutase
SOS	Southern Oxidant Study
SO <sub>x</sub>	sulfur oxides
SoyFACE	Soybean Free Air gas Concentration Enrichment Facility
SP	surfactant protein (e.g., SPA, SPD); substance P
SPF	specific pathogen free
SRaw, sRaw,	specific airway resistance
SRBC	sheep red blood cell
SRES	Special Report on Emissions Scenarios
SRM	standard reference method
SSCP	single-strand conformation polymorphism
STE	stratosphere-troposphere exchange

STEP	Stratospheric-Tropospheric-Exchange Project
STN	speciation trends network
STP	standard temperature and pressure
STPD	standard temperature and pressure, dry
STRF	Spatio-Temporal Random Field (theory)
SUM00	sum of all hourly average concentrations
SUM06	seasonal sum of all hourly average concentrations $\geq$ 0.06 ppm
SUM07	seasonal sum of all hourly average concentrations $\geq$ 0.07 ppm
SUM08	seasonal sum of all hourly average concentrations $\geq$ 0.08 ppm
SURE	Sulfate Regional Experiment Program
SZA	solar zenith angle
$\tau$	tau, photochemical lifetime; atmospheric lifetime
T	time; duration of exposure
t	t-test statistical value; t statistic
T cell	T lymphocyte
T lymphocytes	thymus-dependent lymphocytes
T <sub>3</sub>	triiodothyronine
T <sub>4</sub>	thyroxine
TAR	IPCC Third Assessment Report
TAR WGI	IPCC Third Assessment Report of Working Group I
TB	tracheobronchial; terminal bronchioles; tuberculosis
TBA	thiobarbituric acid
TBARS	thiobarbituric acid reactive substances
TC	total carbon
<sup>99m</sup> Tc	Technetium-99m
<sup>99m</sup> Tc-DTPA	99mTc-diethylenetriaminepentaacetic acid
T-cells	Thymus-derived lymphocytes
T <sub>co</sub>	core temperature
T <sub>CTL</sub>	cytotoxic T-lymphocytes
TDLAS	Tunable Diode Laser Absorption Spectrometer
T <sub>e</sub>	expiratory time
TEM	transmission electron microscopy; Terrestrial Ecosystem Model
TexAQS	Texas Air Quality Field Study
Tg	teragram(s)
TGF	transforming growth factor
TGF $\beta$	$\beta$ transforming growth factor
Th	T helper type

tHcy	total homocysteine
T <sub>i</sub>	inspiratory time
Ti	titanium
TIA	transient ischemic attack
TiO <sub>2</sub>	titanium dioxide
TLC	total lung capacity
TLNISE	two-level normal independent sampling estimation
TLR	Toll-like receptor
TMPO	tetramethylphrrolise 1-oxide
TNC	total nonstructural carbohydrate
TNF	tumor necrosis factor (e.g., TNF- $\alpha$ )
TNFR	tumor necrosis factor receptor
TNF- $\alpha$	tissue necrosis factor alpha
TOMS	Total Ozone Mapping/Monitoring Satellite; total ozone mapping spectrometer
TOPSE	Tropospheric Ozone Production About the Spring Equinox
TPLIF	two-photon laser-induced fluorescence
TREGRO	Tree Growth Model
TRIFFID	Top-down Representation of Interactive Foliage and Flora Including Dynamics
TRIM	Total Risk Integrated Methodology (model)
TRIM.Expo	Total Risk Integrated Methodology Exposure Event (model)
TSH	thyroid stimulating hormone
TSP	total suspended particles
TTFMS	two-tone frequency-modulated spectroscopy
TVA	Tennessee Valley Authority
TWA	time-weighted average
TX	tromboxane (e.g., TXB <sub>2</sub> )
U.K.	United Kingdom
U.S.	United States of America
U.S.C.; USC	U.S. Code
UA	uric acid
UAM	Urban Airshed Model
UCL	upper 95th% confidence limit
UDGT	UDP -galactose-1,2,-diacylglycerol galactosyltransferase
UDP	uridine diphosphate
ULLI	unit length labeling index

UN ECE ICP- Vegetation	United Nations Economic Commission for Europe International Cooperative Programme on effects of air pollution and other stresses on crops and non-woody plants (UN/ECE-Vegetation; formerly -Crops)
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environmental Programme
UNFCCC	United Nations Framework Convention on Climate Change
URI	upper respiratory infection
URS	upper respiratory symptoms
URT	upper respiratory tract; upper airways
USDA	U.S. Department of Agriculture
USFS	U.S. Forest Service
USGCRP	U.S. Global Change Research Program
USGS	U.S. Geological Survey
UT	Universal Time
UTC	Coordinated Universal Time
UV	ultraviolet radiation
UV-A	ultraviolet radiation at wavelengths of 320 to 400 nm
UV-B	ultraviolet radiation at wavelengths of 280 to 320 nm
UV-C	ultraviolet radiation at wavelengths of 200 to 280 nm
UV-DIAL	Ultraviolet Differential Absorption Lidar
V	vanadium
V, mV, $\mu$ V	volt, millivolt, microvolt
$V_A$	alveolar ventilation
Val	valine
VC	vital capacity
VCAM	vascular cell adhesion molecule
$V_d$	deposition rate, deposition velocity (cm/s)
$V_D$	volume of the anatomic or physiological dead space
VE	ventilatory volume
$V_E$	ventilation rate; minute ventilation
$V_{E_{max}}$	maximum minute ventilation
$V_{max}$	maximum velocity
$V_{max25\%}$	maximum expiratory flow at 25% of the vital capacity
$V_{max50\%}$	maximum expiratory flow at 50% of the vital capacity
$V_{max75\%}$	maximum expiratory flow at 75% of the vital capacity
VMD	volume median diameter
$V_n$	Nasal volume

VO <sub>2</sub>	oxygen consumption
VO <sub>2max</sub>	maximum volume per time, of oxygen (maximal oxygen consumption, maximal oxygen uptake or aerobic capacity)
VOC(s)	volatile organic compound(s)
V <sub>P</sub>	volumetric penetration
V <sub>P50%</sub>	volume at which 50% of an inhaled bolus is absorbed
VPD	vapor pressure deficit; Vehicles per day; Ventricular premature depolarization
V <sub>T</sub>	tidal volume
V <sub>TB</sub>	terminal bronchiole region volume
V <sub>Tmax</sub>	maximum tidal volume
V <sub>UA</sub>	volume of the upper airways
vWF	von Willebrand factor
W	width; wilderness
W/m <sup>2</sup> , W m <sup>-2</sup>	watts per square meter
w/v	weight per volume
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
WCB	warm conveyor belt
WF, WFM	White Face Mountain site
WHI	Women's Health Initiative
WHO	World Health Organization
wk	week(s)
WMO	World Meteorological Organization
WMO/UNEP	World Meteorological Organization/United Nations Environment Program
Ws	Wassilewskija Arabidopsis ecotype
WS	wood smoke
WT	wild type; White Top Mountain site
wt %	percent by weight
yr	year
ZAPS	Zonal Air Pollution System
ZELIG	a forest succession simulation model
Zn	zinc

# Chapter 1. Introduction

1 The Integrated Science Assessment (ISA) is a concise evaluation and synthesis of the most  
2 policy-relevant science for reviewing the national ambient air quality standards (NAAQS). Because  
3 the ISA communicates critical science judgments relevant to the NAAQS review, it forms the  
4 scientific foundation for the review of the NAAQS for ozone (O<sub>3</sub>). The existing primary O<sub>3</sub> standard  
5 includes an 8-hour (h) average (avg) standard set at 75 parts per billion (ppb) and not to be exceeded  
6 more than once per year. The secondary standard for O<sub>3</sub> is set equal to the primary standard.

7 The ISA accurately reflects “the latest scientific knowledge useful in indicating the kind and  
8 extent of identifiable effects on public health which may be expected from the presence of [a]  
9 pollutant in ambient air” (1990, [080701](#)). Key information and judgments formerly contained in the  
10 Air Quality Criteria Document (AQCD) for O<sub>3</sub> are incorporated in this assessment. Additional  
11 details of the pertinent scientific literature published since the last review, as well as selected older  
12 studies of particular interest, are included. This ISA thus serves to update and revise the evaluation of  
13 the scientific evidence available at the time of the completion of the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
14 2006, [088089](#)).

15 The draft *Integrated Review Plan for the Ozone National Ambient Air Quality Standards (IRP)*  
16 (U.S. EPA, 2009, [684024](#)) identified key policy-relevant questions that provided a framework for  
17 this assessment of the scientific evidence. These questions frame the entire review of the NAAQS for  
18 O<sub>3</sub> and thus are informed by both science and policy considerations. The ISA organizes, presents,  
19 and integrates the scientific evidence which is considered along with findings from risk analyses and  
20 policy considerations to help the U.S. Environmental Protection Agency (EPA) address these  
21 questions during the NAAQS review. In evaluating the health evidence, the focus of this assessment  
22 is on scientific evidence that is most relevant to the following questions taken directly from the  
23 Integrated Review Plan:

- 24       ▪ To what extent has new scientific information become available that alters or  
25       substantiates our understanding of the health effects associated with various time periods  
26       of exposure to ambient O<sub>3</sub>, including short-term (1-3 hours), prolonged (6-8 hours), and  
27       chronic (months to years) exposures?
  
- 28       ▪ To what extent has new scientific information become available that alters or  
29       substantiates our understanding of the health effects of O<sub>3</sub> on at-risk populations,  
30       including those with potentially increased susceptibility such as children and  
31       disadvantaged populations?

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

- 1           ▪ To what extent has new scientific information become available that alters or  
2           substantiates conclusions from previous reviews regarding the plausibility of adverse  
3           health effects caused by O<sub>3</sub> exposure?
  
- 4           ▪ At what levels of O<sub>3</sub> exposure are health effects observed? Is there evidence of effects at  
5           exposure levels lower than those previously observed, and what are the important  
6           uncertainties associated with that evidence? What is the nature of the exposure-response  
7           relationships of O<sub>3</sub> for the various health effects evaluated?
  
- 8           ▪ To what extent has new scientific information become available that alters or  
9           substantiates our understanding of non-O<sub>3</sub>-exposure factors that might influence the  
10          associations between O<sub>3</sub> levels and health effects being considered (e.g., weather-related  
11          factors; behavioral factors such as heating/air conditioning use; driving patterns; and  
12          time-activity patterns)?
  
- 13          ▪ To what extent do risk and/or exposure analyses suggest that exposures of concern for  
14          O<sub>3</sub>-related health effects are likely to occur with current ambient levels of O<sub>3</sub> or with  
15          levels that just meet the O<sub>3</sub> standard? Are these risks/exposures of sufficient magnitude  
16          such that the health effects might reasonably be judged to be important from a public  
17          health perspective? What are the important uncertainties associated with these  
18          risk/exposure estimates?
  
- 19          ▪ To what extent have important uncertainties identified in the last rulemaking been  
20          addressed and/or have new uncertainties emerged?

## 1.1. Legislative Requirements

21           Two sections of the Clean Air Act (CAA) (2011, [013410](#)) govern the establishment and  
22           revision of the NAAQS. Section 108 (42 USC §7408) directs the Administrator to identify and list  
23           certain air pollutants and then to issue air quality criteria for those pollutants. The Administrator is to  
24           list those air pollutants that in her “judgement; cause or contribute to air pollution which may  
25           reasonably be anticipated to endanger public health or welfare” and whose “presence...in the  
26           ambient air results from numerous or diverse mobile or stationary sources.”(1990, [080701](#)). Air  
27           quality criteria are intended to “accurately reflect the latest scientific knowledge useful in indicating  
28           the kind and extent of identifiable effects on public health or welfare which may be expected from  
29           the presence of [a] pollutant in ambient air . . . (42 USC §7408(b)).

30           Section 109 (1990, [037658](#)) directs the Administrator to propose and promulgate “primary”  
31           and “secondary” NAAQS for pollutants for which air quality criteria have been issued. Section

1 109(b)(1) defines a primary standard as one “the attainment and maintenance of which in the  
2 judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are  
3 requisite to protect the public health.”<sup>1</sup> A secondary standard, as defined in section 109(b)(2), must  
4 “specify a level of air quality the attainment and maintenance of which, in the judgment of the  
5 Administrator, based on such criteria, is required to protect the public welfare from any known or  
6 anticipated adverse effects associated with the presence of [the] pollutant in the ambient air.”<sup>2</sup>

7 The requirement that primary standards include an adequate margin of safety was intended to  
8 address uncertainties associated with inconclusive scientific and technical information available at  
9 the time of standard setting. It was also intended to provide a reasonable degree of protection against  
10 hazards that research has not yet identified. See *Lead Industries Association v. EPA*, 647 F.2d 1130,  
11 1154 (D.C. Cir 1980) (1980, [090977](#)), cert. denied, 449 U.S. 1042 (1980); *American Petroleum*  
12 *Institute v. Costle*, 665 F.2d 1176, 1186 (D.C. Cir. 1981) (1981, [090978](#)), cert. denied, 455 U.S. 1034  
13 (1982). Both kinds of uncertainties are components of the risk associated with pollution at levels  
14 below those at which human health effects can be said to occur with reasonable scientific certainty.  
15 Thus, in selecting primary standards that include an adequate margin of safety, the Administrator is  
16 seeking not only to prevent pollution levels that have been demonstrated to be harmful but also to  
17 prevent lower pollutant levels that may pose an unacceptable risk of harm, even if the risk is not  
18 precisely identified as to nature or degree.

19 In selecting a margin of safety, the EPA considers such factors as the nature and severity of the  
20 health effects involved, the size of the sensitive population(s) at risk, and the kind and degree of the  
21 uncertainties that must be addressed. The selection of any particular approach to providing an  
22 adequate margin of safety is a policy choice left specifically to the Administrator’s judgment. See  
23 *Lead Industries Association v. EPA*, supra, 647 F.2d at 1161-1162 (1980, [090977](#)).

24 In setting standards that are “requisite” to protect public health and welfare, as provided in  
25 Section 109(b), EPA’s task is to establish standards that are neither more nor less stringent than  
26 necessary. In so doing, EPA may not consider the costs of implementing the standards. See generally  
27 *Whitman v. American Trucking Associations*, 531 U.S. 457, 465-472, 475-76 (2001, [043004](#)).

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

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<sup>1</sup> 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, 91<sup>st</sup> Cong., 2d Sess. 10 (1970)].

<sup>2</sup> 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.” (2005, [090976](#)).

1 existing criteria and standards as may be appropriate ...". Since the early 1980's, this independent  
2 review function has been performed by CASAC.

## 1.2. History of the NAAQS for Ozone

3 Tropospheric (ground-level) O<sub>3</sub> is the indicator for the mix of photochemical oxidants (e.g.,  
4 peroxyacetyl nitrate, hydrogen peroxide) formed from biogenic and anthropogenic precursor  
5 emissions. Naturally occurring O<sub>3</sub> in the troposphere can result from biogenic organic precursors  
6 reacting with naturally occurring nitrogen oxides (NO<sub>x</sub>) and by stratospheric O<sub>3</sub> intrusion into the  
7 troposphere. Anthropogenic precursors of O<sub>3</sub>, especially NO<sub>x</sub>, and volatile organic compounds  
8 (VOCs), originate from a wide variety of stationary and mobile sources. Ambient O<sub>3</sub> concentrations  
9 produced by these emissions are directly affected by temperature, solar radiation, wind speed, and  
10 other meteorological factors.

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

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**Table 1-1. 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) (1971, <a href="#">039176</a> )	Total photochemical oxidants	1-h	0.08	Not to be exceeded more than 1 hour per year
1979 (44 FR 8202) (1979, <a href="#">039177</a> )	O <sub>3</sub>	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) (1993, <a href="#">043977</a> )	EPA decided that revisions to the standards were not warranted at the time.			
1997 (62 FR 38856) (1997, <a href="#">083356</a> )	O <sub>3</sub>	8-h	0.08	Annual fourth-highest daily maximum 8-h concentration averaged over 3 years
2008 (73 FR 16483) (2008, <a href="#">684051</a> )	O <sub>3</sub>	8-h	0.075	Form of the standards remained unchanged relative to the 1997 standard

1 Table 1-1 summarizes the O<sub>3</sub> NAAQS that have been promulgated to date. In each review, the  
2 secondary standard has been set to be identical to the primary standard. These reviews are briefly  
3 described below.

4 EPA first established primary and secondary NAAQS for photochemical oxidants in 1971  
5 (U.S. EPA, 1971, [039176](#)). Both primary and secondary standards were set at a level of 0.08 parts  
6 per million (ppm), 1-h avg, total photochemical oxidants, not to be exceeded more than 1 hour per  
7 year. The standards were based on scientific information contained in the 1970 AQCD (U.S. EPA,  
8 1970, [014681](#)).

9 In 1977, EPA announced the first periodic review of the 1970 AQCD (U.S. EPA, 1970,  
10 [014681](#)) in accordance with Section 109(d)(1) of the Clean Air Act. In 1978, EPA published an  
11 AQCD (U.S. EPA, 1978, [040586](#)). Based on the 1978 AQCD, EPA published proposed revisions to  
12 the original NAAQS in (1978, [684050](#)) and final revisions in 1979 (1979, [039177](#)). The level of the  
13 primary and secondary standards was revised from 0.08 to 0.12 ppm; the indicator was revised from  
14 photochemical oxidants to O<sub>3</sub>; and the form of the standards was revised from a deterministic to a  
15 statistical form, which defined attainment of the standards as occurring when the expected number of  
16 days per calendar year with maximum hourly average concentration greater than 0.12 ppm is equal  
17 to or less than one.

18 In 1982 (Air quality criteria document for ozone and other photochemical oxidants, 1982,  
19 [043971](#)), EPA announced plans to revise the 1978 AQCD (U.S. EPA, 1978, [040586](#)). In 1983, EPA  
20 announced that the second periodic review of the primary and secondary standards for O<sub>3</sub> had been  
21 initiated (Review of the national ambient air quality standards for ozone, 1983, [043972](#)). EPA  
22 subsequently published the 1986 O<sub>3</sub> AQCD (U.S. EPA, 1986, [017607](#)) and 1989 Staff Paper  
23 (U.S. EPA, 1989, [041919](#)). Following publication of the 1986 O<sub>3</sub> AQCD, a number of scientific  
24 abstracts and articles were published that appeared to be of sufficient importance concerning  
25 potential health and welfare effects of O<sub>3</sub> to warrant preparation of a Supplement to the 1986 O<sub>3</sub>  
26 AQCD (U.S. EPA, 1992, [042599](#)). Under the terms of a court order, on August 10, 1992, EPA  
27 published a proposed decision (1992, [043976](#)) stating that revisions to the existing primary and  
28 secondary standards were not appropriate at the time (1992, [043976](#)). This notice explained that the  
29 proposed decision would complete EPA's review of information on health and welfare effects of O<sub>3</sub>  
30 assembled over a 7-year period and contained in the 1986 O<sub>3</sub> AQCD (U.S. EPA, 1986, [017607](#)) and  
31 its Supplement to the 1986 O<sub>3</sub> AQCD (U.S. EPA, 1992, [042599](#)). The proposal also announced  
32 EPA's intention to proceed as rapidly as possible with the next review of the air quality criteria and  
33 standards for O<sub>3</sub> in light of emerging evidence of health effects related to 6- to 8-hour O<sub>3</sub> exposures.  
34 On March 9, 1993, EPA concluded the review by deciding that revisions to the standards were not  
35 warranted at that time (1993, [043977](#)).

36 In August 1992, EPA announced plans to initiate the third periodic review of the air quality  
37 criteria and O<sub>3</sub> NAAQS (1992, [043976](#)). On the basis of the scientific evidence contained in the  
38 1996 O<sub>3</sub> AQCD (U.S. EPA, 1996, [017831](#)) and the 1996 Staff Paper (U.S. EPA, 1996, [039046](#)), and  
39 related technical support documents, linking exposures to ambient O<sub>3</sub> to adverse health and welfare

1 effects at levels allowed by the then existing standards, EPA proposed to revise the primary and  
2 secondary O<sub>3</sub> standards on December 13, 1996 (U.S. EPA, 1996, [031951](#)). The EPA proposed to  
3 replace the then existing 1-hour primary and secondary standards with 8-h avg O<sub>3</sub> standards set at a  
4 level of 0.08 ppm (equivalent to 0.084 ppm using standard rounding conventions). The EPA also  
5 proposed, in the alternative, to establish a new distinct secondary standard using a biologically based  
6 cumulative seasonal form. The EPA completed the review on July 18, 1997 by setting the primary  
7 standard at a level of 0.08 ppm, based on the annual fourth-highest daily maximum 8-h avg  
8 concentration, averaged over 3 years, and setting the secondary standard identical to the revised  
9 primary standard (U.S. EPA, 1997, [083356](#)).

10 On May 14, 1999, in response to challenges to EPA's 1997 decision by industry and others, the  
11 U.S. Court of Appeals for the District of Columbia Circuit (D.C. Circuit Court) remanded the O<sub>3</sub>  
12 NAAQS to EPA, finding that Section 109 of the CAA, as interpreted by EPA, effected an  
13 unconstitutional delegation of legislative authority. In addition, the D.C. Circuit Court directed that,  
14 in responding to the remand, EPA should consider the potential beneficial health effects of O<sub>3</sub>  
15 pollution in shielding the public from the effects of solar ultraviolet (UV) radiation, as well as  
16 adverse health effects. On January 27, 2000, EPA petitioned the U.S. Supreme Court for certiorari on  
17 the constitutional issue (and two other issues) but did not request review of the D.C. Circuit Court  
18 ruling regarding the potential beneficial health effects of O<sub>3</sub>. On February 27, 2001, the U.S.  
19 Supreme Court unanimously reversed the judgment of the D.C. Circuit Court on the constitutional  
20 issue, holding that Section 109 of the CAA does not delegate legislative power to the EPA in  
21 contravention of the Constitution, and remanded the case to the D.C. Circuit Court to consider  
22 challenges to the O<sub>3</sub> NAAQS that had not been addressed by that Court's earlier decisions. On  
23 March 26, 2002, the D.C. Circuit Court issued its final decision, finding the 1997 O<sub>3</sub> NAAQS to be  
24 "neither arbitrary nor capricious," and denied the remaining petitions for review. In response to the  
25 D.C. Circuit Court remand to consider the potential beneficial health effects of O<sub>3</sub> pollution in  
26 shielding the public from effects of solar (UV) radiation, on November 14, 2001, EPA proposed to  
27 leave the 1997 8-h O<sub>3</sub> NAAQS unchanged (2001, [684026](#)). After considering public comment on the  
28 proposed decision, EPA published its final response to this remand on January 6, 2003, reaffirming  
29 the 8-h O<sub>3</sub> NAAQS set in 1997 (National ambient air quality standards for ozone: Final response to  
30 remand; final rule, 2003, [015702](#)). Finally, on April 30, 2004, EPA announced the decision to make  
31 the 1-h O<sub>3</sub> NAAQS no longer applicable to areas 1 year after the effective date of the designation of  
32 those areas for the 8-h NAAQS (2004, [684054](#)). For most areas, the date that the 1-h NAAQS no  
33 longer applied was June 15, 2005.

34 EPA initiated the next periodic review of the air quality criteria and O<sub>3</sub> standards in September  
35 2000 with a call for information (2000, [080678](#)). The schedule for completion of that rulemaking  
36 later became governed by a consent decree resolving a lawsuit filed in March 2003 by a group of  
37 plaintiffs representing national environmental and public health organizations. Based on the 2006 O<sub>3</sub>  
38 AQCD (U.S. EPA, 2006, [088089](#)) published in March 2006, and the Staff Paper (U.S. EPA, 2007,  
39 [090207](#)) and related technical support documents, the proposed decision was published in the

1 Federal Register on July 11, 2007 (2007, [684055](#)). The EPA proposed to revise the level of the  
2 primary standard to a level within the range of 0.075 to 0.070 ppm. Two options were proposed for  
3 the secondary standard: (1) replacing the current standard with a cumulative, seasonal standard,  
4 expressed as an index of the annual sum of weighted hourly concentrations cumulated over  
5 12 daylight hours during the consecutive 3-month period within the O<sub>3</sub> season with the maximum  
6 index value, set at a level within the range of 7 to 21 ppm-h; and (2) setting the secondary standard  
7 identical to the revised primary standard. The EPA completed the rulemaking with publication of a  
8 final decision on March 27, 2008 (2008, [684051](#)), revising the level of the 8-hour primary O<sub>3</sub>  
9 standard from 0.08 ppm to 0.075 ppm and revising the secondary standard to be identical to the  
10 primary standard.

11 On September 16, 2009, the EPA Administrator announced her decision to reconsider the  
12 March 2008 decisions on revisions to the primary and secondary O<sub>3</sub> NAAQS.

### 1.3. ISA Development

13 EPA initiated the current review of the NAAQS for O<sub>3</sub> on September 29, 2008, with a call for  
14 information from the public (2008, [684057](#)). In addition to the call for information, publications  
15 were identified through an ongoing literature search process that includes extensive computer  
16 database mining on specific topics. Literature searches were conducted routinely to identify studies  
17 published since the last review, focusing on publications since 2005. Search strategies were  
18 iteratively modified to optimize identification of pertinent publications. Additional papers are  
19 identified for inclusion in several ways: review of pre-publication tables of contents for journals in  
20 which relevant papers may be published; independent identification of relevant literature by expert  
21 authors; and identification by the public and CASAC during the external review process.  
22 Publications considered for inclusion in the ISA were added to the Health and Environmental  
23 Research Online (HERO) database recently developed by EPA (<http://hero.epa.gov/>); note that the  
24 references in the ISA include a HERO ID that provides a link to the database. All references that are  
25 considered for inclusion in each chapter, organized by discipline, will be found through the HERO  
26 links provided at the beginning of the individual chapter reference sections. The HERO link provides  
27 the list of references that are included, as well as those that are considered and not included in the  
28 ISA, with bibliographic information and abstracts.

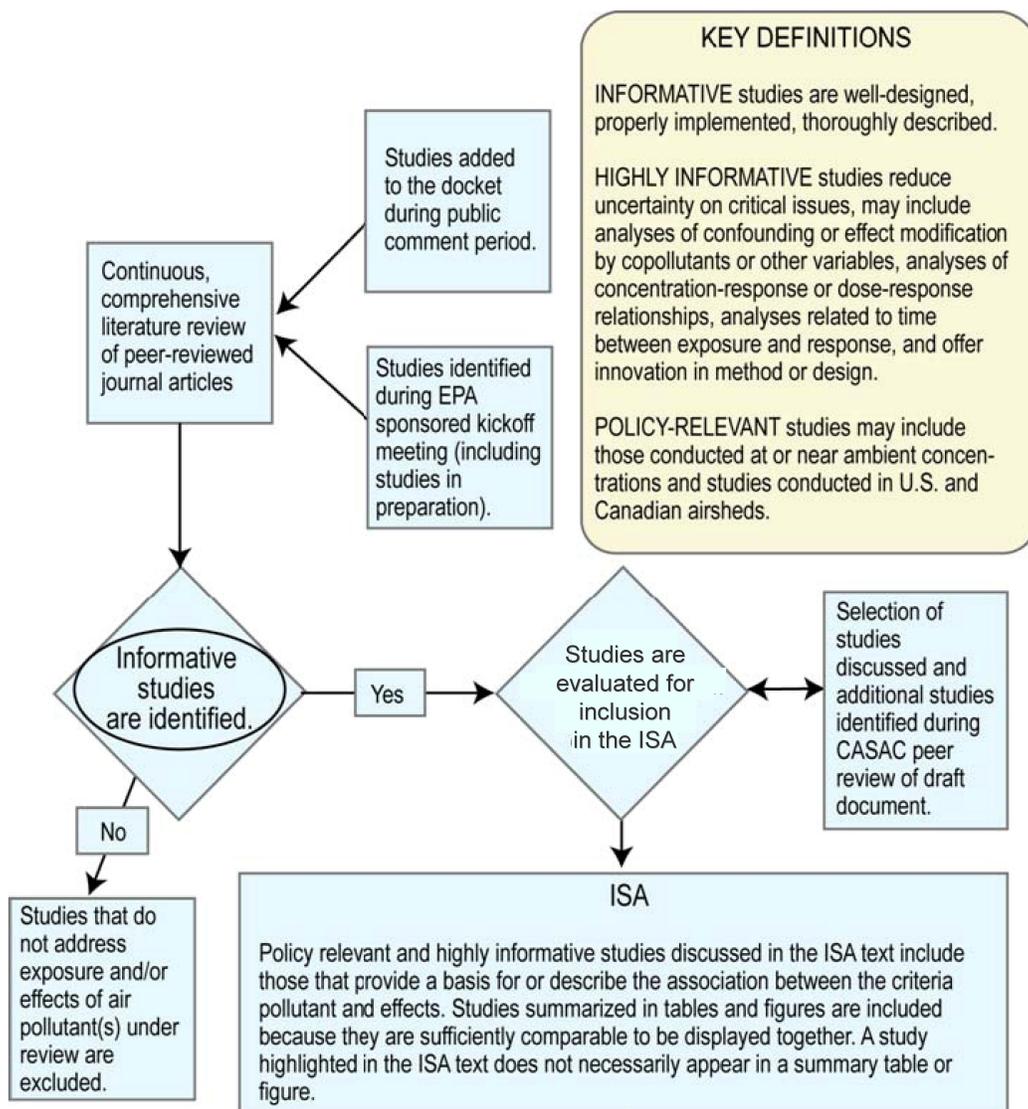
29 Typically, only information that had undergone scientific peer review and had been published  
30 or accepted for publication was considered for inclusion, along with analyses conducted by EPA  
31 using publicly available data. This review has attempted to evaluate all relevant data published since  
32 the last review pertaining to the atmospheric science of O<sub>3</sub>, human exposure to ambient O<sub>3</sub>, and  
33 epidemiologic, controlled human exposure, and animal toxicological studies on O<sub>3</sub>, including those  
34 related to exposure-response relationships, mode(s) of action (MOA), or susceptible populations, and  
35 literature on the ecological or welfare effects of ambient O<sub>3</sub>. Added to the body of research on O<sub>3</sub>

1 effects were EPA's analyses of air quality and emissions data, studies on atmospheric chemistry,  
2 transport, and fate of these emissions, as well as issues related to exposure to O<sub>3</sub>.

3 In general, in assessing the scientific quality and relevance of health and environmental effects  
4 studies, the following considerations have been taken into account when selecting studies for  
5 inclusion in the ISA. The selection process for studies included in this ISA is shown in Figure 1-1.

- 6       ▪ Are the study populations, subjects, or animal models adequately selected, and are they  
7       sufficiently well defined to allow for meaningful comparisons between study or exposure  
8       groups?
  
- 9       ▪ Are the statistical analyses appropriate, properly performed, and properly interpreted?  
10       Are likely covariates adequately controlled or taken into account in the study design and  
11       statistical analysis?
  
- 12       ▪ Are the air quality data, exposure, or dose metrics of adequate quality and sufficiently  
13       representative of information regarding ambient O<sub>3</sub>?
  
- 14       ▪ Are the health, ecological or welfare effect measurements meaningful and reliable?

15 In selecting epidemiologic studies, EPA considered whether a given study presented  
16 information on associations with short- or long-term O<sub>3</sub> exposures at or near ambient levels of O<sub>3</sub>;  
17 considered approaches to evaluate issues related to potential confounding by other pollutants;  
18 assessed potential effect modifiers; addressed health endpoints and populations not previously  
19 extensively researched; and evaluated important methodological issues (e.g., lag or time period  
20 between exposure and effects, model specifications, thresholds, mortality displacement) related to  
21 interpretation of the health evidence. Among the epidemiologic studies selected, particular emphasis  
22 was placed on those studies most relevant to the review of the NAAQS. Specifically, studies  
23 conducted in the United States (U.S.) or Canada were discussed in more detail than those from other  
24 geographical regions. Particular emphasis was placed on: (1) recent multicity studies that employ  
25 standardized analysis methods for evaluating effects of O<sub>3</sub> and that provide overall estimates for  
26 effects, based on combined analyses of information pooled across multiple cities; (2) studies that  
27 help understand quantitative relationships between exposure concentrations and effects; (3) new  
28 studies that provide evidence on effects in susceptible populations; and (4) studies that consider and  
29 report O<sub>3</sub> as a component of a complex mixture of air pollutants.



**Figure 1-1. Identification of studies for inclusion in the ISA.**

1 Criteria for the selection of research evaluating controlled human exposure or animal  
 2 toxicological studies included a focus on studies conducted using relevant pollutant exposures. For  
 3 both types of studies, relevant pollutant exposures are considered to be those generally within one or  
 4 two orders of magnitude of ambient O<sub>3</sub> concentrations. Studies in which higher doses were used may  
 5 also be considered if they provide information relevant to understanding modes of action or  
 6 mechanisms, as noted below.

7 Evaluation of controlled human exposure studies focused on those that approximated expected  
 8 human exposure conditions in terms of concentration and duration. In the selection of controlled  
 9 human exposure studies, emphasis is placed on studies that: (1) investigate potentially susceptible

1 populations such as people with cardiovascular diseases; (2) address issues such as concentration-  
2 response or time-course of responses; (3) include control exposures to filtered air; and (4) have  
3 sufficient statistical power to assess findings.

4 Review of the animal toxicological evidence focused on studies that approximate expected  
5 human dose conditions, which will vary depending on the toxicokinetics and biological sensitivity of  
6 the particular laboratory animal species or strains studied. Due to resource constraints on exposure  
7 duration and numbers of animals tested, animal studies typically utilize high-concentration  
8 exposures to acquire data relating to mechanisms and assure a measurable response. Such studies  
9 were considered to the extent that they provided useful information to inform our understanding of  
10 interspecies differences and potential sensitivity differences between healthy and susceptible human  
11 populations.

12 Evaluation of the ecological impact of O<sub>3</sub> focused on studies of vegetation and effects on  
13 ecosystems that occur in the U.S. and report endpoints or processes most relevant to the review of  
14 the secondary standard. Many studies have been published about vegetation and ecosystems outside  
15 of U.S. and North America, largely in Europe and Asia. This document includes discussion of studies  
16 of vegetation and ecosystems outside of North America if those studies contribute to the  
17 understanding of O<sub>3</sub> effects across species and ecosystems. For example, studies outside North  
18 America that deal with physiological and biochemical processes that contribute to the effects of O<sub>3</sub>  
19 across species are discussed. Also, ecosystem studies outside of North America that contribute to the  
20 understanding of O<sub>3</sub> effects on ecosystem processes are discussed. In addition, the specific role that  
21 tropospheric O<sub>3</sub> plays in the earth's radiation budget and how perturbations in tropospheric O<sub>3</sub> might  
22 affect (1) climate through its role as a greenhouse gas and (2) health, ecology and welfare through its  
23 role in shielding ultraviolet radiation are assessed.

24 These criteria provide benchmarks for evaluating various studies and for focusing on the  
25 policy-relevant studies in assessing the body of health and welfare effects evidence. Detailed critical  
26 analysis of all O<sub>3</sub> health, ecological and welfare effects studies, especially in relation to the above  
27 considerations, is beyond the scope of this document. Of most relevance for evaluation of studies is  
28 whether they provide useful qualitative or quantitative information on exposure-effect or  
29 exposure-response relationships for effects associated with current ambient air concentrations of O<sub>3</sub>  
30 that can inform decisions on whether to retain or revise the standards.

31 In developing the O<sub>3</sub> ISA, EPA began by reviewing and summarizing the evidence on  
32 atmospheric sciences and exposure and the health effects evidence from in vivo and in vitro  
33 toxicological studies, controlled human exposure studies, and epidemiologic studies. In August 2010,  
34 EPA held a public workshop, in which EPA experts and several non-EPA experts were asked to  
35 review the scientific content of preliminary draft materials for the draft ISA. The purpose of the  
36 initial review workshop was to ensure that the ISA is up to date and focused on the most policy-  
37 relevant findings, and to assist EPA with integration of evidence within and across disciplines.  
38 Subsequently, EPA addressed comments and completed the initial integration and synthesis of the  
39 evidence.

1           The integration of evidence on health, and ecological or welfare effects, involves collaboration  
2 between scientists from various disciplines. As described in the section below, the ISA organization  
3 is based on health and ecological effect categories. As an example, an evaluation of health effects  
4 evidence would include summaries of findings from epidemiologic, controlled human exposure, and  
5 toxicological studies, and integration of the results to draw conclusions – based on the causal  
6 framework described below. Using the causal framework described in Section 1.6, EPA scientists  
7 consider aspects such as strength, consistency, coherence, and biological plausibility of the evidence,  
8 and develop draft causality judgments on the nature of the relationships. The draft integrative  
9 synthesis sections and conclusions are reviewed by EPA internal experts and, as appropriate, by  
10 outside expert authors. In practice, causality determinations often entail an iterative process of  
11 review and evaluation of the evidence. The draft ISA is released for review by the CASAC and the  
12 public, and comments received on the characterization of the science as well as the implementation  
13 of the causal framework are carefully considered in revising and completing the ISA.

## 1.4. Document Organization

14           The ISA is composed of 10 chapters. This introductory chapter presents background  
15 information and provides an overview of EPA’s framework for making causal judgments. Chapter 2  
16 is an integrated summary of key findings and conclusions regarding the source to dose paradigm,  
17 MOA, important health effects of O<sub>3</sub>, including respiratory, cardiovascular, nervous system,  
18 perinatal/developmental, and mortality outcomes, and ecological or welfare effects. Chapter 3  
19 highlights key concepts and evidence relevant to understanding the sources, ambient concentrations,  
20 and atmospheric behavior of ambient O<sub>3</sub>. Chapter 4 evaluates the evidence on human exposure to  
21 ambient O<sub>3</sub>. Chapter 5 describes the dosimetry of O<sub>3</sub> as well as a discussion of the MOA of O<sub>3</sub>.  
22 Chapter 6 reviews, evaluates and integrates epidemiologic, human clinical, and animal toxicological  
23 information on health effects related to short-term exposures (i.e., hours, days, or weeks) to O<sub>3</sub>,  
24 including respiratory effects, cardiovascular and systemic effects, central nervous system (CNS)  
25 effects, effects on the liver and cutaneous/ocular tissues, and mortality. Chapter 7 is similar to  
26 Chapter 6, but focuses on health effects related to long-term exposures (i.e., months or years) to O<sub>3</sub>.  
27 Chapter 8 summarizes the evidence on potentially susceptible populations for health effects of O<sub>3</sub>  
28 exposure. Chapter 9 reviews, evaluates and integrates evidence on the ecological effects of ambient  
29 O<sub>3</sub>, including crop and forest productivity, visible foliar injury, and ecosystem processes. Chapter 10  
30 presents relevant evidence on the welfare effects of O<sub>3</sub>, focusing primarily on the effects on climate  
31 and UV exposure. As noted above, these discussions focus on the most policy-relevant studies, and  
32 the broader body of literature considered is included in HERO; and additional HERO links are  
33 provided at the beginning of the individual chapter reference sections.

## 1.5. Document Scope

1 For the current review of the primary O<sub>3</sub> standard, relevant scientific information on human  
2 exposures and health effects associated with exposure to ambient O<sub>3</sub> has been assessed. Previous  
3 reviews have included an extensive body of evidence from all three major health disciplines –  
4 toxicology, controlled human exposure studies and epidemiology – on the health effects of O<sub>3</sub>  
5 exposure (U.S. EPA, 2006, [088089](#)). In this ISA, the conclusions from previous reviews are  
6 summarized at the beginning of each health outcome discussion to provide the foundation for  
7 consideration of evidence from recent studies. Results of key studies from previous reviews are  
8 included in discussions or tables and figures, as appropriate, and conclusions are drawn based on the  
9 synthesis of evidence from recent studies with the extensive literature summarized in previous  
10 reviews.

11 The ISA also includes the assessment of scientific information associated with known or  
12 anticipated ecological and public welfare effects that is relevant to the review of the secondary O<sub>3</sub>  
13 standard. Research on the ecological effects of O<sub>3</sub>, including impacts on vegetation, have been  
14 discussed extensively in previous AQCDs (U.S. EPA, 2006, [088089](#)). The welfare effects of O<sub>3</sub>,  
15 particularly focusing on climate forcing effects and shielding of UV light, are discussed. The current  
16 document incorporates findings of recent studies, building upon previous evaluations and  
17 conclusions.

## 1.6. EPA Framework for Causal Determination

18 The EPA has developed a consistent and transparent basis to evaluate the causal nature of air  
19 pollution-induced health or environmental effects. The framework described below establishes  
20 uniform language concerning causality and brings more specificity to the findings. This standardized  
21 language was drawn from across the federal government and wider scientific community, especially  
22 from the recent National Academy of Sciences (NAS) Institute of Medicine (IOM) document,  
23 *Improving the Presumptive Disability Decision-Making Process for Veterans*, (2008, [156586](#)) the  
24 most recent comprehensive work on evaluating causality.

25 The introductory portion of this section focuses on the evaluation of health effects evidence.  
26 While focusing on human health outcomes, the concepts are also generally relevant to causality  
27 determination for welfare effects. This section:

- 28       ▪ describes the kinds of scientific evidence used in establishing a general causal  
29       relationship between exposure and health effects;
- 30       ▪ defines cause, in contrast to statistical association;
- 31       ▪ discusses the sources of evidence necessary to reach a conclusion about the existence of  
32       a causal relationship;

- 1           ▪ highlights the issue of multifactorial causation;
- 2           ▪ identifies issues and approaches related to uncertainty; and
- 3           ▪ provides a framework for classifying and characterizing the weight of evidence in
- 4           support of a general causal relationship.

5           Approaches to assessing the separate and combined lines of evidence (e.g., epidemiologic,  
6 human clinical, and animal toxicological studies) have been formulated by a number of regulatory  
7 and science agencies, including the IOM of the NAS (2008, [156586](#)), International Agency for  
8 Research on Cancer (2006, [093206](#)), *EPA Guidelines for Carcinogen Risk Assessment* (2005,  
9 [086237](#)), and Centers for Disease Control and Prevention (2004, [056384](#)). These formalized  
10 approaches offer guidance for assessing causality. The frameworks are similar in nature, although  
11 adapted to different purposes, and have proven effective in providing a uniform structure and  
12 language for causal determinations. Moreover, these frameworks have supported decision-making  
13 under conditions of uncertainty.

### 1.6.1. Scientific Evidence Used in Establishing Causality

14           Causality determinations are based on the evaluation and synthesis of evidence from across  
15 scientific disciplines; the type of evidence that is most important for such determinations will vary  
16 by pollutant or assessment. The most compelling evidence of a causal relationship between pollutant  
17 exposures and human health effects comes from human clinical studies. This type of study  
18 experimentally evaluates the health effects of administered exposures in human volunteers under  
19 highly controlled laboratory conditions.

20           In epidemiologic or observational studies of humans, the investigator does not control  
21 exposures or intervene with the study population. Broadly, observational studies can describe  
22 associations between exposures and effects. These studies fall into several categories:  
23 cross-sectional, prospective cohort, and time-series studies. “Natural experiments” offer the  
24 opportunity to investigate changes in health with a change in exposure; these include comparisons of  
25 health effects before and after a change in population exposures, such as closure of a pollution  
26 source.

27           Experimental animal data can help characterize effects of concern, exposure-response  
28 relationships, susceptible populations and MOAs. In the absence of controlled human exposure or  
29 epidemiologic data, animal data alone may be sufficient to support a likely causal determination,  
30 assuming that humans respond similarly to the experimental species.

## 1.6.2. Association and Causation

1 “Cause” is a significant, effectual relationship between an agent and an effect on health or  
2 public welfare. “Association” is the statistical dependence among events, characteristics, or other  
3 variables. An association is *prima facie* evidence for causation; alone, however, it is insufficient  
4 proof of a causal relationship between exposure and disease. Unlike an association, a causal claim  
5 supports the creation of counterfactual claims; that is, a claim about what the world would have been  
6 like under different or changed circumstances (IOM, 2008, [156586](#)). Much of the newly available  
7 health information evaluated in this ISA comes from epidemiologic studies that report a statistical  
8 association between ambient exposure and health outcome.

9 Many of the health and environmental outcomes reported in these studies have complex  
10 etiologies. Diseases such as asthma, coronary heart disease (CHD) or cancer are typically initiated  
11 by multiple agents. Outcomes depend on a variety of factors, such as age, genetic susceptibility,  
12 nutritional status, immune competence, and social factors (Gee and Payne-Sturges, 2004, [093070](#);  
13 IOM, 2008, [156586](#)). Effects on ecosystems are often also multifactorial with a complex web of  
14 causation. Further, exposure to a combination of agents could cause synergistic or antagonistic  
15 effects. Thus, the observed risk represents the net effect of many actions and counteractions.

## 1.6.3. Evaluating Evidence for Inferring Causation

16 Moving from association to causation involves the elimination of alternative explanations for  
17 the association. In estimating the causal influence of an exposure on health or environmental effects,  
18 it is recognized that scientific findings incorporate uncertainty. “Uncertainty” can be defined as a  
19 state of having limited knowledge where it is impossible to exactly describe an existing state or  
20 future outcome, e.g., the lack of knowledge about the correct value for a specific measure or  
21 estimate. Uncertainty characterization and uncertainty assessment are two activities that lead to  
22 different degrees of sophistication in describing uncertainty. Uncertainty characterization generally  
23 involves a qualitative discussion of the thought processes that lead to the selection and rejection of  
24 specific data, estimates, scenarios, etc. Uncertainty assessment is more quantitative. The process  
25 begins with simpler measures (e.g., ranges) and simpler analytical techniques and progresses, to the  
26 extent needed to support the decision for which the assessment is conducted, to more complex  
27 measures and techniques. Data may not be available for all aspects of an assessment and those data  
28 that are available may be of questionable or unknown quality. In these situations, evaluation of  
29 uncertainty can include professional judgment or inferences based on analogy with similar situations.  
30 The net result is that the assessment will be based on a number of assumptions with varying degrees  
31 of uncertainty. Uncertainties commonly encountered in evaluating health evidence for the criteria air  
32 pollutants are outlined below for epidemiologic and experimental studies. Various approaches to  
33 evaluating uncertainty include classical statistical methods, sensitivity analysis, or probabilistic  
34 uncertainty analysis, in order of increasing complexity and data requirements. The ISA generally

1 evaluates uncertainties qualitatively in assessing the evidence from across studies; in some situations  
2 quantitative analysis approaches, such as metaregression, may be used.

3 Meta-analysis may be a valuable tool for evaluating evidence by combining results from a  
4 body of studies. Blair et al. (1995, [079190](#)) observed that meta-analysis can enhance understanding  
5 of associations between exposures and effects that are not readily apparent in examination of  
6 individual study results and can be particularly useful for formally examining sources of  
7 heterogeneity. However, these authors noted that meta-analysis may not be useful when the  
8 relationship between the exposure and outcome is obvious, when only a few studies are available for  
9 a particular exposure-outcome relationship, where there is limited access to data of sufficient quality,  
10 or where there is substantial variation in study design or population. In addition, important  
11 differences in effect estimates, exposure metrics, or other factors may limit or even preclude  
12 quantitative statistical combination of multiple studies.

13 Controlled human exposure studies evaluate the effects of exposures to a variety of pollutants  
14 in a highly controlled laboratory setting. Also referred to as human clinical studies, these  
15 experiments allow investigators to expose subjects to known concentrations of air pollutants under  
16 carefully regulated environmental conditions and activity levels. In some instances, controlled  
17 human exposure studies can also be used to characterize concentration-response relationships at  
18 pollutant concentrations relevant to ambient conditions. Controlled human exposures are typically  
19 conducted using a randomized crossover design, with subjects exposed both to O<sub>3</sub> and a clean air  
20 control. In this way, subjects serve as their own controls, effectively controlling for many potential  
21 confounders. However, human clinical studies are limited by a number of factors, including a small  
22 sample size and short exposure times. The repetitive nature of ambient O<sub>3</sub> exposures at levels that  
23 can vary widely may lead to cumulative health effects, but this type of exposure is not practical to  
24 replicate in a laboratory setting. In addition, although subjects do serve as their own controls,  
25 personal exposure to pollutants in the hours and days preceding the controlled exposures may vary  
26 significantly between and within individuals. Finally, human clinical studies require investigators to  
27 adhere to stringent health criteria for a subject to be included in the study, and therefore the results  
28 cannot necessarily be generalized to an entire population. Although some human clinical studies  
29 have included health-compromised individuals such as those with respiratory or cardiovascular  
30 disease, these individuals must also be relatively healthy and do not represent the most sensitive  
31 individuals in the population. Thus, a lack of observation of effects from human clinical studies does  
32 not necessarily mean that a causal relationship does not exist. While human clinical studies provide  
33 important information on the biological plausibility of associations observed between air pollutant  
34 exposure and health outcomes in epidemiologic studies, observed effects in these studies may  
35 underestimate the response in certain populations.

36 Epidemiologic studies provide important information on the associations between health  
37 effects and exposure of human populations to ambient air pollution. In the evaluation of  
38 epidemiologic evidence, one important consideration is potential confounding. Confounding is "... a  
39 confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because

1 the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which  
2 may be null)” (Rothman and Greenland, 1998, [086599](#)). One approach to remove spurious  
3 associations due to possible confounders is to control for characteristics that may differ between  
4 exposed and unexposed persons; this is frequently termed “adjustment.” Scientific judgment is  
5 needed regarding likely sources and magnitude of confounding, together with consideration of how  
6 well the existing constellation of study designs, results, and analyses address this potential threat to  
7 inferential validity.

8 One key consideration in this review is evaluation of the potential contribution of O<sub>3</sub> to health  
9 effects when it is a component of a complex air pollutant mixture. Reported O<sub>3</sub> effect estimates in  
10 epidemiologic studies may reflect independent O<sub>3</sub> effects on health outcomes. Ambient O<sub>3</sub> may also  
11 be serving as an indicator of complex ambient air pollution mixtures, particularly the photochemical  
12 oxidant mixture. Alternatively, co-pollutants may mediate the effects of O<sub>3</sub>, or O<sub>3</sub> may influence the  
13 toxicity of co-pollutants.

14 Another important consideration in the evaluation of epidemiologic evidence is effect  
15 modification. “Effect-measure modification differs from confounding in several ways. The main  
16 difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove  
17 from the effect estimate, effect-measure modification is a property of the effect under study . . . In  
18 epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-  
19 measure modification” (Rothman and Greenland, 1998, [086599](#)). When a risk factor is a confounder,  
20 it is the true cause of the association observed between the exposure and the outcome; when a risk  
21 factor is an effect modifier, it changes the magnitude of the association between the exposure and the  
22 outcome in stratified analyses. Examples of potential effect modifiers in some of the studies  
23 evaluated in this ISA may include environmental variables, such as temperature or humidity,  
24 individual risk factors, such as education, cigarette smoking status, age in a prospective cohort study,  
25 and community factors, such as percent of population >65 years old. It is often possible to stratify  
26 the relationship between health outcome and exposure by one or more of these potential effect  
27 modifiers. For variables that modify the association, effect estimates in each stratum will be different  
28 from one another and different from the overall estimate, indicating a different exposure-response  
29 relationship may exist in populations represented by these variables. Effect modifiers may be  
30 encountered (1) within single-city time-series studies; or (2) across cities in a two-stage hierarchical  
31 model or meta-analysis.

32 Several statistical methods are available to detect and control for potential confounders, with  
33 none of them being completely satisfactory. Multivariable regression models constitute one tool for  
34 estimating the association between exposure and outcome after adjusting for characteristics of  
35 participants that might confound the results. The use of multi-pollutant regression models has been  
36 the prevailing approach for controlling potential confounding by co-pollutants in air pollution health  
37 effects studies. Finding the likely causal pollutant from multi-pollutant regression models is made  
38 difficult by the possibility that one or more air pollutants may be acting as a surrogate for an  
39 unmeasured or poorly measured pollutant or for a particular mixture of pollutants. In addition, more

1 than one pollutant may exert similar health effects, resulting in independently observed associations  
2 for multiple pollutants. For example, O<sub>3</sub>, NO<sub>2</sub> and SO<sub>2</sub> have each been linked to respiratory effects in  
3 epidemiologic studies. Correlation between O<sub>3</sub> concentrations and various co-pollutants makes it  
4 difficult to quantitatively interpret associations between different pollutant exposures and health  
5 effects. Thus, results of models that attempt to distinguish O<sub>3</sub> effects from those of co-pollutants  
6 must be interpreted with caution. The number and degree of diversity of covariates, as well as their  
7 relevance to the potential confounders, remain matters of scientific judgment. Despite these  
8 limitations, the use of multi-pollutant models is still the prevailing approach employed in most air  
9 pollution epidemiologic studies and provides some insight into the potential for confounding or  
10 interaction among pollutants.

11 Another way to adjust for potential confounding is through stratified analysis, i.e., examining  
12 the association within homogeneous groups with respect to the confounding variable. The use of  
13 stratified analyses has an additional benefit: it allows examination of effect modification through  
14 comparison of the effect estimates across different groups. If investigators successfully measured  
15 characteristics that distort the results, adjustment of these factors help separate a spurious from a true  
16 causal association. Appropriate statistical adjustment for confounders requires identifying and  
17 measuring all reasonably expected confounders. Deciding which variables to control for in a  
18 statistical analysis of the association between exposure and disease or health outcome depends on  
19 knowledge about possible mechanisms and the distributions of these factors in the population under  
20 study. Identifying these mechanisms makes it possible to control for potential sources that may result  
21 in a spurious association.

22 Adjustment for potential confounders can be influenced by differential exposure measurement  
23 error. There are several components that contribute to exposure measurement error in epidemiologic  
24 studies, including the difference between true and measured ambient concentrations, the difference  
25 between average personal exposure to ambient pollutants and ambient concentrations at central  
26 monitoring sites, and the use of average population exposure rather than individual exposure  
27 estimates. Consideration of issues important for evaluation of exposure to ambient O<sub>3</sub> include the  
28 relationship between O<sub>3</sub> measured at central site monitors with exposure to ambient O<sub>3</sub> in indoor  
29 environments, since penetration of O<sub>3</sub> into buildings may be limited. Previous AQCDs have  
30 examined the role of measurement error for non-reactive pollutants in time-series epidemiologic  
31 studies using simulated data and mathematical analyses and suggested that transfer of effects from  
32 the “causal” variable to the confounder would only occur under unusual circumstances (i.e., “true”  
33 predictors having high positive or negative correlation; substantial measurement error; or extremely  
34 negatively correlated measurement errors) (U.S. EPA, 2004, [056905](#)).

35 Confidence that unmeasured confounders are not producing the findings is increased when  
36 multiple studies are conducted in various settings using different subjects or exposures, each of  
37 which might eliminate another source of confounding from consideration. Thus, multicity studies  
38 which use a consistent method to analyze data from across locations with different levels of

1 covariates can provide insight on potential confounding in associations. Intervention studies, because  
2 of their quasi-experimental nature, can be particularly useful in characterizing causation.

3 In addition to clinical and epidemiologic studies, the tools of experimental biology have been  
4 valuable for developing insights into human physiology and pathology. Laboratory tools have been  
5 extended to explore the effects of putative toxicants on human health, especially through the study of  
6 model systems in other species. These studies evaluate the effects of exposures to a variety of  
7 pollutants in a highly controlled laboratory setting and allow exploration of MOAs or mechanisms  
8 by which a pollutant may cause effects. Understanding the biological mechanisms underlying  
9 various health outcomes can prove crucial in establishing or negating causality. There are, however,  
10 uncertainties associated with quantitative extrapolations between laboratory animals and humans on  
11 the pathophysiological effects of any pollutant. Animal species can differ from each other in  
12 fundamental aspects of physiology and anatomy (e.g., metabolism, airway branching, hormonal  
13 regulation) that may limit extrapolation.

14 Interpretations of experimental studies of air pollution effects in laboratory animals, as in the  
15 case of environmental comparative toxicology studies, are affected by limitations associated with  
16 extrapolation models. The differences between humans and other species with regard to pollutant  
17 absorption and distribution profiles based on metabolism, hormonal regulation, breathing pattern,  
18 exposure dose, and differences in lung structure and anatomy, all have to be taken into consideration.  
19 Also, in spite of a high degree of homology and the existence of a high percentage of orthologous  
20 genes across humans and rodents (particularly mice), extrapolation of molecular alterations at the  
21 gene level is complicated by species-specific differences in transcriptional regulation. Given these  
22 molecular differences, at this time there are uncertainties associated with quantitative extrapolations  
23 between laboratory animals and humans of observed pollutant-induced pathophysiological  
24 alterations under the control of widely varying biochemical, endocrine, and neuronal factors.

#### 1.6.4. Application of Framework for Causal Determination

25 EPA uses a two-step approach to evaluate the scientific evidence on health or ecological  
26 effects of criteria pollutants. The first step determines the weight of evidence in support of causation  
27 and characterizes the strength of any resulting causal classification. The second step includes further  
28 evaluation of the quantitative evidence regarding the concentration-response relationships and the  
29 loads or levels, duration and pattern of exposures at which effects are observed.

**Table 1-2. 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 epidemiologic associations may be strengthened by other lines of evidence (e.g., clinical and animal studies) 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 paleological/historical reconstructions). The coherence of evidence from various fields greatly adds to the strength of an inference of causality. The absence of other lines of evidence, however, is not a reason to reject causality.
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. A lack of biologic understanding, however, is not a reason to reject causality.
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). There are, however, many possible reasons that a study may fail to detect an exposure-response relationship. Thus, although the presence of a biologic gradient may support causality, the absence of an exposure-response relationship does not exclude a causal relationship.
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, given a truly causal agent, a small magnitude in the effect could follow from a lower level of exposure, a lower potency, or the prevalence of other agents causing similar effects. While large effects support causality, modest effects therefore do not preclude it.
Experimental evidence	The strongest evidence for causality can be provided when a change in exposure brings about 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	As originally intended, this refers to increased inference of causality if one cause is associated with a single effect or disease (Hill, 1965, <a href="#">071664</a> ). Based on our current understanding, this is now considered one of the weaker guidelines for causality; for example, many agents cause respiratory disease and respiratory disease has multiple causes. At the scale of ecosystems, as in epidemiology, complexity is such that single agents causing single effects, and single effects following single causes, are extremely unlikely. The ability to demonstrate specificity under certain conditions remains, however, a powerful attribute of experimental studies. Thus, although the presence of specificity may support causality, its absence does not exclude it.
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”<sup>1</sup> of causality have been discussed by many philosophers  
2 and scientists. The most widely cited aspects of causality in epidemiology, and public health, in  
3 general, were articulated by Sir Austin Bradford Hill (1965, [071664](#)) and have been widely used  
4 (CDC, 2004, [056384](#); IARC, 2006, [093206](#); IOM, 2008, [156586](#); U.S. EPA, 2005, [086237](#)). These  
5 aspects (Hill, 1965, [071664](#)) have been modified (Table 1-2) for use in causal determinations  
6 specific to health and welfare effects or pollutant exposures (U.S. EPA, 2009, [179916](#)).<sup>2</sup> Some  
7 aspects are more likely than others to be relevant for evaluating evidence on the health or ecological  
8 effects of criteria air pollutants. For example, the “analogy” aspect does not always apply, especially  
9 for the gaseous criteria pollutants, and specificity would not be expected for multi-etiological health

<sup>1</sup> The “aspects” described by Hill (1965, [071664](#)) 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.

<sup>2</sup> 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 outcomes, such as asthma or cardiovascular disease, or ecological effects related to acidification.  
2 Aspects that usually play a larger role in determination of causality are consistency of results across  
3 studies, coherence of effects observed in different study types or disciplines, biological plausibility,  
4 exposure-response relationship, and evidence from “natural” experiments.

5 Although these aspects provide a framework for assessing the evidence, they do not lend  
6 themselves to being considered in terms of simple formulas or fixed rules of evidence leading to  
7 conclusions about causality (Hill, 1965, [071664](#)). For example, one cannot simply count the number  
8 of studies reporting statistically significant results or statistically nonsignificant results and reach  
9 credible conclusions about the relative weight of the evidence and the likelihood of causality. Rather,  
10 these important considerations are taken into account with the goal of producing an objective  
11 appraisal of the evidence, informed by peer and public comment and advice, which includes  
12 weighing alternative views on controversial issues. In addition, it is important to note that the aspects  
13 in Table 1-2 cannot be used as a strict checklist, but rather to determine the weight of the evidence  
14 for inferring causality. In particular, not meeting one or more of the principles does not automatically  
15 preclude a determination of causality (See discussion in CDC, 2004, [056384](#)).

### 1.6.5. Determination of Causality

16 In the ISA, EPA assesses the results of recent relevant publications, building upon evidence  
17 available during the previous NAAQS review, to draw conclusions on the causal relationships  
18 between relevant pollutant exposures and health or environmental effects. This ISA uses a five-level  
19 hierarchy that classifies the weight of evidence for causation, not just association<sup>1</sup>; that is, whether  
20 the weight of scientific evidence makes causation at least as likely as not, in the judgment of the  
21 reviewing group. In developing this hierarchy, EPA has drawn on the work of previous evaluations,  
22 most prominently the IOM’s *Improving the Presumptive Disability Decision-Making Process for*  
23 *Veterans* (2008, [156586](#)), EPA’s Guidelines for Carcinogen Risk Assessment (2005, [086237](#)), and the  
24 U.S. Surgeon General’s smoking report (CDC, 2004, [056384](#)). In the ISA, EPA uses a series of five  
25 descriptors to characterize the weight of evidence for causality. This weight of evidence evaluation is  
26 based on various lines of evidence from across the health and environmental effects disciplines.  
27 These separate judgments are integrated into a qualitative statement about the overall weight of the  
28 evidence and causality. The five descriptors for causal determination are described in Table 1-3.

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<sup>1</sup> It should be noted that the 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.

**Table 1-3. Weight of evidence for causal determination**

	<b>Health Effects</b>	<b>Ecological and Welfare Effects</b>
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. 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 replicated and consistent high-quality studies by multiple investigators.	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures. 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 co-pollutant 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 replicated and high-quality studies by multiple investigators.	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 because chance, bias and confounding cannot be ruled out. For example, at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent.	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 susceptible 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.

1 For the O<sub>3</sub> ISA, determination of causality involved the evaluation of evidence for different  
2 types of health effects associated with short- and long-term exposure periods. In making  
3 determinations of causality, evidence was evaluated for health outcome categories, such as  
4 respiratory effects, and then conclusions were drawn based upon the integration of evidence from  
5 across disciplines (e.g., epidemiology, clinical studies and toxicology) and also across the suite of  
6 related individual health outcomes. To accomplish this integration, evidence from multiple and  
7 various types of studies was considered. Response was evaluated over a range of observations which  
8 was determined by the type of study, methods of exposure or dose, and response measurements.  
9 Results from different protocols were compared and contrasted. EPA focuses on health outcome  
10 categories, rather than very specific endpoints, since the coherence of evidence across a spectrum of  
11 related endpoints (e.g., effects ranging from inflammatory effects to respiratory mortality) is an  
12 important aspect for drawing conclusions regarding causality.

1 In drawing judgments regarding causality for the criteria air pollutants, EPA focuses on  
2 evidence of effects at relevant pollutant exposures. To best inform reviews of the NAAQS, these  
3 evaluations go beyond a determination of causality at any dose or concentration to emphasize the  
4 relationship apparent at relevant pollutant exposures. Concentrations generally within an order of  
5 magnitude or two of ambient pollutant measurements are considered to be relevant for this  
6 determination. Building upon the determination of causality are questions relevant to quantifying  
7 health or environmental risks based on our understanding of the quantitative relationships between  
8 pollutant exposures and health or welfare effects. While the causality determination is based  
9 primarily on evaluation of health or environmental effects evidence, EPA also evaluates evidence  
10 related to the doses or levels at which effects are observed. Considerations relevant to evaluation of  
11 quantitative relationships for health and environmental effects are summarized below.

### 1.6.5.1. Effects on Human Populations

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

- 14 ■ What is the concentration-response, exposure-response, or dose-response relationship in  
15 the human population?
- 16 ■ What is the interrelationship between incidence and severity of effect?
- 17 ■ What exposure conditions (dose or exposure, duration and pattern) are important?
- 18 ■ What populations appear to be differentially affected (i.e., more susceptible to effects)?

19 To address these questions, the entirety of policy-relevant quantitative evidence is evaluated to  
20 best quantify those concentration-response relationships that exist. This requires evaluation of  
21 pollutant concentrations and exposure durations at which effects were observed for exposed  
22 populations, including potentially susceptible populations. This integration of evidence resulted in  
23 identification of a study or set of studies that best approximated the concentration-response  
24 relationships between health outcomes and O<sub>3</sub>, given the current state of knowledge and the  
25 uncertainties that surrounded these estimates. To accomplish this, evidence is considered from  
26 multiple and diverse types of studies. To the extent available, the ISA evaluates results from across  
27 epidemiologic studies that use various methods to evaluate the form of relationships between O<sub>3</sub> and  
28 health outcomes and draws conclusions on the most well-supported shape of these relationships.  
29 Animal data may also inform evaluation of concentration-response relationships, particularly relative  
30 to MOAs and characteristics of susceptible populations. Controlled human exposure studies have  
31 provided the strongest and most quantifiable exposure-response data on the human health effects of  
32 O<sub>3</sub>. Chapter 2 presents the integrated findings informative for evaluation of population risks.

1 An important consideration in characterizing the public health impacts associated with  
2 exposure to a pollutant is whether the concentration-response relationship is linear across the full  
3 concentration range encountered or if nonlinear relationships exist along any part of this range. Of  
4 particular interest is the shape of the concentration-response curve at and below the level of the  
5 current standards. The shape of the concentration-response curve varies, depending on the type of  
6 health outcome, underlying biological mechanisms and dose. At the human population level,  
7 however, various sources of variability and uncertainty, such as the low data density in the lower  
8 concentration range, possible influence of exposure measurement error, and individual differences in  
9 susceptibility to air pollution health effects, tend to smooth and “linearize” the concentration-  
10 response function. In addition, many chemicals and agents may act by perturbing naturally occurring  
11 background processes that lead to disease, which also linearizes population concentration-response  
12 relationships (Clewell and Crump, 2005, [156359](#); Crump et al., 1976, [003192](#); Hoel, 1980, [156555](#)).  
13 These attributes of population dose-response may explain why the available human data at ambient  
14 concentrations for some environmental pollutants (e.g., PM, O<sub>3</sub>, lead [Pb], environmental tobacco  
15 smoke [ETS], radiation) do not exhibit evident thresholds for cancer or noncancer health effects,  
16 even though likely mechanisms include nonlinear processes for some key events. These attributes of  
17 human population dose-response relationships have been extensively discussed in the broader  
18 epidemiologic literature (Rothman and Greenland, 1998, [086599](#)).

19 Publication bias is a source of uncertainty regarding the magnitude of health risk estimates. It  
20 is well understood that studies reporting non-null findings are more likely to be published than  
21 reports of null findings, and publication bias can also result in overestimation of effect estimate sizes  
22 (Ioannidis, 2008, [188317](#)). For example, effect estimates from single-city epidemiologic studies have  
23 been found to be generally larger than those from multicity studies (Anderson et al., 2005, [087916](#))  
24 Although publication bias commonly exists for many research areas, it may be present to a lesser  
25 degree for epidemiologic studies on O<sub>3</sub>. Many epidemiologic studies have focused on the effects of  
26 PM, and O<sub>3</sub> was largely considered as a potentially confounding co-pollutant of PM. Thus, O<sub>3</sub>-effect  
27 estimates may have been presented in these studies regardless of the statistical significance of the  
28 results.

29 Finally, identification of the susceptible population groups contributes to an understanding of  
30 the public health impact of pollutant exposures. In this ISA, the term “susceptible population” will  
31 be used as an overarching concept to encompass populations variously described as susceptible,  
32 vulnerable, or sensitive. “Susceptible populations” is defined here as those populations that have a  
33 greater likelihood of experiencing health effects related to exposure to an air pollutant (e.g., O<sub>3</sub>) due  
34 to a variety of factors including but not limited to: genetic or developmental factors, race, gender,  
35 lifestage, lifestyle (e.g., smoking status and nutrition) or preexisting disease; as well as population-  
36 level factors that can increase an individual's exposure to an air pollutant (e.g., O<sub>3</sub>) such as  
37 socioeconomic status [SES], which encompasses reduced access to health care, low educational  
38 attainment, residential location, and other factors. Epidemiologic studies can help identify  
39 susceptible populations by evaluating health responses in the study population. Examples include

1 stratified analyses for subsets of the population under study or testing for interactions or effect  
2 modification by factors such as gender, age group, or health status. Experimental studies using  
3 animal models of susceptibility or disease can also inform the extent to which health risks are likely  
4 greater in specific population groups. Further discussion of these groups is presented in Section 5.7.

### 1.6.5.2. Effects on Ecosystems or Public Welfare

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

- 7       ▪ What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations,  
8       functions, etc.) appear to be affected, or are more sensitive to effects?
  
- 9       ▪ Under what exposure conditions (amount deposited or concentration, duration and  
10      pattern) are effects seen?
  
- 11      ▪ What is the shape of the concentration-response or exposure-response relationship?

12 Evaluations of causality generally consider the probability of quantitative changes in  
13 ecological and welfare effects in response to exposure. A challenge to the quantification of exposure-  
14 response relationships for ecological effects is the great regional and local variability in ecosystems.  
15 Thus, exposure-response relationships are often determined for a specific ecological system and  
16 scale, rather than at the national or even regional scale. Quantitative relationships therefore are  
17 available site by site. For example, an ecological response to deposition of a given pollutant can  
18 differ greatly between ecosystems. Where results from greenhouse or animal ecotoxicological  
19 studies are available, they may be used to aid in characterizing exposure-response relations,  
20 particularly relative to mechanisms of action, and characteristics of sensitive biota.

### 1.6.6. Concepts in Evaluating Adversity of Health Effects

21 In evaluating the health evidence, a number of factors can be considered in determining the  
22 extent to which health effects are “adverse” for health outcomes such as changes in lung function or  
23 in cardiovascular health measures. Some health outcome events, such as hospitalization for  
24 respiratory or cardiovascular diseases, are clearly considered adverse; what is more difficult is  
25 determining the extent of change in the more subtle health measures that is adverse. What constitutes  
26 an adverse health effect may vary between populations. Some changes in healthy individuals may  
27 not be considered adverse; while those of a similar type and magnitude are potentially adverse in  
28 more susceptible individuals.

29 For example, the extent to which changes in lung function are adverse has been discussed by  
30 the American Thoracic Society (ATS) in an official statement titled *What Constitutes an Adverse*  
31 *Health Effect of Air Pollution?* (2000, [011738](#)). This statement updated the guidance for defining

1 adverse respiratory health effects that had been published 15 years earlier (ATS, 1985, [006522](#)),  
2 taking into account new investigative approaches used to identify the effects of air pollution and  
3 reflecting concern for impacts of air pollution on specific susceptible groups. In the 2000 update,  
4 there was an increased focus on quality of life measures as indicators of adversity and a more  
5 specific consideration of population risk. Exposure to air pollution that increases the risk of an  
6 adverse effect to the entire population is viewed as adverse, even though it may not increase the risk  
7 of any identifiable individual to an unacceptable level. For example, a population of asthmatics  
8 could have a distribution of lung function such that no identifiable individual has a level associated  
9 with significant impairment. Exposure to air pollution could shift the distribution such that no  
10 identifiable individual experiences clinically relevant effects. This shift toward decreased lung  
11 function, however, would be considered adverse because individuals within the population would  
12 have diminished reserve function and therefore would be at increased risk to further environmental  
13 insult.

14 It is important to recognize that the more subtle health outcomes may be linked to health  
15 events that are clearly adverse. For example, air pollution has been shown to affect markers of  
16 transient myocardial ischemia such as ST-segment abnormalities and onset of exertional angina. In  
17 some cases, these effects are silent yet may still increase the risk of a number of cardiac events,  
18 including MI and sudden death.

## 1.7. Summary

19 This draft ISA is a concise evaluation and synthesis of the most policy-relevant science for  
20 reviewing the NAAQS for O<sub>3</sub>, and it is the chief means for communicating the critical science  
21 judgments relevant to that NAAQS review. It reviews the most policy-relevant evidence from  
22 atmospheric science, exposure, health, and ecological and welfare effects studies; and includes  
23 mechanistic evidence from basic biological science. A framework for making critical judgments  
24 concerning causality was presented in this chapter. It relies on a widely accepted set of principles and  
25 standardized language to express evaluation of the evidence. This approach can bring rigor and  
26 clarity to current and future assessments. Once complete, the ISA should assist EPA and others, now  
27 and in the future, to accurately represent what is presently known and what remains unknown  
28 concerning the effects of O<sub>3</sub> on human health and public welfare.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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# Chapter 2. Integrative Health and Welfare Effects Overview

1           The subsequent chapters of this ISA will present the most policy-relevant information related  
2 to this review of the NAAQS for O<sub>3</sub>. This chapter integrates the key findings from the disciplines  
3 evaluated in this current assessment of the O<sub>3</sub> scientific literature, which includes the atmospheric  
4 sciences, ambient air data analyses, exposure assessment, dosimetry, health studies  
5 (e.g., toxicological, controlled human exposure, and epidemiologic), and welfare effects. The EPA  
6 framework for causal determinations described in Chapter 1 has been applied to the body of  
7 scientific evidence in order to collectively examine the health or welfare effects attributed to O<sub>3</sub>  
8 exposure in a two-step process.

9           As described in Chapter 1, EPA assesses the results of recent relevant publications, building  
10 upon evidence available during the previous NAAQS review, to draw conclusions on the causal  
11 relationships between relevant pollutant exposures and health or environmental effects. This ISA  
12 uses a five-level hierarchy that classifies the weight of evidence for causation:

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

18           Beyond judgments regarding causality are questions relevant to quantifying health or  
19 environmental risks based on our understanding of the quantitative relationships between pollutant  
20 exposures and health or welfare effects. Once a determination is made regarding the causal  
21 relationship between the pollutant and outcome category, important questions regarding quantitative  
22 relationships include:

- 23           ▪ What is the concentration-response or dose-response relationship?
- 24           ▪ Under what exposure conditions (amount deposited, dose or concentration, duration and  
25           pattern) are effects observed?

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

- 1           ▪ What populations appear to be differentially affected i.e., more susceptible to effects?
- 2           ▪ What elements of the ecosystem (e.g., types, regions, taxonomic groups, populations,
- 3           functions, etc.) appear to be affected or are more sensitive to effects?

4           To address these questions, in the second step of the EPA framework, the entirety of  
5 quantitative evidence is evaluated to identify and characterize potential concentration-response  
6 relationships. This requires evaluation of levels of pollutant and exposure durations at which effects  
7 were observed for exposed populations including potentially susceptible populations.

8           This chapter summarizes and integrates the newly available scientific evidence that best  
9 informs consideration of the policy-relevant questions that frame this assessment, presented in  
10 Chapter 1. Section 2.1 discusses the trends in ambient concentrations and sources of O<sub>3</sub> and provides  
11 a brief summary of ambient air quality for short- and long-term exposure durations. Section 2.2  
12 presents the evidence regarding personal exposure to ambient O<sub>3</sub> in outdoor and indoor  
13 microenvironments, and it discusses the relationship between ambient O<sub>3</sub> concentrations and  
14 exposure to O<sub>3</sub> from ambient sources. Section 2.3 provides a discussion of the dosimetry and mode  
15 of action evidence for O<sub>3</sub> exposure. Section 2.4 integrates the evidence for studies that examine the  
16 health effects associated with short- and long-term exposure to O<sub>3</sub> and discusses important  
17 uncertainties identified in the interpretation of the scientific evidence. Section 2.5 provides a  
18 discussion of policy-relevant considerations, such as potentially susceptible populations, lag  
19 structure, and the O<sub>3</sub> concentration-response relationship. Section 2.6 integrates the health evidence  
20 from the different scientific disciplines and exposure durations. Finally, Section 2.7 summarizes the  
21 evidence for welfare effects related to O<sub>3</sub> exposure, and Section 2.8 reviews the literature on climate  
22 and UV-B.

## 2.1. Atmospheric Chemistry and Ambient Concentrations

23           In the stratosphere, O<sub>3</sub> serves the beneficial role of blocking the Sun's harmful ultraviolet  
24 radiation and preventing the majority of it from reaching the Earth's surface. In the troposphere,  
25 however, O<sub>3</sub> and other photochemical oxidants are air pollutants with potentially harmful effects on  
26 living organisms and materials. Chapter 3 of this review addresses the atmospheric chemistry  
27 associated with tropospheric O<sub>3</sub> and other related photochemical oxidants and provides a detailed  
28 analysis of recent surface-level concentrations. This material builds on information reported in the  
29 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). Topics covered below and addressed in further detail in  
30 Chapter 3 include: (1) physical and chemical processes of O<sub>3</sub> formation and removal;  
31 (2) atmospheric modeling; (3) policy relevant background concentrations; (4) monitoring techniques  
32 and networks; and (5) ambient concentrations.

## 2.1.1. Physical and Chemical Processes

1 Ozone in the troposphere is a secondary pollutant; it is formed by photochemical reactions of  
2 precursor gasses and is not directly emitted from specific sources. Ozone and other oxidants, such as  
3 peroxyacetyl nitrate (PAN) and hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) form in polluted areas by atmospheric  
4 reactions involving two main classes of precursor pollutants: VOCs and  $\text{NO}_x$ . Carbon monoxide  
5 (CO) is also important for  $\text{O}_3$  formation in polluted areas and in the remote troposphere. The  
6 formation of  $\text{O}_3$ , other oxidants and oxidation products from these precursors is a complex, nonlinear  
7 function of many factors: (1) the intensity and spectral distribution of sunlight; (2) atmospheric  
8 mixing; (3) concentrations of precursors in the ambient air and the rates of chemical reactions of  
9 these precursors; and (4) processing on cloud and aerosol particles.

10 Ozone is present not only in polluted urban atmospheres but throughout the troposphere, even  
11 in remote areas of the globe. The same basic processes involving sunlight-driven reactions of  $\text{NO}_x$ ,  
12 VOCs and CO contribute to  $\text{O}_3$  formation throughout the troposphere. These processes also lead to  
13 the formation of other photochemical products, such as PAN, nitric acid ( $\text{HNO}_3$ ), and sulfuric acid  
14 ( $\text{H}_2\text{SO}_4$ ), and to other compounds, such as formaldehyde (HCHO) and other carbonyl compounds.

### 2.1.1.1. Gas Phase Reactions Leading to Ozone Formation and Loss

15 Photochemical processes involved in  $\text{O}_3$  formation are relatively well understood and were  
16 reviewed in detail in the 2006  $\text{O}_3$  AQCD (U.S. EPA, 2006, [088089](#)). The photochemical formation of  
17  $\text{O}_3$  in the troposphere proceeds through the photolysis of nitrogen dioxide ( $\text{NO}_2$ ) to yield nitric oxide  
18 (NO) and a ground-state oxygen atom,  $\text{O}(^3\text{P})$ , which then reacts with molecular oxygen ( $\text{O}_2$ ) to form  
19  $\text{O}_3$ . Free radicals formed in the atmosphere through the oxidation of VOCs and CO proceed to  
20 oxidize NO back to  $\text{NO}_2$ , hence perpetuating the  $\text{O}_3$  forming cycle. In urban areas, VOCs and CO are  
21 both important for  $\text{O}_3$  formation. In nonurban vegetated areas, biogenic VOCs emitted from  
22 vegetation tend to be the most important. In the remote troposphere, methane ( $\text{CH}_4$ ) – structurally the  
23 simplest VOC – and CO are the main carbon-containing precursors to  $\text{O}_3$  formation. A schematic  
24 overview of the major photochemical cycles influencing  $\text{O}_3$  in the troposphere and the stratosphere is  
25 given in Figure 3-1.

26 Ozone is lost through a number of gas phase reactions and deposition to surfaces. The reaction  
27 of  $\text{O}_3$  with NO to produce  $\text{NO}_2$  mainly results in the recycling of  $\text{O}_3$  downwind via the  
28 recombination of  $\text{O}(^3\text{P})$  with  $\text{O}_2$  to reform  $\text{O}_3$ . By itself, this reaction does not lead to a net change in  
29  $\text{O}_3$  unless the  $\text{NO}_2$  is converted to a stable end product such as  $\text{HNO}_3$  or a temporary reservoir  
30 product such as PAN. Ozone also reacts with unsaturated hydrocarbons and with hydrogen  
31 containing free radicals (OH,  $\text{HO}_2$ ). Recent field studies aimed at obtaining a better understanding of  
32 atmospheric chemical processes involved in  $\text{O}_3$  formation are discussed in Section 3.2.

33 Convective processes and small scale turbulence transport  $\text{O}_3$  and other pollutants both upward  
34 and downward throughout the planetary boundary layer and the free troposphere. In many areas of  
35 the U.S.,  $\text{O}_3$  and its precursors can be transported over long distances, aided by vertical mixing. The

1 transport of pollutants downwind of major urban centers is characterized by the development of  
2 urban plumes. Meteorological conditions, small-scale circulation patterns, localized chemistry, and  
3 mountain barriers can influence mixing on a smaller scale, resulting in frequent heterogeneous O<sub>3</sub>  
4 concentrations across an individual urban area. More details and observations of these processes are  
5 included in Section 3.2 and Section 3.6.

### 2.1.1.2. Sources of Precursors Involved in Ozone Formation

6 Emissions of O<sub>3</sub> precursor compounds (NO<sub>x</sub>, VOCs, and CO) can be divided into  
7 anthropogenic and natural source categories. Natural sources can be further divided into biogenic  
8 from vegetation, microbes, and animals, and abiotic from biomass burning, lightning, and geogenic  
9 sources. However, the distinction between natural sources and anthropogenic sources is often  
10 difficult to make in practice, as human activities affect directly or indirectly emissions from what  
11 would have been considered natural sources during the preindustrial era. The magnitudes of O<sub>3</sub>  
12 precursor sources are strongly location- and time-dependent and so average emission estimates  
13 should not be used to apportion sources of exposure. More details on O<sub>3</sub> precursor emission  
14 inventories are included in Section 3.2.

### 2.1.2. Atmospheric Modeling

15 Chemistry-transport models (CTMs) have been widely used to compute the interactions  
16 among atmospheric pollutants and their transformation products, and the transport and deposition of  
17 pollutants. They have also been widely used to improve our basic understanding of atmospheric  
18 chemical processes and to develop control strategies. The main components of a comprehensive  
19 atmospheric chemistry modeling system are shown in Figure 3-5 and are discussed in more detail in  
20 Section 3.3.

21 The domains of CTMs extend from a few hundred kilometers on a side to the entire globe.  
22 Most major regional (i.e., sub-continental) scale air-related modeling efforts at EPA rely on the  
23 Community Multi-scale Air Quality modeling system (CMAQ). CMAQ's horizontal domain  
24 typically extends over North America with efforts underway to extend it over the entire Northern  
25 Hemisphere. The upper boundary for CMAQ is typically set at 100 hPa, which is located on average  
26 at about 16-km altitude. CMAQ is most often driven by the MM5 mesoscale meteorological model,  
27 though it may be driven by other meteorological models including the Weather Research Forecasting  
28 (WRF) model and the Regional Atmospheric Modeling System (RAMS). Other major air quality  
29 systems used for regional scale applications include The Comprehensive Air Quality Model with  
30 extensions (CAMx) and the Weather Research and Forecast model with Chemistry (WRF/Chem).

31 Fine scale resolution is necessary to resolve features which can affect pollutant concentrations  
32 such as urban heat island circulation; sea breezes; mountain and valley breezes; and the nocturnal  
33 low-level jet. Horizontal domains are typically modeled by nesting a finer grid model within a larger  
34 domain model of coarser resolution. Caution must be exercised in using nested models because

1 certain parameterizations like those for convection might be valid on a relatively coarse grid scale  
2 but may not be valid on finer scales and because incompatibilities can occur at the model boundaries.  
3 The use of finer resolution in CTMs will require advanced parameterizations of meteorological  
4 processes such as boundary layer fluxes, deep convection, and clouds, and necessitate finer-scale  
5 inventories of land use, source locations, and emission inventories.

6 Because of the large number of chemical species and reactions that are involved in the  
7 oxidation of realistic mixtures of anthropogenic and biogenic hydrocarbons, condensed mechanisms  
8 must be used to simplify atmospheric models. These mechanisms can be tested by comparison with  
9 smog chamber data. However, the existing chemical mechanisms often neglect many important  
10 processes such as the formation and subsequent reactions of long-lived carbonyl compounds, the  
11 incorporation of the most recent information about intermediate compounds, and heterogeneous  
12 reactions involving cloud droplets and aerosol particles. As a result, models such as CMAQ have had  
13 difficulties with capturing the regional nature of O<sub>3</sub> episodes, in part because of uncertainty in the  
14 chemical pathways converting NO<sub>x</sub> to HNO<sub>3</sub> and recycling of NO<sub>x</sub>.

15 Each of the model components shown in Figure 3-5 has associated uncertainties and the  
16 relative importance of these uncertainties varies with the modeling application. The largest errors in  
17 photochemical modeling are still thought to arise from the meteorological and emissions inputs to  
18 the model. Algorithms must be used for simulating meteorological processes that occur on spatial  
19 scales smaller than the model's grid spacing and for calculating the dependence of emissions on  
20 meteorology and time. Significant errors in emissions can occur if inappropriate assumptions are  
21 used in these parameterizations.

22 The performance of CTMs must be evaluated by comparison with field data as part of a cycle  
23 of model evaluations and subsequent improvements. Discrepancies between model predictions and  
24 observations can be used to point out gaps in current understanding of atmospheric chemistry and to  
25 spur improvements in parameterizations of atmospheric chemical and physical processes.

### 2.1.3. Policy Relevant Background Concentrations

26 The background concentrations of O<sub>3</sub> that are useful for risk and policy assessments informing  
27 decisions about the NAAQS are referred to as policy-relevant background (PRB) concentrations.  
28 PRB concentrations have historically been defined by EPA as those concentrations that would occur  
29 in the U.S. in the absence of anthropogenic emissions in continental North America (CNA) defined  
30 here as the U.S., Canada, and Mexico. For this document, PRB concentrations include contributions  
31 from natural sources everywhere in the world and from anthropogenic sources outside CNA.

32 Contributions to PRB O<sub>3</sub> include photochemical reactions involving natural emissions of  
33 VOCs, NO<sub>x</sub>, and CO as well as the long-range transport of O<sub>3</sub> and its precursors from outside CNA  
34 and the stratospheric-tropospheric exchange (STE) of O<sub>3</sub>. Natural sources of O<sub>3</sub> precursors include  
35 biogenic emissions, wildfires, and lightning. Biogenic emissions from agricultural activities in CNA  
36 are not considered in the formation of PRB O<sub>3</sub>. PRB O<sub>3</sub> sources and concentrations are summarized  
37 here with further details in Section 3.4.

### **2.1.3.1. Contributions from anthropogenic emissions outside North America**

1 Because the mean tropospheric lifetime of O<sub>3</sub> is 30-35 days, O<sub>3</sub> can be transported from  
2 continent to continent and around the globe in the Northern Hemisphere and O<sub>3</sub> produced by U.S.  
3 emissions can be recirculated around northern mid-latitudes back to the U.S. High elevation sites are  
4 most susceptible to the intercontinental transport of pollution, particularly during spring. Surface  
5 PRB O<sub>3</sub> contributions are much smaller than those derived in the free troposphere because of  
6 dilution and chemical destruction during downward transport to the surface. There are no instances  
7 where direct observation of PRB contributions from anthropogenic emissions outside North America  
8 are directly observable; careful screening of observations and application of photochemical models  
9 must be used instead to estimate anthropogenic contributions to PRB from sources outside North  
10 America.

### **2.1.3.2. Contributions from the stratosphere**

11 Ozone is produced naturally by photochemical reactions in the stratosphere and some of this  
12 O<sub>3</sub> is transported downward into the troposphere throughout the year in a process known as  
13 tropopause folding. Maximum stratospheric contributions occur during late winter and early spring,  
14 particularly behind cold fronts that mix tropospheric and stratospheric air. Stratospheric intrusions  
15 that reach the surface are rare. Much more common are intrusions which penetrate only to the middle  
16 and upper troposphere. However, O<sub>3</sub> transported to the upper and middle troposphere can still affect  
17 surface concentrations through various exchange mechanisms that mix air from the free troposphere  
18 with air in the planetary boundary layer. There is considerable uncertainty in the magnitude and  
19 distribution of this potentially important source of tropospheric O<sub>3</sub>.

### **2.1.3.3. Natural sources of precursors to PRB Ozone formation**

20 Biogenic sources of VOC and CO emissions contribute to precursors to PRB O<sub>3</sub> formation.  
21 These sources were discussed above in Section 2.1.1.1 with further details in Section 3.2.

22 Biomass burning in the form of wildfires and prescribed fires contribute to NO<sub>x</sub>, CO and  
23 VOCs, precursors to PRB O<sub>3</sub> formation. Biomass burning exhibits strong seasonality and interannual  
24 variability, with most biomass burned during the local dry season. There is considerable uncertainty  
25 in attributing the fraction of wildfire emissions to human activities because the emissions from  
26 naturally occurring fires that would have been present in the absence of fire suppression practices are  
27 not known.

28 Lightning is also a source for NO<sub>x</sub> production. Although total column estimates of lightning  
29 produced NO<sub>x</sub> are substantial, this source does not contribute substantially to the NO<sub>x</sub> burden in the  
30 continental boundary layer. This is because only 2% of NO<sub>x</sub> production by lightning occurs within  
31 the boundary layer and most occurs in the free troposphere where much of the NO<sub>x</sub> produced is  
32 converted to more oxidized nitrogen species during downward transport.

#### 2.1.3.4. Estimating PRB Concentrations

1           There are two approaches to estimating PRB concentrations that have been considered thus  
2 far. The first involves using measurements and the second the use of chemistry-transport models.  
3 The 2006 O<sub>3</sub> AQCD (Section 3.9) (U.S. EPA, 2006, [088089](#)) noted that estimates of PRB  
4 concentrations cannot be obtained solely by examining measurements of O<sub>3</sub> obtained at relatively  
5 remote monitoring sites in the U.S. because of the long-range transport from anthropogenic source  
6 regions within North America. The 2006 AQCD also noted that it is impossible to determine sources  
7 of O<sub>3</sub> without ancillary data that could be used as tracers of sources or to calculate photochemical  
8 production and loss rates. Furthermore, the use of monitoring data is limited to the edges of the  
9 domain of interest because PRB O<sub>3</sub> entering from outside North America is destroyed over North  
10 America either through chemical reactions or by deposition. Within North America, PRB O<sub>3</sub> is only  
11 produced by natural sources. Therefore, the current definition of PRB implies that only CTMs can be  
12 used to estimate the range of PRB values. A further advantage to using models is that the entire range  
13 of O<sub>3</sub> concentrations in different environments can be used to evaluate model performance.  
14 However, there may be specific instances such as stratospheric intrusions that occur on spatial scales  
15 too fine to be resolved by the current generation of global CTMs.

16           Estimates of PRB concentrations for April-May, 2001 (Figure 3-9) and June-August, 2001  
17 (Figure 3-10) from the GEOS-Chem model used in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#))  
18 are described in Section 3.4. These estimates indicated that PRB O<sub>3</sub> concentrations in the U.S.  
19 surface air were generally 15-35 ppb from June through August. Concentrations decline from spring  
20 to summer and are generally <25 ppb under conditions conducive to high O<sub>3</sub> episodes. PRB O<sub>3</sub>  
21 concentrations may be higher, especially at high altitude sites during the spring, due to enhanced  
22 contributions from (1) pollution sources outside North America; and (2) stratospheric O<sub>3</sub> exchange.  
23 Simulated monthly mean concentrations in different quadrants of the U.S. are typically within  
24 5 ppbv of observations at remote CASTNET sites, with no significant bias, except in the Southeast  
25 in summer when the model is 8-12 ppbv too high. This bias might be due to excessive background  
26 O<sub>3</sub> transported in from the Gulf of Mexico and the tropical Atlantic Ocean or to inaccuracies in  
27 emissions inventories within the U.S. The model reproduced the occurrences of relatively high O<sub>3</sub> at  
28 remote sites, and shows that these can generally be explained by North American pollution.

29           Although many of the features of the day-to-day variability of O<sub>3</sub> at relatively remote  
30 monitoring sites in the U.S. are simulated reasonably well, uncertainties in the calculation of the  
31 temporal variability of O<sub>3</sub> originating from different sources on shorter time scales must be  
32 recognized. The uncertainties stem in part from an underestimate in the seasonal variability in the  
33 STE of O<sub>3</sub>, the geographical variability of this exchange, and the variability in the exchange between  
34 the free troposphere and the planetary boundary layer in the model. In addition, the relatively coarse  
35 spatial resolution in the model (2°×2.5°) limited the ability to provide separate estimates for cities  
36 located close to each other, and so only regional estimates were provided for the 2006 O<sub>3</sub> AQCD  
37 (U.S. EPA, 2006, [088089](#)).

## 2.1.4. Monitoring

### 2.1.4.1. Routine Monitoring Techniques

1           The Federal Reference Method (FRM) for O<sub>3</sub> measurement is called the Chemiluminescence  
2 Method (CLM) and is based on the detection of chemiluminescence resulting from the reaction of O<sub>3</sub>  
3 with ethylene gas. The first ultraviolet (UV) absorption photometric analyzers were approved as  
4 Federal Equivalent Methods (FEMs) in 1977 and gained rapid acceptance for NAAQS compliance  
5 purposes due to ease of operation, relatively low cost, and reliability. Almost all of the state or local  
6 air monitoring stations (SLAMS) that reported data to EPA Air Quality System (AQS) from 2005 to  
7 2009 used UV absorption photometer FEMs and greater than 96% of O<sub>3</sub> monitors met precision and  
8 bias goals during this period. The rationale, history, and calibration of O<sub>3</sub> measurements were  
9 summarized in the 1996 O<sub>3</sub> AQCD (U.S. EPA, 1996, [017831](#)) and the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
10 2006, [088089](#)) and focused on the state of ambient O<sub>3</sub> measurements at that time as well as  
11 evaluation of interferences and new developments. Section 3.5 in this review includes the current  
12 state of O<sub>3</sub> measurements, interferences, and new developments for the period 2005-2009.

13           Satellite observations for O<sub>3</sub> are growing as a resource for many purposes, including model  
14 evaluation, assessing emissions reductions, pollutant transport, and air quality management. Satellite  
15 remote sensing instruments do not directly measure the composition of the atmosphere. Satellite  
16 retrievals are conducted using the solar backscatter or thermal infrared emission spectra and a variety  
17 of algorithms. Most satellite measurement systems have been developed for stratospheric  
18 measurement of the total O<sub>3</sub> column. Mathematical techniques have been developed and must be  
19 applied to derive information from these systems about tropospheric O<sub>3</sub>.

### 2.1.4.2. Ambient Ozone Network Design

20           To support the NAAQS, state and local monitoring agencies must operate O<sub>3</sub> monitors at  
21 various locations depending on the area size and typical peak concentrations (expressed in  
22 percentages below, or near the O<sub>3</sub> NAAQS). SLAMS make up the ambient air quality monitoring  
23 sites that are primarily needed for NAAQS comparisons and include Photochemical Assessment  
24 Monitoring Stations (PAMS), National Core (NCore), and all other State or locally-operated stations  
25 except for the monitors designated as special purpose monitors (SPMs).

26           In 2009, there were 1208 SLAMS O<sub>3</sub> monitors reporting values to the EPA AQS database  
27 (Figure 3-16). Since O<sub>3</sub> levels decrease significantly in the colder parts of the year in many areas, O<sub>3</sub>  
28 is required to be monitored at SLAMS monitoring sites only during the “O<sub>3</sub> season.” PAMS provides  
29 more comprehensive data on O<sub>3</sub> in areas classified as serious, severe, or extreme nonattainment for  
30 O<sub>3</sub>. There were a total of 119 PAMS reporting values to the EPA AQS database in 2009. NCore is a  
31 new multi-pollutant monitoring network currently being implemented to meet multiple monitoring  
32 objectives. Each state is required to operate at least one NCore site and the network will consist of  
33 about 60 urban and 20 rural sites nationwide.

1 The Clean Air Status and Trends Network (CASTNET) is a regional monitoring network  
2 established to assess trends in acidic deposition and also provides concentration measurements of O<sub>3</sub>.  
3 CASTNET O<sub>3</sub> monitors operate year round and are primarily located in rural areas. At the beginning  
4 of 2010, there were 80 CASTNET sites located in, or near, rural areas. The NPS also operates a  
5 Portable Ozone Monitoring Systems (POMS) network. The POMS couples the small, low-power O<sub>3</sub>  
6 monitor with a data logger, meteorological measurements, and solar power in a self contained system  
7 for monitoring in remote locations. Twenty NPS POMS reported O<sub>3</sub> data to AQS in 2010. A map of  
8 the current and proposed rural NCore sites, along with the CASTNET, and the NPS POMS sites is  
9 shown in Figure 3-17.

## 2.1.5. Ambient Concentrations

10 Ozone is the only photochemical oxidant other than NO<sub>2</sub> that is routinely monitored and for  
11 which a comprehensive database exists. Data for other photochemical oxidants typically have been  
12 obtained only as part of special field studies. Most continuous O<sub>3</sub> monitors report hourly average  
13 concentrations. This data can be used as reported 1-h avg, or reported as a daily metric such as: (1)  
14 the average of the hourly observations over a 24-h period (24-h avg); (2) the maximum hourly  
15 observation occurring in a 24-h period (1-h daily max); and (3) the maximum 8-h running average of  
16 the hourly observations occurring in a 24-h period (8-h daily max).

17 Section 3.6.1 includes an analysis of U.S. O<sub>3</sub> data reported to AQS between 2007 and 2009.  
18 The median 1-h daily max, 8-h daily max, and 24-h avg O<sub>3</sub> concentrations across all sites were 44,  
19 40, and 29 ppb, respectively. The 98th percentiles of these same metrics across all sites were 86, 74,  
20 and 55 ppb, respectively. The 8-h daily max and 1-h daily max metrics were highly correlated  
21 (median r = 0.97, IQR = 0.96-0.98) while comparisons with the 24-h avg metric were lower (e.g.,  
22 median r = 0.83, IQR = 0.78-0.88 for comparison between the 24-h avg and the 1-h daily max). The  
23 ratio and correlation between these metrics, however, can be very site-specific.

### 2.1.5.1. Urban-Focused Spatial Variability

24 AQS O<sub>3</sub> concentrations were used to investigate urban-focused spatial variability in  
25 Section 3.6.2. Figure 3-22 contains the county-scale 8-h daily max O<sub>3</sub> concentrations from the  
26 highest monitor within each U.S. county for 2007-2009 (top map) with seasonal stratification  
27 (bottom 4 maps). This map is only meant to illustrate the general spatial and temporal distribution in  
28 nationwide O<sub>3</sub> concentrations, and is limited by monitor availability, resulting in the majority of U.S.  
29 counties not having available data. Furthermore, this map is not representative of O<sub>3</sub> concentrations  
30 at all locations or times within the counties shown; considerable spatial variability can and does exist  
31 within a county.

32 The highest 3-yr avg (2007-2009) 8-h daily max O<sub>3</sub> concentrations (≥ 50 ppb), shown in  
33 Figure 3-22, occur in counties in southern California, Arizona, Colorado and Tennessee. The lowest  
34 monitored 3-yr avg 8-h daily max O<sub>3</sub> concentrations (<30 ppb) occur in Pacific Coast counties in

1 northern California and Washington, as well as in two northeastern counties in Pennsylvania and  
2 Massachusetts. The seasonally-stratified county-scale maps in the lower half of Figure 3-22 illustrate  
3 the strong seasonality in 8-h daily max O<sub>3</sub> concentrations.

4 To investigate urban-scale variability, 20 focus cities were selected for closer analysis here and  
5 in Section 3.6.2; these cities were selected based on their importance in O<sub>3</sub> epidemiology studies and  
6 on their geographic distribution across the U.S. The warm season (May-September) distribution of  
7 the 8-h daily max O<sub>3</sub> concentrations from 2007-2009 for the 20 focus cities is included in Table 3-10.

8 Box plots of the distribution of 2007-2009 warm-season 8-h daily max O<sub>3</sub> data from each  
9 individual monitor in the 20 focus cities were used in Section 3.6.2 to investigate individual city  
10 variability in O<sub>3</sub> concentrations. Several cities had relatively little spatial variability in 8-h daily max  
11 O<sub>3</sub> concentrations (e.g., correlations ranging from 0.61 to 0.96 in Atlanta) while other cities exhibited  
12 considerably more variability in O<sub>3</sub> concentrations (e.g., correlations ranging from -0.06 to 0.97 for  
13 Los Angeles). The negative and near-zero correlations in Los Angeles were between monitors with a  
14 relatively large separation distance (>150 km), but even some of the closer monitor pairs were not  
15 very highly correlated. Similar to the correlation, the coefficient of divergence (COD) was found to  
16 be highly dependent on the urban area under investigation. As a result, caution should be observed in  
17 using data from a sparse network of ambient O<sub>3</sub> monitors to approximate community-scale  
18 exposures.

### 2.1.5.2. Rural-Focused Spatial Variability

19 AQS O<sub>3</sub> data for monitors located within six rural monitoring sites were used in Section 3.6.2  
20 to investigate rural-focused O<sub>3</sub> concentration variability. These rural monitoring sites tend to be less  
21 directly affected by obvious anthropogenic pollution sources than urban sites. However, they can be  
22 regularly affected by transport of O<sub>3</sub> or O<sub>3</sub> precursors from upwind urban areas, or by local  
23 anthropogenic emissions within the rural areas such as emissions from motor vehicles, power  
24 generation, biomass combustion, or oil and gas operations. As a result, monitoring data from these  
25 rural locations are not unaffected by anthropogenic emissions.

26 Box plots of 8-h daily max O<sub>3</sub> concentrations measured at the 6 rural monitoring sites during  
27 the warm season (May-September) between 2007 and 2009 are shown in Figure 3-37. The sites  
28 include one in Adirondack State Park (ADSP) on Whiteface Mountain in Upstate NY, one in Mount  
29 Mitchell State Park (MMSP) in NC, five in Great Smoky Mountain National Park (SMNP) in NC  
30 and TN, one in Rocky Mountain National Park (RMNP) in CO, one in San Bernardino National  
31 Forest (SBNF), CA, and two in Sequoia National Park (SENP), CA. Within SMNP, the median  
32 warm-season 8-h daily max O<sub>3</sub> concentration ranged from 47 ppb at the lowest elevation site  
33 (elevation = 564 m; site ID = 470090102) to 60 ppb at the highest elevation site (elevation = 2021 m;  
34 site ID = 471550102), with correlations between the 5 sites ranging from 0.78 to 0.92 and CODs  
35 ranging from 0.04 to 0.16. The correlation between the 2 sites in SENP was 0.86 and the COD was  
36 0.09. A host of factors may contribute to variations observed at these rural sites, including proximity  
37 to local O<sub>3</sub> precursor emissions, variations in boundary-layer influences, meteorology and

1 stratospheric intrusion as a function of elevation, and differences in wind patterns and transport  
2 behavior due to local topography. Expanded analyses of O<sub>3</sub> concentrations measured using the more  
3 rural-focused CASTNET monitoring network are included in Chapter 9.

4 Since O<sub>3</sub> produced from emissions in urban areas is transported to more rural downwind  
5 locations, elevated O<sub>3</sub> concentrations can occur at considerable distances from urban centers. In  
6 addition, major sources of O<sub>3</sub> precursors such as highways, power plants, biomass combustion, and  
7 oil and gas operations are commonly found in rural areas, adding to the O<sub>3</sub> in these areas. Due to  
8 lower chemical scavenging in nonurban areas, O<sub>3</sub> tends to persist longer in rural than in urban areas  
9 which tends to lead to higher cumulative exposures in rural areas influenced by anthropogenic  
10 precursor emissions. The persistently high O<sub>3</sub> concentrations observed at many of these rural sites  
11 investigated here indicate that cumulative exposures for humans and vegetation in rural areas can be  
12 substantial and often higher than cumulative exposures in urban areas.

### 2.1.5.3. National Trends

13 Nationally, O<sub>3</sub> concentrations have declined over the last decade, as shown in Figure 3-41  
14 from the 2010 National Air Quality Status and Trends report (U.S. EPA, 2010, [647278](#)). The  
15 majority of this decline occurred before 2004 with national average concentrations remaining  
16 relatively flat between 2004 and 2008. The large decreases in 2003 and 2004 coincides with NO<sub>x</sub>  
17 emissions reductions resulting from implementation of the NO<sub>x</sub> State Implementation Plan (SIP)  
18 Call rule, which began in 2003 and was fully implemented in 2004. This rule was designed to reduce  
19 NO<sub>x</sub> emissions from power plants and other large combustion sources in the eastern U.S.

20 As noted in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), trends in national parks and rural  
21 areas are similar to nearby urban areas, reflecting the regional nature of O<sub>3</sub> pollution. However,  
22 caution should be exercised in using trends calculated at national parks to infer contributions from  
23 distant sources either inside or outside of North America because of the influence of regional  
24 pollution.

### 2.1.5.4. Hourly Variations

25 Ozone concentrations show a strong degree of diel variability resulting from daily patterns in  
26 temperature, sunlight, and precursor emissions. Other factors, such as the relative importance of  
27 transport versus local photochemical production and loss rates, the timing for entrainment of air from  
28 the nocturnal residual boundary layer, and the diurnal variability in mixing layer height also play a  
29 role in daily O<sub>3</sub> patterns. Urban diel variations investigated in Section 3.6.3.2 of this assessment  
30 show no substantial change in patterns since the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). The 1-h  
31 max concentrations tend to occur in mid-afternoon and 1-h min concentrations tend to occur in early  
32 morning, with more pronounced peaks in the warm months relative to the cold months. Diel patterns  
33 in O<sub>3</sub> have remained stable over the last 20 years, with times of occurrence of the daily maxima  
34 varying by no more than an hour from year to year. There is city-to-city variability in these times,

1 however, and caution is raised in extrapolating results from one city to another in determining the  
2 time of day for O<sub>3</sub> maxima and minima.

### 2.1.5.5. Associations with Co-pollutants

3 Since O<sub>3</sub> is a secondary pollutant formed in the atmosphere from precursor emissions, it is not  
4 expected to be highly correlated with primary pollutants such as CO and NO<sub>x</sub>. Furthermore, O<sub>3</sub>  
5 formation is strongly influenced by meteorology, entrainment, and transport of both O<sub>3</sub> and O<sub>3</sub>  
6 precursors, resulting in a broad range in correlations with other pollutants which can vary  
7 substantially with season. To investigate correlations with co-pollutants, 8-h daily max O<sub>3</sub> was  
8 compared with co-located 24-h avg CO, SO<sub>2</sub>, NO<sub>2</sub>, PM<sub>2.5</sub> and PM<sub>10</sub> obtained from AQS for  
9 2007-2009. Figure 3-43 contains co-pollutant box plots of the correlation between co-located  
10 monitors for the year-round data set and broken down by season.

11 The year-round 8-h daily max O<sub>3</sub> data exhibited a very wide range in correlations with all the  
12 24-h avg co-pollutants. A clearer pattern emerged when the data are stratified by season with mostly  
13 negative correlations in the winter and mostly positive correlations in the summer for all co-  
14 pollutants. The median seasonal correlations are modest at best with the highest positive correlation  
15 at 0.52 for PM<sub>2.5</sub> in the summer and the highest negative correlation at -0.38 for PM<sub>2.5</sub> in the winter.  
16 Spring and fall lie in between with spring having a slightly narrower distribution than fall for all co-  
17 pollutants. Expanded discussion of co-pollutant correlation can be found in Section 3.6.4.

## 2.2. Human Exposure

### 2.2.1. Exposure Measurement

#### 2.2.1.1. Measurement of Ozone Exposure

18 Passive badge samplers are the most widely used technique for measuring personal O<sub>3</sub>  
19 exposure. They operate on the nitrite-nitrate conversion principle, and are convenient since they  
20 require no pumps or wet chemistry in the field. They represent a cumulative (rather than continuous)  
21 sample, and their detection limit makes them suitable for monitoring periods of 24 hours or greater.  
22 This limits their applicability in measuring short-term daily fluctuations in personal exposure. Over a  
23 24-h period, the detection limit of the badges is approximately 5-10 ppb, which may result in an  
24 appreciable fraction of the samples being below the detection limit. An active sampler based on the  
25 nitrite-nitrate conversion reaction is also available, with a reported detection limit of 10 ppb-h,  
26 enabling measurement of sub-daily O<sub>3</sub> concentrations. A portable continuous O<sub>3</sub> monitor based on a  
27 different principle, UV absorption, has recently become available. Its size and weight make it  
28 suitable for use in a backpack configuration, although its use for personal exposure measurements  
29 has been limited.

1 Several studies described in the 2006 O<sub>3</sub> AQCD, along with a few new studies published since,  
2 describe the relationship between indoor O<sub>3</sub> concentration and the O<sub>3</sub> concentration immediately  
3 outside the indoor microenvironment. These studies show that the indoor concentration is often  
4 substantially lower than the outdoor concentration unless indoor sources are present. Low indoor O<sub>3</sub>  
5 concentrations can be explained by reaction of O<sub>3</sub> with surfaces and airborne constituents. However,  
6 the indoor-outdoor relationship is greatly affected by the air exchange rate; under conditions of high  
7 air exchange rate, such as open windows, the indoor O<sub>3</sub> concentration may approach the outdoor  
8 concentration. In residential microenvironments, studies report indoor-outdoor ratios ranging from  
9 approximately 0.1-0.4, with the highest ratios observed in the summer O<sub>3</sub> season and for homes with  
10 increased window ventilation. A correlation of 0.58 was reported between indoor and outdoor O<sub>3</sub>  
11 concentrations, indicating that variations in outdoor concentration may be reflected indoors, though  
12 the magnitude of the concentration is lower. Indoor-outdoor ratios at schools were similar, with  
13 higher ratios observed during the school day when opening doors and windows may lead to  
14 increased air exchange rates. In vehicles, high air exchange rates that would normally lead to high  
15 interior-exterior concentration ratios are offset by O<sub>3</sub> scavenging through vehicle-emitted NO,  
16 resulting in reported in-vehicle concentrations that were approximately 50% of those measured at the  
17 roadside.

18 The relationship between personal exposure and ambient O<sub>3</sub> concentrations has been evaluated  
19 in several research studies, many of which were conducted prior to 2005 and are discussed in the  
20 2006 O<sub>3</sub> AQCD. The results of these studies indicate that personal exposures are moderately well  
21 correlated with ambient concentrations, and that the ratio of personal exposure to ambient  
22 concentration is higher in outdoor microenvironments and during the summer season. In situations  
23 where a lack of correlation was observed, this may be due in part to a high proportion of personal  
24 measurements below the detection limit. Correlations reported for daily or multi-day measurements  
25 range from approximately 0.3-0.8, with the upper end of the range reflecting longer-duration (4-day)  
26 community average measurements that may limit the influence of inter-individual variability in  
27 exposure. Hourly measurements in specific microenvironments show greater variability in  
28 correlations between personal exposure and ambient concentration, with residential indoor  
29 correlations <0.1 and outdoor correlations of 0.7-0.9. Slopes from regression analyses of personal  
30 exposure on ambient concentration generally ranged from approximately 0.1-0.3. Higher slopes were  
31 observed in studies that either adjusted for activity pattern and air exchange rate (0.54) or focused on  
32 outdoor shoe cleaners (0.56), who may have increased exposure due to spending a substantial  
33 fraction of the day outdoors. Ratios of personal exposure to ambient concentration showed similar  
34 results, with a ratio of 0.3 reported for a year-round study in southern California, while ratios ranged  
35 from 0.28-0.96 for outdoor workers, increasing with time spent outdoors.

36 Taken together, results from previous and recently published studies indicate that while the  
37 relationship between personal exposures and ambient concentrations varies due to a number of  
38 factors, such as activity patterns, housing characteristics, and season, O<sub>3</sub> concentrations measured at  
39 central-site monitors are representative of day-to-day changes in average personal O<sub>3</sub> exposure,

1 which is the important parameter for time-series epidemiologic studies. Another important finding is  
2 that the magnitude of personal exposures is smaller than concentrations reported at fixed-site  
3 monitors due to time spent indoors and the low indoor penetration of O<sub>3</sub>.

### 2.2.1.2. Co-Exposure to Ozone and Other Pollutants

4 Individuals may be exposed to other pollutants in conjunction with exposure to O<sub>3</sub>. Personal  
5 exposure to O<sub>3</sub> shows variable association with personal exposure to other pollutants, with  
6 differences in association depending on factors such as season, city-specific characteristics, and  
7 spatial variability of the co-pollutant. For PM<sub>2.5</sub>, a rank correlation of 0.14 was reported between  
8 daily O<sub>3</sub> and PM<sub>2.5</sub> exposures during spring and fall in Atlanta. Positive slopes were reported during  
9 summer in both Baltimore and Boston, although the slopes were somewhat different (0.21 and 0.72,  
10 respectively). The summertime slope in Baltimore was higher for children (0.37) than for adults  
11 (0.07), which may be the result of different activity patterns and time spent outdoors. Additional  
12 evidence of variation by season and city is provided by the differing signs of the wintertime slopes,  
13 with Baltimore showing a negative slope and Boston showing a positive slope. Interindividual  
14 variability likely played a role as well, since both cities showed a wide range (including both  
15 negative and positive values) for individual-specific personal O<sub>3</sub>- PM<sub>2.5</sub> slopes. For EC and NO<sub>2</sub>,  
16 near-zero correlations were reported with O<sub>3</sub> during spring and fall in Atlanta. These extremely low  
17 correlations for the traffic-related and spatially variable pollutants EC and NO<sub>2</sub> contrast with the  
18 higher correlation observed for PM<sub>2.5</sub>, a regional pollutant.

19 In near-road and on-road microenvironments, correlations between O<sub>3</sub> and traffic-related  
20 pollutants are moderately to strongly negative, with the most strongly negative correlations observed  
21 for NO<sub>2</sub> (-0.8 to -0.9). This is consistent with the chemistry of NO oxidation, in which O<sub>3</sub> is  
22 consumed to form NO<sub>2</sub>. The more moderate negative correlations observed for PM<sub>2.5</sub>, UFP, and VOC  
23 may reflect reduced concentrations of O<sub>3</sub> in more polluted environments due to other scavenging  
24 reactions. A similar process occurs indoors, where infiltrated O<sub>3</sub> reacts with airborne or surface-  
25 associated materials to form secondary compounds, such as formaldehyde. Although such reactions  
26 decrease indoor O<sub>3</sub> exposure, they result in increasing exposure to other species which may  
27 themselves have health effects.

### 2.2.2. Exposure Modeling

28 Exposures estimates in urban areas may be improved by constructing a concentration surface  
29 over a geographic domain using a model to compensate for missing data. The calculated  
30 concentration surface can then be used to estimate exposures outside residences, schools,  
31 workplaces, roadways, or other locations of interest. This technique does not estimate exposure  
32 directly because it does not account for activity patterns or concentrations in different  
33 microenvironments. Most such modeling efforts have focused on the less-reactive pollutants PM or  
34 NO<sub>2</sub>. In a study that extended CALINE4 NO<sub>x</sub> modeling results to evaluate the impact on residential

1 O<sub>3</sub> concentrations, O<sub>3</sub> concentrations were reduced by 0.51 ppb O<sub>3</sub> per 1 ppb NO<sub>x</sub>. This intra-urban  
2 traffic-related variability in O<sub>3</sub> concentrations suggests that differences in traffic density between the  
3 central site monitor and individual homes could result in either an overestimate or underestimate of  
4 residential O<sub>3</sub>.

5 A separate class of models, known as microenvironmental models, estimate time-weighted  
6 exposure for modeled individuals by summing exposure in each microenvironment visited during the  
7 exposure period. Stochastic microenvironmental models, such as APEX and SHEDS, utilize  
8 distributions of pollutant-related and individual-level variables, such as ambient and local O<sub>3</sub>  
9 concentration contributions and breathing rate respectively, to compute the distribution of individual  
10 exposures across the modeled population. The models also have the capability to estimate received  
11 dose through a dosimetry model. Using distributions of input parameters in the model framework  
12 rather than point estimates allows the models to incorporate uncertainty and variability explicitly into  
13 exposure estimates. For the APEX model, an analysis has been conducted indicating that the  
14 uncertainty in model exposure estimates for asthmatic children during moderate exercise is small to  
15 moderate; however, APEX appears to substantially underestimate the frequency of multiple high-  
16 exposure events for a single individual. Microenvironmental models, such as EMI, are also being  
17 developed to use individual-specific information derived from measurements or questionnaires,  
18 rather than population distributions, to estimate exposures. This approach is particularly suitable for  
19 panel health studies where information is available for each participant, and may reduce uncertainty  
20 in health effect estimates by improving exposure estimates.

### 2.2.3. Implications for Epidemiologic Studies

21 Exposure error can be an important contributor to variability in epidemiologic study results,  
22 although this may be less of an issue for O<sub>3</sub> because it is a secondary pollutant with relatively low  
23 spatial variability across an urban area. For example, an epidemiologic study in Atlanta observed  
24 similar associations between heart rate variability (HRV) parameters and either ambient  
25 concentrations or personal exposures of O<sub>3</sub> and PM<sub>2.5</sub>, another regional pollutant. The importance of  
26 exposure error varies with study design and is dependent on the spatial and temporal aspects of the  
27 design. Several factors that could influence exposure estimates include nonambient exposure, spatial  
28 and temporal variability, and the presence of O<sub>3</sub> in a mixture of pollutants. Nonambient exposure is  
29 unlikely to influence health effect estimates because of the lack of indoor O<sub>3</sub> sources and because  
30 indoor-generated O<sub>3</sub> exposures are unlikely to be correlated with ambient O<sub>3</sub> exposure. Compared  
31 with directly emitted pollutants such as CO and NO<sub>x</sub>, O<sub>3</sub> exhibits relatively low spatial variability  
32 across urban areas, as discussed in Chapter 3. Averaging data from a large number of samplers will  
33 dampen intersampler variability, and use of multiple monitors over smaller land areas may allow for  
34 more variability to be incorporated into an epidemiologic analysis. Evidence from a study comparing  
35 the effect of spatial variability on effect estimates for O<sub>3</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, and CO suggests that choice of  
36 monitor for spatially homogenous pollutants such as O<sub>3</sub> may have little impact on the results of  
37 epidemiologic studies. Season, however, may have a substantial effect due to much lower O<sub>3</sub>

1 concentrations during the winter, along with the higher correlations between ambient concentrations  
2 and personal exposures observed during the summer. Studies conducted during the O<sub>3</sub> season or in  
3 periods when communities are likely to have high air exchange rates (e.g., during mild weather) may  
4 be less prone to exposure error than studies conducted only during winter. Year-round studies that  
5 include both the O<sub>3</sub> and non-O<sub>3</sub> seasons may have an intermediate level of exposure error. Exposure  
6 to mixtures of pollutants containing O<sub>3</sub> also complicates interpretation of epidemiologic results.  
7 Moderate to strong negative correlations between O<sub>3</sub> and traffic-related pollutants, particularly NO<sub>2</sub>,  
8 make it difficult to determine to what extent O<sub>3</sub>-based effect estimates quantitatively reflect the  
9 independent effect of O<sub>3</sub> itself, or the effect of another pollutant or pollutants in the mixture.  
10 Interpretation of O<sub>3</sub> effects in the presence of PM is additionally complicated by the highly variable  
11 correlations observed, which differ by city, season, and population characteristics (e.g., children  
12 versus adults). Although these sources of exposure error should be considered in evaluating  
13 epidemiologic results, previous and recently published exposure research indicate that O<sub>3</sub>  
14 concentrations measured at central-site monitors are indicative of day-to-day changes in average  
15 personal O<sub>3</sub> exposure, making ambient concentrations a useful parameter for epidemiologic studies.

## 2.3. Dosimetry and Mode of Action

16 Ozone is a highly reactive and poorly water soluble gas allowing it to penetrate into targets in  
17 the lower respiratory tract. The fact that it is so chemically reactive suggests that the effective dose at  
18 target sites exists in the form of secondary oxidation products such as aldehydes and peroxides.  
19 Reaction products are formed when O<sub>3</sub> interacts with components of the extracellular lining fluid  
20 (ELF) such as lipids, proteins, and antioxidants. Ozone uptake relates directly to these ELF substrate  
21 reactions and is termed 'reactive absorption'. The level and type of antioxidants varies between  
22 species, regions of the respiratory tract itself, and can be altered by O<sub>3</sub> exposure. ELF constituents  
23 appear in most cases to limit interaction of O<sub>3</sub> with underlying tissues and to prevent penetration of  
24 O<sub>3</sub> deeper into the lung. However, in some cases, the antioxidants and secondary oxidation products  
25 formed in the aqueous phase might penetrate into the cells and cause injury. Ozone toxicity is  
26 observed to some extent in the nasal cavity, however further toxicity exists in the deep lung where  
27 the ELF thickness narrows allowing O<sub>3</sub> to react directly with the epithelial cells and surface  
28 macrophages.

### 2.3.1. Human and Animal Ozone Dosimetry

29 O<sub>3</sub> uptake efficiency is chemical-reaction dependent, driven by the conversion of O<sub>3</sub> to  
30 reaction products. The primary site of O<sub>3</sub> uptake and greatest O<sub>3</sub> dose in the lungs is the centriacinar  
31 region (CAR), containing the respiratory bronchioles. Recent studies have provided evidence for hot  
32 spots of O<sub>3</sub> flux around bifurcations in the airways. Ozone uptake is 80-95% efficient in humans and  
33 approximately 54% efficient in rats. The nasopharyngeal region provides defense against O<sub>3</sub> entering  
34 the lungs and removes ~50% of the absorbed O<sub>3</sub> in both species. Ozone uptake efficiency is sensitive

1 to a number of factors. Fractional absorption will decrease with increased flow and increase  
2 proportional to tidal volume ( $V_T$ ). Increased breathing frequency ( $f_B$ ) and oronasal breathing, as  
3 occurs during exercise, will shift the  $O_3$  dose distribution deeper and lead to a greater dose to the  
4 pulmonary region, increasing the potential of damage to bronchiolar and alveolar tissues. Individual  
5 total airway  $O_3$  uptake efficiency is also sensitive to large changes in  $O_3$  concentration, exposure  
6 time, and minute ventilation ( $V_E$ ). Major sources of variability in absorption of  $O_3$  include  $O_3$   
7 concentration, exposure time, breathing frequency, minute volume, and tidal volume, but the  
8 interindividual variation is the greatest source of variability uptake efficiency. However, to date, no  
9 studies have shown that the large differences in biological response between subjects (forced  
10 expiratory volume in 1 sec [ $FEV_{1s}$ ], bronchoalveolar lavage fluid [BAL], cell inflammatory response,  
11 etc.) are explainable by the differences in  $O_3$  uptake.

12 Interspecies differences limit quantitative comparison between species; however, the acute and  
13 chronic functional responses of laboratory animals to  $O_3$  appear qualitatively homologous to that of  
14 the human making them a useful tool in determining mechanistic and cause-effect relationships with  
15  $O_3$  exposure. Recent studies have shown that varied  $O_3$  response in different mouse strains was not  
16 due to differences in delivered dose of  $O_3$  to the lung but more likely genetic sensitivity. Dose  
17 comparison between humans and rats shows that exercising humans accumulated 4-5 times higher  
18  $O_3$  reactants in BAL compared to similarly exposed resting rats and it was necessary to expose  
19 resting rats to 2 ppm  $O_3$  to achieve increases in BAL protein and polymorphonuclear cells [PMNs]  
20 similar to those of the 0.4 ppm exposed humans.

### 2.3.2. Possible Pathways/Modes of Action

21 Three distinct short-term responses have been well-characterized in humans challenged with  
22  $O_3$ : decreased pulmonary function, airways inflammation, and increased bronchial reactivity. In  
23 addition, evidence has been accumulating that  $O_3$  exposure exacerbates, and possibly causes, asthma  
24 and allergic airways disease in humans. Effects on the nasal airways and distal lung of humans,  
25 including inflammation and injury, have also been described. Animal studies have demonstrated a  
26 wide range of respiratory system effects. While the respiratory tract is the primary target tissue,  
27 cardiovascular and other organ effects occur following short- and long-term exposures of animals to  
28  $O_3$ . Mechanisms responsible for these effects are incompletely understood.

29 The initial key event in the  $O_3$  toxicity pathway is the formation of secondary oxidation  
30 products in the respiratory tract. Pathways for the removal of those products are also of great  
31 importance. Due to the highly reactive nature of  $O_3$ , direct reactions most likely involve components  
32 of the ELF and/or plasma membranes of surface macrophages which extend beyond the ELF.  
33 Reaction products likely mediate  $O_3$  effects on respiratory tract epithelium.

34 Another key event in the  $O_3$  toxicity pathway is the activation of neural reflexes which leads to  
35 decrements in pulmonary function. Evidence is accumulating that secondary oxidation products are  
36 responsible for this effect. Eicosanoids have been implicated in humans while eicosanoids and  
37 aldehydes are effective in animal models. Different receptors on bronchial C-fibers have been shown

1 to mediate separate effects of O<sub>3</sub> on pulmonary function. Nociceptor sensory nerves are involved in  
2 the involuntary truncation of respiration which results in decreases in forced vital capacity (FVC),  
3 FEV<sub>1</sub>, tidal volume and an increase in respiratory frequency and pain upon deep inspiration. Opioids  
4 block these responses while atropine does not. New evidence in an animal model suggests that  
5 TRPA1 receptors on bronchial C-fibers mediate this pathway. Ozone exposure also results in  
6 activation of vagal sensory nerves and a mild increase in airways obstruction measured as increased  
7 specific airway resistance (sRaw). Atropine and beta-adrenergic agonists blocked this response in  
8 one study indicating that the airway obstruction was due to bronchoconstriction. Other studies in  
9 humans implicated SP release from bronchial C-fibers resulting in airway narrowing due to either  
10 neurogenic edema or bronchoconstriction. New evidence in an animal model suggests that the SP-  
11 NK receptor pathway caused bronchoconstriction following O<sub>3</sub> exposure. Considerable inter-  
12 individual variability exists in O<sub>3</sub> responsiveness measured by decrements in pulmonary function.  
13 Further, attenuation of these pulmonary function decrements occurs following O<sub>3</sub> exposure for  
14 several consecutive days. Mechanisms responsible for these effects are not known but may be related  
15 to inherent differences in neural sensitivity.

16 Injury and inflammation are additional key events in the O<sub>3</sub> toxicity pathway. Secondary  
17 oxidation products have been implicated in a number of these processes. Although there may be  
18 inter-species differences with respect to specific mediators, mechanisms involved in the acute  
19 responses to O<sub>3</sub> include epithelial injury and airways neutrophilia. Longer-term exposures may result  
20 in mucus cell metaplasia of nasal epithelium or airways remodeling and fibrosis. Work from several  
21 laboratories in humans and animal models suggest that O<sub>3</sub> triggers the release of tachykinins such as  
22 SP from airway sensory nerves which could contribute to downstream effects including injury and  
23 inflammation. New investigations show that O<sub>3</sub> exposure leads to the generation of hyaluronan  
24 fragments which activate TLR4 and CD44-dependent signaling pathways in macrophages and result  
25 in a greater turnover of macrophage populations in the lung. Activation of these pathways occurs  
26 later than the acute neutrophilic response suggesting that they may contribute to longer-term effects  
27 of O<sub>3</sub>. The mechanisms involved in clearing O<sub>3</sub>-provoked inflammation remain to be clarified.  
28 Similar to the pulmonary function responses, considerable inter-individual variability exists in O<sub>3</sub>  
29 responsiveness as measured by airways neutrophilia. Further, attenuation of the inflammatory  
30 response occurs following O<sub>3</sub> exposure for several consecutive days. However evidence suggests  
31 that injury may continue despite the dampening of the inflammatory response during repeated  
32 exposures. Mechanisms responsible for inter-individual variability and response attenuation, or the  
33 lack thereof, are not known. It should be noted that inflammation, as measured by airways  
34 neutrophilia, is not correlated with decrements in pulmonary function as measured by spirometry.  
35 Consequently, spirometric measures are not a good surrogate for the degree of inflammation in any  
36 given individual following O<sub>3</sub> exposure. Furthermore, airways neutrophilia may not be a good  
37 indicator of O<sub>3</sub>-mediated lung injury.

38 Increased bronchial reactivity is a key event in the toxicity pathway of O<sub>3</sub>. It can be both a  
39 rapidly occurring and persistent response, although adaptation can also occur during multi-day

1 exposures. Both direct effects on smooth muscle and neurally-mediated effects on smooth muscle  
2 have been proposed to contribute to airway hyperresponsiveness (AHR) following O<sub>3</sub> exposure.  
3 Currently, more evidence has accumulated for the latter mechanism. In humans exposed to O<sub>3</sub>,  
4 atropine was found to block the early AHR response indicating the involvement of cholinergic  
5 postganglionic pathways. Inhibition of arachidonic acid metabolism was ineffective in blocking this  
6 response in humans while mixed results were found in animal models. Studies in O<sub>3</sub>-exposed  
7 animals have demonstrated a role for SP release from bronchial C fibers in mediating neurally-  
8 mediated effects on smooth muscle. Later phases of increased bronchial reactivity may involve the  
9 induction of interleukin (IL)-1beta which in turn upregulates SP production. In guinea pigs,  
10 eosinophil-derived major basic protein contributed to the stimulation of cholinergic postganglionic  
11 pathways. A novel role for hyaluronan in mediating the later phase effects of O<sub>3</sub> has recently been  
12 demonstrated. High molecular weight polymers of hyaluronan normally found in the ELF were  
13 degraded following O<sub>3</sub> exposure in mice. The resulting hyaluronan fragments stimulated AHR in a  
14 toll-like receptor (TLR4) and CD44 receptor-dependent manner. Previous work has shown that O<sub>3</sub>-  
15 mediated increases in lung permeability required a functioning TLR4 suggesting a possible  
16 relationship between increased epithelial permeability and AHR in this model. Other cytokines and  
17 chemokines have been implicated in the AHR response to O<sub>3</sub> in animal models.

18 Both older and more recent studies provide insight into the ability of O<sub>3</sub> to provoke asthma  
19 exacerbations in humans. Greater airways inflammation and/or greater bronchial reactivity have  
20 been demonstrated in asthmatics compared to non-asthmatics. This pre-existing inflammation and  
21 altered baseline bronchial reactivity may contribute to the enhanced bronchoconstriction seen in  
22 asthmatics exposed to O<sub>3</sub>. Furthermore inflammation may contribute to O<sub>3</sub>-mediated AHR. Animal  
23 studies have demonstrated a role for eosinophil-derived proteins in mediating these effects. Since  
24 airways eosinophilia occurs in both allergic humans and allergic animal models, this pathway may  
25 underlie the exacerbation of allergic asthma by O<sub>3</sub>. In addition, differences have been noted in  
26 epithelial cytokine expression in bronchial biopsy samples of healthy and asthmatic subjects. A Th2  
27 phenotype, indicative of adaptive immune system activation and enhanced allergic responses, was  
28 observed before O<sub>3</sub> exposure and was increased by O<sub>3</sub> exposure in asthmatics. Since eosinophilia is a  
29 hallmark of a Th2 phenotype, these findings support links between allergic asthma, sensitivity to O<sub>3</sub>  
30 and adaptive immunity. Studies in humans and animal models also provide evidence for activation of  
31 innate immunity by O<sub>3</sub>. In humans, O<sub>3</sub> exposure resulted in increased numbers of airways monocytes  
32 and dendritic-like cells. Altered expression of cell surface markers characteristic of innate immunity  
33 and antigen presentation was observed on monocytes and macrophages. Recruitment of these  
34 activated immune cells could lead to activation of allergen-specific memory T cells in allergic  
35 individuals and result in the exacerbation of existing asthma in response to an allergen trigger. In  
36 animal studies, O<sub>3</sub> exposure primed the innate immune system and led to increased endotoxin-  
37 induced AHR by a mechanism involving hyaluronan and TLR4. The exaggerated immune response  
38 to O<sub>3</sub> + endotoxin could lead to a more pronounced lung injury response to a bacterial trigger.  
39 Enhanced bronchial reactivity, airways eosinophilia, Th2 phenotype, recruitment of activated innate

1 immune cells, and enhanced responsiveness to endotoxin all provide biological plausibility for  
2 epidemiologic evidence of asthma exacerbations associated with exposure to O<sub>3</sub>. Thus, the influx of  
3 immunomodulatory cells and the activation of innate and adaptive immunity leads to the  
4 exacerbation of asthma and allergic responses which is emerging as a key event in the toxicity  
5 pathway of O<sub>3</sub>.

6 Recent studies in humans and animal models also provide evidence that O<sub>3</sub> exposure causes  
7 induction of AHR and allergic responses. Both activation of innate immunity and promotion of  
8 adaptive immunity have been implicated. In humans, O<sub>3</sub> exposure resulted in increased numbers of  
9 dendritic-like cells and levels of a cytokine associated with dendritic cell activation in the sputum,  
10 suggesting the presence of a population of activated dendritic cells which could stimulate naïve  
11 T-cells to promote the development of asthma. Evidence for activated dendritic cells was also found  
12 in glutathione S transferase M1 (GSTM1) null human subjects (Section 5.2.9.1) and in allergen-  
13 sensitized animals exposed to O<sub>3</sub>. In the latter study, O<sub>3</sub> acted as an adjuvant for allergic sensitization  
14 and the development of AHR by a mechanism involving TLR4. In a different animal model, O<sub>3</sub>-  
15 induced AHR required the presence of NKT cells and IL-17, both of which indicate innate immune  
16 system activation. Ozone-induced goblet cell metaplasia has also been demonstrated. These findings  
17 suggest that O<sub>3</sub> may be capable of causing new onset asthma and allergic responses in humans. Thus,  
18 promotion of adaptive immunity and activation of innate immunity leads to the induction of AHR  
19 and allergic responses which is emerging as a key event in the toxicity pathway of O<sub>3</sub>.

20 Both older and more recent studies in animal models provide several mechanisms by which O<sub>3</sub>  
21 exposure could enhance susceptibility to lung infections. Both decreased mucociliary particle  
22 clearance and decreased numbers and function of alveolar macrophage have been implicated. Recent  
23 studies suggest that O<sub>3</sub>-mediated oxidation of SP-A oxidation and priming of the innate immune  
24 system may contribute to decreased pathogen clearance. Immune dysfunction outside of the lung has  
25 also been demonstrated. Thus, immune system modulation is emerging as a key event in the O<sub>3</sub>  
26 toxicity pathway.

27 Studies in animals provide evidence for extrapulmonary effects of O<sub>3</sub>. Although it was  
28 suggested that these effects are directly mediated by secondary oxidation products formed in the lung  
29 as a result of O<sub>3</sub> exposure, there is no evidence that these species enter the circulation. Alternatively,  
30 extrapulmonary effects may be due to activation of neural reflexes or to release of diffusible  
31 mediators which may initiate or propagate inflammatory responses in the vascular or systemic  
32 compartments. Recent studies suggest that oxidative/nitrosative stress contributes to O<sub>3</sub>-induced  
33 cardiovascular effects. Thus, systemic inflammation and vascular oxidative/nitrosative stress are  
34 emerging as key events in the toxicity pathway of O<sub>3</sub>.

35 Collectively, older and more recent studies provide evidence for mechanisms which may  
36 underlie the variability in responsiveness seen among individuals. Certain functional genetic  
37 polymorphisms, pre-existing conditions and diseases, lifestages and co-exposures contribute to  
38 enhanced susceptibility to O<sub>3</sub>. Adaptation may also be important, but it is incompletely understood -  
39 both in terms of the pathways involved and the resulting consequences.

1 Overall, key events in the toxicity pathway of O<sub>3</sub> have been identified in humans and animal  
2 models. They include the formation of secondary oxidation products in the lung, activation of neural  
3 reflexes, pulmonary injury and inflammation and increased bronchial reactivity. In addition,  
4 evidence is accumulating that immune system modulation may lead to impaired host defense and the  
5 exacerbation and/or induction of asthma and allergic responses. Systemic inflammation and vascular  
6 oxidative/nitrosative stress may be critical to the extrapulmonary effects of O<sub>3</sub>.

## 2.4. Health Effects

7 This section evaluates the evidence from toxicological, controlled human exposure, and  
8 epidemiologic studies that examined the health effects associated with short- and long-term exposure  
9 to O<sub>3</sub>. The results from the health studies evaluated in combination with the evidence from  
10 atmospheric chemistry and exposure assessment studies contribute to the causal determinations made  
11 for the health outcomes discussed in this assessment (Section 1.6.4). In the following sections a  
12 discussion of the causal determinations will be presented by exposure duration (i.e., short- or long-  
13 term exposure) for the health effects for which sufficient evidence was available to conclude a  
14 causal, likely to be causal or suggestive relationship. Although not presented in depth in this chapter,  
15 a detailed discussion of the underlying evidence used to formulate each causal determination can be  
16 found in Chapters 6 and 7.

### 2.4.1. Effects of Short-Term Exposure to Ozone

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**Table 2-1. Summary of causal determinations for short-term exposure to ozone**

<b>Outcome</b>	<b>Causality Determination</b>
Respiratory Effects	Causal Relationship
Cardiovascular Effects	Suggestive of a Causal Relationship
Central Nervous System Effects	Suggestive of a Causal Relationship
Mortality	Likely to be a Causal Relationship

#### 2.4.1.1. Respiratory Effects

17 The 2006 O<sub>3</sub> AQCD concluded that there was clear, consistent evidence of a causal  
18 relationship between short-term exposure to O<sub>3</sub> and respiratory health effects (U.S. EPA, 2006,  
19 [088089](#)). This causal association was substantiated by the coherence of effects observed across  
20 controlled human exposure, epidemiologic, and toxicological studies indicating associations of  
21 short-term O<sub>3</sub> exposures with a range of respiratory health endpoints from respiratory tract  
22 inflammation to respiratory hospital admissions (HA) and ED visits. Across disciplines, acute O<sub>3</sub>  
23 exposures induced or were associated with statistically significant declines in lung function. An

1 equally strong body of evidence from controlled human exposure and toxicological studies  
2 demonstrated O<sub>3</sub>-induced inflammatory responses, increased epithelial permeability, and airway  
3 hyperresponsiveness (both specific and nonspecific). Toxicological studies provided additional  
4 evidence for O<sub>3</sub>-induced impairment of host defenses. Coherent with inflammation and airway  
5 hyperresponsiveness, epidemiologic studies consistently demonstrated positive associations of  
6 increases in ambient O<sub>3</sub> concentrations with increases in respiratory symptoms and asthma  
7 medication use in asthmatic children and with respiratory-related hospital admissions and asthma-  
8 related emergency department (ED) visits. Although O<sub>3</sub> was consistently associated with  
9 nonaccidental and cardiopulmonary mortality, the contribution of respiratory causes to these findings  
10 was uncertain.

11 Building on the strong body of evidence presented in the 2006 AQCD, recent studies continue  
12 to support associations between short-term O<sub>3</sub> exposure and respiratory effects. In young healthy  
13 adults exposed to O<sub>3</sub> for 6.6 hours, studies demonstrate mean FEV<sub>1</sub> decrements of about 3% at  
14 60 ppb, 5% at 70 ppb, and 6-8% at 80 ppb (Section 6.2.1.2). These studies also show considerable  
15 intersubject variability in responsiveness to O<sub>3</sub>, with the percentage of subjects with >10%  
16 decrement in FEV<sub>1</sub> increasing with increasing concentration of O<sub>3</sub> exposure. The proportion  
17 (uncorrected for filtered air [FA] responses) of individuals with >10% FEV<sub>1</sub> decrements ranges from  
18 3 to 20% at an average O<sub>3</sub> exposure level of 60 ppb and from 17 to 29% at 80 ppb.

19 The collective body of epidemiologic evidence demonstrates associations between ambient O<sub>3</sub>  
20 and decrements in lung function, although recent studies contributed more mixed evidence. A  
21 notable difference among newer studies is the limited investigation of populations engaged in  
22 outdoor recreation, exercise, or work, which contributed to the strength of evidence in previous  
23 AQCDs (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)). Some recent evidence suggests that  
24 public attention to daily AQI may be reducing exposures of some groups. Recent epidemiologic  
25 studies contributed insight into susceptibility factors for O<sub>3</sub>-associated respiratory morbidity. Among  
26 subjects with atopy, asthmatics with concurrent respiratory infection, elderly with AHR or obesity, or  
27 groups with diminished antioxidant enzyme activity, lung function responses to ambient O<sub>3</sub>  
28 exposures generally were exacerbated. The susceptibility of these populations is supported by  
29 extensive laboratory evidence (human and animal) for O<sub>3</sub>-induced exacerbation of allergic  
30 inflammation, increased susceptibility to bacterial and viral infections, exacerbation of O<sub>3</sub>-induced  
31 AHR by obesity, and modulation of O<sub>3</sub> effects by the oxidative stress/antioxidant balance. In recent  
32 controlled human exposure studies, lung function responses to O<sub>3</sub> are enhanced in subjects with  
33 higher body mass index (BMI).

34 As with lung function, recent controlled human exposure studies demonstrate increases in  
35 respiratory symptoms in healthy, young adults following 5.6- to 6.6-h exposure to O<sub>3</sub> at levels  
36 <80 ppb. The collective body of epidemiologic studies strongly demonstrates positive associations of  
37 ambient O<sub>3</sub> exposure with respiratory symptoms and asthma medication use among asthmatic  
38 subjects, especially in populations with additional susceptibility factors such as asthmatics with  
39 atopy, asthmatics with diminished antioxidant enzyme activity, or infants with asthmatic mothers.

1           Recent studies in animals and in vitro models also continue to demonstrate O<sub>3</sub>-induced lung  
2 injury and inflammatory responses. Building on the extensive experimental evidence, new  
3 epidemiologic evidence emerged for ambient O<sub>3</sub>-associated increases in mediators of inflammation  
4 measured in upper and lower airway samples, including eNO, cytokines such as IL-6 or IL-8, and  
5 inflammatory cells such as eosinophils. Epidemiologic studies also report associations of increases in  
6 ambient O<sub>3</sub> with decreased levels of glutathione and increased levels of malondialdehyde in airways.  
7 At the time of the 2006 O<sub>3</sub> AQCD, controlled human studies of dietary antioxidant supplementation  
8 had shown some protective effects of alpha-tocopherol and ascorbate on lung function from O<sub>3</sub>  
9 exposure, but not on the intensity of subjective symptoms and inflammatory response. More recent  
10 evidence indicates that diminished activity of oxidant metabolizing enzymes (e.g., GSTM1, GSTP1)  
11 or intake of antioxidant vitamins influences inflammatory responses to O<sub>3</sub> exposure. Across all three  
12 disciplines, evidence suggests a role antioxidant defenses in modulating responses to O<sub>3</sub>.

13           Recent epidemiologic studies build upon the strong body of evidence that demonstrated  
14 consistent positive associations between daily changes in O<sub>3</sub> exposure and respiratory-related  
15 hospital admissions and ED visits by demonstrating associations in diverse populations across the  
16 U.S., Canada, and Europe. In all-year analyses, recent multicity studies and a multicontinent study  
17 found an approximate 1.6-5.4% increase in all respiratory-related hospital admissions and ED visits  
18 for standardized increases in ambient O<sub>3</sub> concentrations<sup>1</sup>. Positive associations persisted in analyses  
19 restricted to the summer season, but the magnitude varied depending on the study location.  
20 Compared with studies reviewed in the 2006 O<sub>3</sub> AQCD, more recent studies examine associations  
21 between short-term O<sub>3</sub> exposure and specific respiratory outcomes. Although still limited in number,  
22 both single- and multicity studies found consistent, positive associations of daily changes in O<sub>3</sub>  
23 concentrations with asthma and chronic obstructive pulmonary disease (COPD) hospital admissions  
24 and ED visits. Evidence was more limited for pneumonia. Consistent with the conclusions of the  
25 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), in studies that conducted seasonal analyses, larger effects  
26 were estimated for the warm season or summer months than for the cold season or for all seasons,  
27 particularly for asthma and COPD. Although the current body of evidence did not include detailed  
28 age-stratified results, the increased risk of asthma hospital admissions observed for children provided  
29 additional support for the conclusion from the 2006 O<sub>3</sub> AQCD that children are particularly  
30 susceptible to O<sub>3</sub>-induced respiratory effects (U.S. EPA, 2006, [088089](#)). Among studies that  
31 evaluated the potential confounding effects of co-pollutants, O<sub>3</sub> effect estimates for respiratory-  
32 related hospital admissions and ED visits remained relatively robust upon the inclusion of PM and  
33 gaseous pollutants in two-pollutant models. Although the concentration-response relationship  
34 between short-term O<sub>3</sub> exposure and respiratory-related hospital admissions and ED visits has not  
35 been extensively examined, preliminary examinations found no evidence of a threshold between  
36 short-term O<sub>3</sub> exposure and asthma hospital admissions and pediatric asthma ED visits.

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<sup>1</sup> Effect estimates were standardized to a 20-ppb increase for 24-h avg O<sub>3</sub>, a 30-ppb increase for 8-h max O<sub>3</sub>, and a 40 ppb increase for 1-h max O<sub>3</sub>.

1 New evidence extends the potential continuum of well-established O<sub>3</sub>-associated respiratory  
2 effects (e.g., airway inflammation; impaired host defense; lung function decrements; and respiratory  
3 symptoms, ED visits, and hospital admissions) by demonstrating associations between ambient O<sub>3</sub>  
4 exposure and respiratory-related mortality. The multicontinent APHENA study reported primarily  
5 positive associations with respiratory mortality in all-year analyses, with stronger associations  
6 observed in analyses restricted to the summer season. These findings were supported by U.S. and  
7 European multicity studies, in which a majority of respiratory mortality effect estimates ranged from  
8 a 2.3 to 6.8% increase per standardized increase in ambient O<sub>3</sub> concentrations. Although co-pollutant  
9 confounding was not extensively examined, the O<sub>3</sub>-respiratory mortality relationship was moderately  
10 to substantially sensitive (e.g., increased or attenuated) to inclusion of PM<sub>10</sub> in co-pollutant models.  
11 However, interpretation of these results requires caution due to the limited PM datasets used in these  
12 studies.

13 In summary, new studies evaluated in the current review support or expand upon the strong  
14 body of evidence presented in the 2006 O<sub>3</sub> AQCD that short-term O<sub>3</sub> exposure is causally associated  
15 with respiratory health effects. Recent controlled human exposure studies demonstrate decreases in  
16 FEV<sub>1</sub> in the range of 2.8 to 3.6% with prolonged O<sub>3</sub> exposures (6.6 hours) as low as 60 ppb in  
17 concentration. By demonstrating O<sub>3</sub>-induced airway hyperresponsiveness, activation of neural  
18 reflexes, allergic responses, lung injury, impaired host defense, and airway inflammation,  
19 toxicological studies have characterized O<sub>3</sub> modes of action and provided biological plausibility for  
20 epidemiologic observations of associations of ambient O<sub>3</sub> exposure with decreases in lung function  
21 and increases in respiratory symptoms. The coherence of results across studies for O<sub>3</sub>-associated  
22 changes in lung function, airway inflammation, and respiratory symptoms, in turn, provides the  
23 biological plausibility for epidemiologic findings of consistently positive associations of ambient O<sub>3</sub>  
24 exposure with respiratory hospital admissions and ED visits in diverse populations across the U.S.,  
25 Europe, and Canada. Additionally, a multicontinent study and several multicity studies reported  
26 positive associations between ambient O<sub>3</sub> exposures and respiratory mortality. New epidemiologic  
27 studies provide evidence for associations of ambient O<sub>3</sub> exposure with biological markers of airway  
28 inflammation and oxidative stress and indicated that groups with diminished antioxidant capacity or  
29 comorbidities such as atopy, AHR, or obesity may have increased susceptibility to respiratory  
30 morbidity associated with O<sub>3</sub> exposure. This new information is consistent with previously available  
31 toxicological and clinical evidence as well as current information on modes of action. A common  
32 observation among epidemiologic studies of respiratory morbidity and mortality was stronger  
33 associations in analyses restricted to warm seasons compared to cold seasons. Additionally, although  
34 co-pollutant confounding was evaluated infrequently, O<sub>3</sub> effect estimates generally remained  
35 statistically significant in co-pollutant models with PM<sub>2.5</sub>, PM<sub>10</sub>, or NO<sub>2</sub>. Collectively, the evidence  
36 integrated across controlled human exposure, epidemiologic, and toxicological studies as well as  
37 across the spectrum of respiratory health endpoints continues to demonstrate that **there is a causal**  
38 **relationship between short-term O<sub>3</sub> exposure and respiratory health effects.**

### 2.4.1.2. Cardiovascular Effects

1 In past O<sub>3</sub> AQCDs, the effects of O<sub>3</sub> to the cardiovascular system could not be thoroughly  
2 evaluated due to the paucity of information available. However, in recent years, investigation of O<sub>3</sub>-  
3 induced cardiovascular events has advanced. In general, compared with the epidemiologic evidence,  
4 the toxicological evidence is more supportive of an O<sub>3</sub>-induced cardiovascular effect. Epidemiologic  
5 evidence does not consistently demonstrate a positive relationship between short-term O<sub>3</sub> exposure  
6 and cardiovascular morbidity. However, most epidemiologic studies have not extensively  
7 investigated the cardiovascular effects of O<sub>3</sub> exposure in susceptible populations, which may further  
8 support the toxicological findings. Although the epidemiologic evidence is limited, single-city  
9 studies reviewed in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), recent multicity studies, and the  
10 multicontinent APHENA study provide evidence of consistent positive associations between short-  
11 term O<sub>3</sub> exposure and cardiovascular mortality. However, in contrast with respiratory effects, there is  
12 weak coherence between the associations for cardiovascular morbidity and mortality. Further, there  
13 is no apparent biological mechanism to explain the association observed between short-term O<sub>3</sub>  
14 exposure and cardiovascular mortality and not for cardiovascular morbidity.

15 Animal toxicological studies (O<sub>3</sub> concentration 0.5-0.8 ppm) provide evidence for O<sub>3</sub>-induced  
16 cardiovascular effects, specifically enhanced ischemia/reperfusion injury, disrupted NO-induced  
17 vascular reactivity, decreased cardiac function, and increased HRV. The observed increase in HRV is  
18 supported by a recent controlled human exposure study that also finds increased high frequency  
19 HRV, but not altered blood pressure, following O<sub>3</sub> exposure. Toxicological studies investigating the  
20 role of O<sub>3</sub> in heart rate regulation are mixed with both bradycardic and tachycardic responses  
21 observed. These changes in cardiac function provide evidence for O<sub>3</sub>-induced alterations in the  
22 autonomic nervous system leading to cardiovascular complications. Epidemiologic studies showing  
23 positive associations between O<sub>3</sub> and arrhythmias confirm the development of autonomic  
24 dysfunction following O<sub>3</sub> exposure. It is still uncertain how O<sub>3</sub> inhalation may cause systemic  
25 toxicity, however the cardiovascular effects of O<sub>3</sub> found in animals correspond to the development  
26 and maintenance of a extrapulmonary oxidative, proinflammatory environment.

27 Overall, animal toxicological studies provide stronger evidence for O<sub>3</sub> exposure leading to  
28 cardiovascular morbidity than epidemiologic evidence which observed a lack of coherent evidence.  
29 Based on the relatively strong body of toxicological evidence, and the consistent evidence of an  
30 association between O<sub>3</sub> and cardiovascular mortality, but weak coherence and biological plausibility  
31 for O<sub>3</sub>-induced cardiovascular morbidity, the generally limited body of evidence **is suggestive of a**  
32 **causal relationship between relevant short-term exposures to O<sub>3</sub> and cardiovascular effects.**

### 2.4.1.3. Central Nervous System Effects

33 In rodents, O<sub>3</sub> exposure has been shown to cause physicochemical changes in the brain  
34 indicative of oxidative stress and inflammation. Recent toxicological studies add to earlier evidence  
35 that acute exposures to O<sub>3</sub> can produce a range of effects on the central nervous system (CNS) and

1 behavior. Previously observed effects, including neurodegeneration, alterations in neurotransmitters,  
2 short- and long-term memory, and sleep patterns, have been further supported by recent studies. In  
3 instances where pathology and behavior are both examined, animals exhibit decrements in behaviors  
4 tied to the brain regions or chemicals found to be affected or damaged. For example, damage in the  
5 hippocampus, which is important for memory acquisition, was correlated with impaired performance  
6 in tests designed to assess memory. Thus the brain is functionally affected by O<sub>3</sub> exposure. The  
7 single epidemiologic study conducted showed that O<sub>3</sub> affects memory in humans as well, albeit on a  
8 long-term exposure basis. Notably, exposure to O<sub>3</sub> levels as low as 0.25 ppm has resulted in  
9 progressive neurodegeneration and deficits in both short- and long-term memory in rodents.  
10 Additionally, changes in the CNS, including biochemical, cellular, and behavioral effects, have been  
11 observed in animals whose sole exposure occurred in utero, at levels as low as 0.3 ppm. Although  
12 evidence from epidemiologic and controlled human exposure studies is lacking, the toxicological  
13 evidence for the impact of O<sub>3</sub> on the brain and behavior is strong, and **is suggestive of a causal**  
14 **relationship between O<sub>3</sub> exposure and adverse CNS effects.**

#### 2.4.1.4. Mortality

15 The 2006 O<sub>3</sub> AQCD concluded that the overall body of evidence was highly suggestive that O<sub>3</sub>  
16 directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality, but  
17 additional research was needed to more fully establish underlying mechanisms by which such effects  
18 occur. The evaluation of new multicity studies that examined the association between short-term O<sub>3</sub>  
19 exposure and mortality found evidence which supports the conclusions of the 2006 O<sub>3</sub> AQCD. These  
20 new studies reported consistent positive associations between short-term O<sub>3</sub> exposure and total  
21 (nonaccidental) mortality, with associations being stronger during the warm season, as well as  
22 additional support for associations between O<sub>3</sub> exposure and cardiovascular mortality being similar  
23 or larger in magnitude compared to respiratory mortality. Additionally, these new studies examined  
24 previously identified areas of uncertainty in the O<sub>3</sub>-mortality relationship.

25 Recent studies further examined potential confounders (i.e., co-pollutants and seasonality) of  
26 the O<sub>3</sub>-mortality relationship (Section 6.6.2.1). Unlike previous studies that were limited to primarily  
27 examining the confounding effects of PM<sub>10</sub>, these studies expanded their analyses to include multiple  
28 PM indices (i.e., PM<sub>10</sub>, PM<sub>2.5</sub>, and PM components). Co-pollutant models found evidence that  
29 associations between O<sub>3</sub> and total mortality were robust to the inclusion of PM<sub>10</sub> or PM<sub>2.5</sub>, while  
30 other studies found evidence for a modest reduction (~20-30%) when examining PM<sub>10</sub> and by age  
31 group or cause-specific mortality (i.e., cardiovascular). Additional reductions in O<sub>3</sub>-mortality risk  
32 estimates were also observed when examining PM components, specifically sulfate, in co-pollutant  
33 models. Overall, the impact of PM indices on O<sub>3</sub>-mortality risk estimates was found to be much  
34 smaller than the variation in O<sub>3</sub>-mortality risk estimates across cities. Although some studies suggest  
35 that O<sub>3</sub>-mortality risk estimates may be confounded by PM or its chemical components, the  
36 interpretation of these results requires caution due to the limited datasets used in these studies. When  
37 examining the potential for seasonal confounding of the O<sub>3</sub>-mortality relationship it was observed

1 that the extent of smoothing or the methods used for adjustment can influence O<sub>3</sub> risk estimates  
2 because of the opposing seasonal trends of O<sub>3</sub> and mortality when not instituting enough degrees of  
3 freedom (df) to control for temporal/seasonal trends.

4 The multicity studies evaluated in this review also examined the potential regional  
5 heterogeneity in O<sub>3</sub>-mortality risk estimates (Section 6.6.2.2). These studies provide evidence which  
6 suggests generally higher O<sub>3</sub>-mortality risk estimates in northeastern U.S. cities with some regions  
7 showing no associations between O<sub>3</sub> exposure and mortality (e.g., Southwest, urban Midwest).  
8 Multicity studies that examined individual- and community-level characteristics identified factors  
9 that may explain the observed regional heterogeneity in O<sub>3</sub>-mortality risk estimates as well as  
10 characteristics of populations potentially susceptible to O<sub>3</sub>-related health effects. An examination of  
11 community-level characteristics found an increase in the O<sub>3</sub>-mortality risk estimates in cities with  
12 higher unemployment, percentage of the population Black/African-American, percentage of the  
13 working population that uses public transportation, lower temperatures, and lower prevalence of  
14 central air conditioning.

15 Additional studies were evaluated that examined factors, such as multi-day effects, mortality  
16 displacement, adaptation, and whether a threshold exists in the O<sub>3</sub>-mortality relationship, which may  
17 influence the shape of the O<sub>3</sub>-mortality concentration-response (C-R) curve. An examination of  
18 multiday effects in a U.S. and European multicity study found conflicting evidence for mortality  
19 displacement, but the evidence suggests that the positive associations between O<sub>3</sub> and mortality are  
20 observed mainly in the first few days after exposure. Additionally, a U.S. multicity study found  
21 evidence of an adaptive response to O<sub>3</sub> exposure, with the highest risk estimates earlier in the O<sub>3</sub>  
22 season (i.e., July) and diminished effects later (i.e., August). However, the evidence of adaptive  
23 effects has an implication for the interpretation of multi-day effects, and requires further analysis.  
24 Analyses that specifically focused on the O<sub>3</sub>-mortality C-R relationship found no evidence of a  
25 threshold, but did observe evidence for potential differences in the C-R relationship across cities.  
26 Overall, this evidence supports the 2006 O<sub>3</sub> AQCD which concluded that “if a population threshold  
27 level exists in O<sub>3</sub> health effects, it is likely near the lower limit of ambient O<sub>3</sub> concentrations in the  
28 U.S.” (U.S. EPA, 2006, [088089](#)). Taken together, the body of evidence indicates that **there is likely**  
29 **to be a causal relationship between short-term exposures to O<sub>3</sub> and all-cause mortality.**

## 2.4.2. Effects of Long-Term Exposure to Ozone

**Table 2-2. Summary of causal determinations for long-term exposure to ozone**

<b>Outcome</b>	<b>Causality Determination</b>
Respiratory Effects	Likely to be a Causal Relationship
Cardiovascular Effects	Suggestive of a Causal Relationship
Mortality	Suggestive of a Causal Relationship
Reproductive and Developmental	Suggestive of a Causal Relationship
Central Nervous System Effects	Suggestive of a Causal Relationship
Cancer, Mutagenicity, and Genotoxicity	Inadequate to Infer a Causal Relationship

### 2.4.2.1. Respiratory Effects

1           The epidemiologic studies reviewed in the 2006 O<sub>3</sub> AQCD detected no associations between  
2 long-term O<sub>3</sub> exposures and asthma-related symptoms, asthma prevalence or allergy to common  
3 aeroallergens among children after controlling for covariates. Little evidence was available to relate  
4 long-term exposure to current ambient O<sub>3</sub> concentrations to deficits in the growth of lung function in  
5 children. Additionally, limited evidence was available evaluating the relationship between long-term  
6 O<sub>3</sub> levels and pulmonary inflammation and other endpoints.

7           Recent studies examine the relationship between long-term O<sub>3</sub> exposure and new onset asthma  
8 in children (Section 7.2.1). Studies have provided evidence for a relationship between different  
9 genetic variants (e.g., heme oxygenase [HMOX], GSTs, arginase [ARG]) that, in combination with  
10 O<sub>3</sub> exposure, are related to new onset asthma. Studies using a cross-sectional design provide support  
11 for a relationship between long-term O<sub>3</sub> exposure and health effects in asthmatics, including  
12 bronchitic symptoms and respiratory-related school absences. Additionally, chronic O<sub>3</sub> exposure was  
13 related to childhood asthma hospital admissions.

14           Studies of long-term exposure to O<sub>3</sub> and pulmonary function effects are inconclusive, with  
15 some new epidemiologic studies relating effects at higher exposure levels. Information from  
16 toxicological studies in adult and infant non-human primates indicates that long-term exposure to O<sub>3</sub>  
17 during development can result in irreversible morphological changes in the lung along with changes  
18 in pulmonary function.

19           The strongest evidence for a relationship between long-term O<sub>3</sub> exposure and respiratory  
20 morbidity in recent studies demonstrates associations between long-term measures of O<sub>3</sub> exposure  
21 and new-onset asthma in children and increased respiratory symptom effects in asthmatics. While the  
22 evidence may be limited, these U.S. multi-community prospective cohort studies demonstrate that  
23 asthma risk is associated with the important relationships between genetic variability, environmental  
24 O<sub>3</sub> exposure, and behavior. These relationships are complex. The genes evaluated in these studies are  
25 both key candidates in the oxidative stress pathway and have been shown to play an important role in

1 asthma development. Reduced risk for asthma development is reported in some studies in children  
2 living in low-O<sub>3</sub> communities. Other recent studies provide coherent evidence for long-term O<sub>3</sub>  
3 exposure and respiratory morbidity effects such as first asthma hospitalization and respiratory  
4 symptoms in asthmatics. Studies considering other pollutants provide data supporting the notion that  
5 the effects related to O<sub>3</sub> are independent from potential effects of the other pollutants. Some studies  
6 provide evidence for a positive concentration-response relationship. Generally, the epidemiologic  
7 and toxicological evidence provides a compelling case that supports the hypothesis that a  
8 relationship exists between long-term exposure to ambient O<sub>3</sub> and measures of respiratory morbidity.  
9 The 2006 O<sub>3</sub> AQCD concluded the evidence was suggestive but inconclusive at that time. Building  
10 upon that evidence, the more recent epidemiologic evidence, combined with toxicological studies in  
11 rodents and non-human primates, provides biologically plausible evidence that **there is likely to be**  
12 **a causal relationship between long-term exposure to O<sub>3</sub> and respiratory morbidity.**

#### 2.4.2.2. Cardiovascular Effects

13 Previous AQCDs did not address the cardiovascular effects of long-term O<sub>3</sub> exposure. The  
14 evidence remains limited; however the emerging data is supportive of a role for O<sub>3</sub> in chronic  
15 cardiovascular diseases. Two epidemiologic studies have investigated cardiovascular morbidity after  
16 long-term O<sub>3</sub> exposure and both assessed cardiovascular disease related biomarkers. A study of the  
17 relationship between O<sub>3</sub> and cardiovascular mortality reported no association after adjustment for  
18 PM<sub>2.5</sub> levels. Additional epidemiologic studies on cardiovascular morbidity and mortality after long-  
19 term exposure have not been published.

20 Toxicological evidence of long-term O<sub>3</sub> exposure is also limited but three strong toxicological  
21 studies have been published since the previous AQCD. These studies provide evidence for O<sub>3</sub>  
22 enhanced atherosclerosis and ischemia/reperfusion injury, corresponding with development of a  
23 systemic oxidative, proinflammatory environment (Section 7.3.1.2). Although questions exist for  
24 how O<sub>3</sub> inhalation causes systemic effects, a recent study proposes a mechanism for development of  
25 vascular pathology that involves activation of LOX-1 by O<sub>3</sub> oxidized lipids. This activation may also  
26 be responsible for O<sub>3</sub> induced changes in genes involved in proteolysis, thrombosis, and  
27 vasoconstriction. Taking into consideration the positive toxicological studies reported, the generally  
28 limited body of evidence is **suggestive of a causal relationship between relevant long-term**  
29 **exposures to O<sub>3</sub> and cardiovascular effects.**

#### 2.4.2.3. Reproductive and Developmental Effects

30 The 2006 O<sub>3</sub> AQCD concluded that the limited number of studies that investigated O<sub>3</sub>  
31 demonstrated no associations between O<sub>3</sub> and birth outcomes, with the possible exception of birth  
32 defects. The current review included an expanded body of evidence of the associations between O<sub>3</sub>  
33 and reproductive and developmental effects. Recent toxicological studies provide evidence for an  
34 effect of prenatal exposure to O<sub>3</sub> on ultrastructural changes in bronchiole development, alterations in  
35 placental and offspring cytokines, and increased offspring airway hyper-reactivity (Section 7.4.7).

1 Also, there is limited toxicological evidence for an effect of prenatal and early life exposure on  
2 central nervous system effects, including laterality, brain morphology, neurobehavioral  
3 abnormalities, and sleep aberration (Section 7.4.8). Recent epidemiologic studies have begun to  
4 explore the effects of O<sub>3</sub> on sperm quality, and provide limited evidence for decrements in sperm  
5 concentration, while there is limited toxicological evidence for testicular degeneration caused by O<sub>3</sub>  
6 (Section 7.4.2). There is no evidence that prenatal or early life O<sub>3</sub> concentrations are associated with  
7 infant mortality.

8 Collectively, there is limited though positive toxicological evidence for O<sub>3</sub>-induced  
9 developmental effects, including effects on pulmonary structure and function and central nervous  
10 system effects. Limited epidemiologic evidence exists for an association with O<sub>3</sub> concentration and  
11 decreased sperm concentration. A recent toxicological study provides limited evidence for a possible  
12 biological mechanism (histopathology showing impaired spermatogenesis) for such an association.  
13 Additionally, though the evidence for an association between O<sub>3</sub> concentrations and adverse birth  
14 outcomes is generally inconsistent, there are several influential studies that indicate an association  
15 with reduced birth weight and restricted fetal growth. Taking into consideration the positive evidence  
16 for developmental and reproductive outcomes from toxicological and epidemiological studies, and  
17 the few influential birth outcome studies, the evidence **is suggestive of a causal relationship**  
18 **between long-term exposures to O<sub>3</sub> and reproductive and developmental effects.**

#### 2.4.2.4. Central Nervous System Effects

19 Recent research in the area of O<sub>3</sub>-induced neurotoxicity has included several long-term  
20 exposure studies. Notably, the first epidemiologic study to examine the relationship between O<sub>3</sub>  
21 exposure and neurobehavioral effects observed an association between annual O<sub>3</sub> levels and an  
22 aging-related cognitive performance decline in tests measuring coding ability and attention/short-  
23 term memory. This observation is supported by studies in rodents which demonstrate oxidative stress  
24 in the brain and associated decrements in behavioral tests, including those measuring memory, after  
25 subchronic exposure to 0.25 ppm O<sub>3</sub>. Additionally, neurobehavioral changes are evident in animals  
26 whose only exposure to O<sub>3</sub> occurred in utero. Collectively, the limited epidemiologic and  
27 toxicological evidence is coherent and **is suggestive of a causal relationship between O<sub>3</sub> exposure**  
28 **and adverse CNS effects.**

#### 2.4.2.5. Cancer, Mutagenicity and Genotoxicity

29 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) reported that evidence did not support ambient  
30 O<sub>3</sub> as a pulmonary carcinogen. Since the 2006 AQCD, very few epidemiologic and toxicological  
31 studies have been published that examine O<sub>3</sub> as a carcinogen, but collectively, study results indicate  
32 that O<sub>3</sub> may contribute to DNA damage. Overall, the evidence **is inadequate to determine if a**  
33 **causal relationship exists between ambient O<sub>3</sub> exposures and cancer.**

## 2.4.2.6. Mortality

1           The 2006 O<sub>3</sub> AQCD concluded that an insufficient amount of evidence existed “to suggest a  
2 causal relationship between chronic O<sub>3</sub> exposure and increased risk for mortality in humans”  
3 (U.S. EPA, 2006, [088089](#)). Two additional studies have been conducted since the last review, an  
4 ecologic study that finds no association between mortality and O<sub>3</sub>, and a reanalysis of the ACS  
5 cohort that specifically points to a relationship between long-term O<sub>3</sub> exposure and an increased risk  
6 of respiratory mortality (Section 7.7.1). The findings from the reanalysis of the ACS cohort are  
7 consistent and coherent with the evidence from epidemiologic, controlled human exposure, and  
8 animal toxicological studies for the effects of short- and long-term exposure to O<sub>3</sub> on respiratory  
9 effects. Additionally, the evidence for short- and long-term respiratory morbidity provides biological  
10 plausibility for mortality due to respiratory disease. Collectively, the evidence **is suggestive of a**  
11 **causal relationship between long-term O<sub>3</sub> exposures and all-cause mortality.**

## 2.5. Policy Relevant Considerations

### 2.5.1. Potentially Susceptible Populations

12           Upon evaluating the association between short- and long-term exposure to O<sub>3</sub> and various  
13 health outcomes, studies also attempted to identify populations that are more susceptible<sup>1</sup> to O<sub>3</sub>.  
14 These studies did so by conducting stratified epidemiologic analyses; by examining individuals with  
15 an underlying health condition in controlled human exposure studies; or by developing animal  
16 models that mimic the pathophysiological conditions associated with an adverse health effect. These  
17 studies identified a multitude of factors that could potentially contribute to whether an individual is  
18 susceptible to O<sub>3</sub> (Table 8-1). The examination of susceptible populations to O<sub>3</sub> exposure allows for  
19 the NAAQS to provide an adequate margin of safety for both the general population and for sensitive  
20 populations.

21           The populations identified in Chapter 8 that are most susceptible to O<sub>3</sub>-related health effects  
22 are individuals with influenza/infection, individuals with asthma, and older age groups. There were a  
23 small number of studies on influenza/infection but both reported influenza/infection to modify the  
24 association between O<sub>3</sub> exposure and respiratory effects, with individuals having influenza or an  
25 infection being at increased susceptibility. Asthma as a susceptibility factor was supported by  
26 controlled human exposure and toxicological studies, as well as some evidence from epidemiologic  
27 studies. Most studies comparing age groups reported greater effects of short-term O<sub>3</sub> exposure on  
28 mortality among older adults. Diet and obesity are also both likely susceptibility factors. Multiple  
29 epidemiologic, controlled human exposure, and toxicological studies reported that diets deficient in

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<sup>1</sup> Populations that have a greater likelihood of experiencing health effects related to exposure to an air pollutant (e.g., O<sub>3</sub>) due to a variety of factors including, but not limited to: genetic background, birth outcomes (e.g., low birth weight, birth defects), race, sex, lifestage, lifestyle (e.g., smoking status, nutrition), preexisting disease, SES (e.g., educational attainment, reduced access to health care), and characteristics that may modify exposure to O<sub>3</sub> (e.g., time spent outdoors)

1 Vitamins E and C are associated with susceptibility to O<sub>3</sub>-related health effects. Similarly, studies of  
2 effect measure modification by BMI observed greater O<sub>3</sub>-related respiratory decrements for  
3 individuals who were obese.

4 Other potential factors [pre-existing conditions (such as COPD and CVD) young age, sex, and  
5 multiple genes (such as GSTM1, GSTP1, HMOX-1, NQO1, and TNF-α)] provided some evidence  
6 of susceptibility, but further evidence is needed. In addition, examination of modification of the  
7 associations between O<sub>3</sub> exposure and health effects by SES and race were available in a limited  
8 number of studies, and demonstrated possible increased odds of health effects related to O<sub>3</sub> exposure  
9 among those with low SES and Blacks.

10 Individuals involved in outdoor activities were examined in a recent study but no effect  
11 modification was observed. However, previous evidence along with biological plausibility from  
12 toxicological and controlled human studies has shown this population to be susceptible to O<sub>3</sub>-related  
13 health effects. The only studies examining effect measure modification by diabetes examined O<sub>3</sub>  
14 exposure and cardiovascular outcomes, but none of the studies reported any change in the  
15 association by diabetes.

16 Studies of air conditioning use, physical conditioning, and smoking were conducted but not  
17 much evidence was available to determine whether susceptibility to O<sub>3</sub>-related health effects is  
18 present for these factors. Toxicological studies also identified hyperthyroidism and the lifestage of  
19 gestation to be factors warranting further examination. Future research on these will provide  
20 additional insight into whether these factors affect susceptibility to O<sub>3</sub>-related health effects.

## 2.5.2. Lag Structure of Ozone-Morbidity and Ozone-Mortality Associations

21 Epidemiologic studies have attempted to identify the time-frame in which exposure to O<sub>3</sub> can  
22 impart a health effect. Although O<sub>3</sub> exposure-response relationships have traditionally been  
23 examined using air quality data for a defined lag period (e.g., 1 day or average of 0-1 days), the  
24 relationship can potentially be influenced by a multitude of factors, such as the underlying  
25 susceptibility of an individual (e.g., age, pre-existing diseases), which could increase or decrease the  
26 lag times observed.

27 An attempt has been made to identify whether certain lag periods are more strongly associated  
28 with specific health outcomes. The epidemiologic evidence evaluated in the 2006 O<sub>3</sub> AQCD  
29 indicated that one of the remaining uncertainties in characterizing the O<sub>3</sub>-mortality relationship was  
30 identifying the appropriate lag structure (e.g., single-day lags versus distributed lag model).  
31 Currently, many investigators have chosen to examine the lag structure of associations between O<sub>3</sub>  
32 concentration and health outcome instead of focusing on a priori lag times. This approach is  
33 informative because if effects are cumulative, higher overall risks may exist than would be observed  
34 for any given single day lag. An examination of lag times used in the epidemiologic studies  
35 evaluated in this assessment can provide further insight on the relationship between O<sub>3</sub> exposure and  
36 morbidity and mortality outcomes.

### 2.5.2.1. Ozone-Respiratory Effect Associations

1 Collectively, recent epidemiologic studies of lung function, respiratory symptoms, and  
2 biological markers of airway inflammation and oxidative stress examined associations with single-  
3 day ambient O<sub>3</sub> exposures lagged from 0 to 7 days as well as concentrations averaged over 2 to 19  
4 days. Lag 0 and 1 ambient O<sub>3</sub> exposures were associated with decreases in lung function and  
5 increases in respiratory symptoms, airway inflammation, and oxidative stress. In several studies,  
6 multiday averages of O<sub>3</sub> exposure were associated with these endpoints, indicating that exposures  
7 accumulated over several days may be important or may be subject to less measurement error.

8 Studies have suggested that O<sub>3</sub>-related respiratory morbidity may occur via multiple  
9 mechanisms with varying time courses of action. Many epidemiologic studies simultaneously  
10 examined associations of short-term ambient O<sub>3</sub> exposure with lung function, respiratory symptoms,  
11 and biological markers of airway inflammation and oxidative stress and found inconsistent  
12 associations among endpoints whether evaluated at the same or different lags of O<sub>3</sub> exposure. In  
13 most cases, investigators examined a limited number of O<sub>3</sub> exposure lags and did not assign different  
14 O<sub>3</sub> exposure lags for each endpoint based on hypothesized mechanisms of action. These limitations  
15 may explain some of the inconsistencies in associations of O<sub>3</sub> with different respiratory health  
16 endpoints and may contribute to uncertainty over the important lags of ambient O<sub>3</sub> exposure for  
17 particular respiratory endpoints.

18 In studies of respiratory hospital admissions and ED visits, results were somewhat sensitive to  
19 the lag day selected (i.e., reduced when using a single-day lag and increased when using a distributed  
20 lag, up to 0-3 days), though when analyses were restricted to summer months only, the lag period  
21 tended to influence the results much less. Overall, among studies that examined a range of single-day  
22 lags and multiday averages, evidence did not overwhelmingly point to stronger immediate, delayed,  
23 or cumulative effects of O<sub>3</sub> exposure on respiratory effects.

### 2.5.2.2. Ozone-Mortality Associations

24 Epidemiologic studies that focused on the association between short-term O<sub>3</sub> exposure and  
25 mortality (i.e., all-cause, respiratory and cardiovascular) mostly examined a priori lag structures of  
26 either 1 or 0-1 days. Although mortality studies do not often examine alternative lag structures,  
27 several recent studies have conducted more extensive analysis of lag structure to investigate  
28 “mortality displacement” (i.e., deaths are occurring in frail individuals and exposure is only moving  
29 the day of death to a day slightly earlier), with varying results (Section 6.6.2.4). An examination of  
30 multi-day effects in a U.S. and European multicity study found conflicting evidence for mortality  
31 displacement, but the evidence suggests that the positive associations between O<sub>3</sub> and mortality are  
32 observed mainly in the first few days after exposure. A study conducted in 48 U.S. cities during the  
33 warm season (i.e., June-August) for the years 1989-2000 found that larger risk estimates were  
34 observed for distributed lag models compared to the lag 0 day estimates; however, larger risk  
35 estimates at lag 0-3 compared to 0-20 provide additional support for O<sub>3</sub>-induced mortality effects

1 occurring within the first few days after exposure. Although not a traditional mortality displacement  
2 study, the APHENA study found no indication that a distributed lag model with up to a 2-day lag  
3 yielded meaningfully larger O<sub>3</sub> mortality risk estimates than the lag 0-1 and lag 1 results. Finally, a  
4 study conducted in 21 European cities reports that using single-day exposures may overestimate the  
5 effects on all-cause and cardiovascular mortality, but underestimated the effects on respiratory  
6 mortality. Thus, the results in part suggest evidence of mortality displacement for all-cause and  
7 cardiovascular mortality. However, it should be noted that the difference in results observed across  
8 studies may be due to the different model specifications used. Collectively, these studies suggest that  
9 the positive associations between O<sub>3</sub> and mortality are observed mainly in the first few days after  
10 exposure. Overall, the evidence suggests that estimating the mortality risk using a single day of O<sub>3</sub>  
11 exposure may underestimate the public health impact, but the extent of multi-day effects appear to be  
12 limited to a few days.

### 2.5.3. Ozone Concentration-Response Relationship

13 An important consideration in characterizing the O<sub>3</sub>-morbidity and mortality association is  
14 whether the C-R relationship is linear across the full concentration range that is encountered or if  
15 there are concentration ranges where there are departures from linearity (i.e., nonlinearity). In this  
16 ISA studies have been identified that attempt to characterize the shape of the O<sub>3</sub> C-R curve along  
17 with possible O<sub>3</sub> “thresholds” (i.e., O<sub>3</sub> levels which must be exceeded in order to elicit a health  
18 response). The controlled human exposure and epidemiologic studies that examined the shape of the  
19 C-R curve and the potential presence of a threshold have indicated a generally linear C-R function  
20 with no indication of a threshold for O<sub>3</sub> concentrations greater than 30 or 40 ppb, which corresponds  
21 with PRB and the lower bound of O<sub>3</sub> concentrations included in the C-R functions.

#### 2.5.3.1. Concentration-Response Relationship Characterized by Controlled Human Exposure Studies

22 Controlled human exposure studies have provided strong and quantifiable C-R data on the  
23 human health effects of O<sub>3</sub>. The magnitude of respiratory effects in these studies is generally a  
24 function of O<sub>3</sub> exposure, i.e., the product of concentration (C), minute ventilation (V<sub>E</sub>), and exposure  
25 duration. Recent studies provide evidence for a smooth C-R curve without indication of a threshold  
26 in young healthy adults, exposed during moderate exercise for 6.6 hours to O<sub>3</sub> concentrations of  
27 between 40 and 120 ppb (Figure 6-1).

#### 2.5.3.2. Concentration-Response Relationship Characterized by Epidemiologic Studies

28 A study examining the C-R relationship found no evidence of a threshold between short-term  
29 O<sub>3</sub> exposure and pediatric asthma ED visits. One study reports that both quintile and loess dose-  
30 response analyses (Figure 6-11) suggest that there are elevated associations with O<sub>3</sub> at relatively low

1 concentrations, between 30 and 40 ppb, with stronger evidence at concentrations of 40 ppb and  
2 above. In an additional analysis, using a smooth function the authors examined whether the shape of  
3 the C-R curve for short-term exposure to O<sub>3</sub> and asthma hospital admissions (i.e., both general and  
4 ICU for all ages) is linear. When comparing the curve to a linear fit line the authors found that the  
5 linear fit is a reasonable approximation of the C-R relationship between O<sub>3</sub> and asthma hospital  
6 admissions around and below the current NAAQS (Figure 6-9). Although the C-R relationship  
7 between short-term O<sub>3</sub> exposure and respiratory-related hospital admissions and ED visits has not  
8 been extensively examined, preliminary examinations found no evidence of a threshold between  
9 short-term O<sub>3</sub> exposure and pediatric asthma ED visits.

10 Evidence associating long-term O<sub>3</sub> exposure to first asthma hospital admission in a C-R  
11 relationship is provided in a retrospective cohort study (Figure 7.3).

12 Evaluation of the short-term exposure to O<sub>3</sub>-mortality C-R relationship is difficult due to the  
13 highly heterogeneous O<sub>3</sub>-mortality associations among regions in multicity studies (using log-linear  
14 models). In addition, there are numerous issues that may influence the shape of the O<sub>3</sub>-mortality C-R  
15 relationship that warrant examination including: multi-day effects (distributed lags), potential  
16 adaptation and mortality displacement (i.e., hastening of death by a short period). Several recent  
17 studies applied a variety of statistical approaches to examine the shape of the O<sub>3</sub>-mortality C-R  
18 relationship and whether a threshold exists. These studies did not find any evidence that supports a  
19 threshold for the association between short-term exposure to O<sub>3</sub> and mortality. It was also  
20 demonstrated that the heterogeneity in the O<sub>3</sub>-mortality relationship across cities (or regions)  
21 complicates the interpretation of a combined C-R curve and threshold analysis. Additionally, given  
22 the effect modifiers identified in the mortality analyses that are also expected to vary regionally (e.g.,  
23 temperature, air conditioning prevalence), a national or combined analysis may not be appropriate to  
24 identify whether a threshold exists in the O<sub>3</sub>-mortality C-R relationship.

25 Additionally, several studies of long-term exposure to O<sub>3</sub> and birth outcomes have  
26 characterized the C-R relationship. Evidence from the southern California Children's Health Study  
27 identified a C-R relationship of birth weight with 24-h avg O<sub>3</sub> concentrations averaged over the  
28 entire pregnancy that was clearest above the 30 ppb level (Figure 7-4). Relative to the lowest decile  
29 of 24-h avg O<sub>3</sub>, estimates for the next 5 lowest deciles were approximately -40 g to -50 g, with no  
30 clear trend and with 95% confidence bounds that included zero. The highest four deciles of O<sub>3</sub>  
31 exposure showed an approximately linear decrease in birth weight, and all four 95% CIs excluded  
32 zero, and ranged from mean decreases of 74 grams to decreases of 148 grams. Another study  
33 conducted in southern California reported increased risks for cardiac birth defects in a dose-response  
34 manner with second-month O<sub>3</sub> exposure.

## 2.6. Integration of Ozone Health Effects

35 This section summarizes the main conclusions of this assessment regarding the health effects  
36 of O<sub>3</sub> and the concentrations at which those effects are observed. The conclusions from the previous

1 NAAQS review and the causality determinations from this review are summarized in Table 2-3. This  
 2 section also integrates the evidence from short- and long-term exposure studies across scientific  
 3 disciplines (i.e., controlled human exposure studies, toxicology, and epidemiology) in interpreting  
 4 the health effects evidence that spans from prenatal development to death. The clearest evidence for  
 5 health effects associated with short-term exposure to O<sub>3</sub> is provided by studies of respiratory effects.  
 6 The combined health effects evidence supports a causal relationship for this outcome. The evidence  
 7 is also sufficient to infer a relationship that is likely to be causal for short-term exposure to O<sub>3</sub> and  
 8 mortality and long-term exposure to O<sub>3</sub> and respiratory effects.

**Table 2-3. 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**

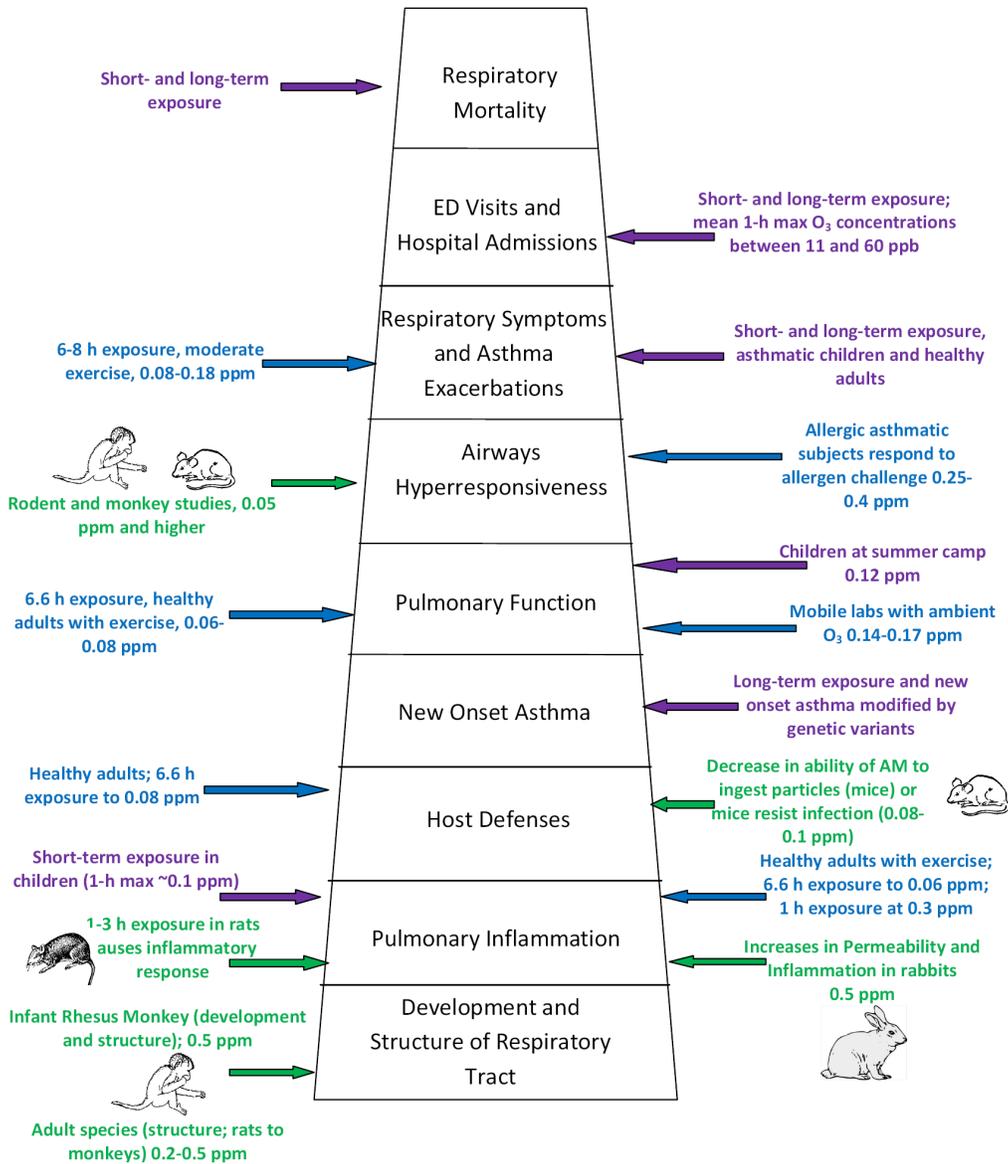
<i>Health Outcome</i>	<i>Conclusions from 2006 O<sub>3</sub> AQCD</i>	<i>Conclusions from 2011 1st Draft ISA</i>
Short-Term Exposure to O <sub>3</sub>		
Respiratory effects	The overall evidence supports a causal relationship between acute ambient O <sub>3</sub> exposures and increased respiratory morbidity outcomes.	Causal relationship
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 <sub>3</sub> 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 demonstrated decreases in FEV <sub>1</sub> in the range of 2.8 to 3.6% with O <sub>3</sub> exposures 6.6 h in duration and as low as <b>60 ppb</b> in concentration. The collective body of epidemiologic evidence demonstrates associations between acute ambient O <sub>3</sub> exposure and decrements in lung function, particularly in asthmatics, 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 <sub>3</sub> 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 <sub>3</sub> . As previously reported in the 2006 O <sub>3</sub> AQCD, <b>50 ppb</b> O <sub>3</sub> induced airway hyperresponsiveness in certain strains of rats, suggesting a genetic component.
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 <sub>3</sub> in inflammatory responses in the airways.	Epidemiologic studies provided new evidence for associations of ambient O <sub>3</sub> with mediators of airway inflammation and oxidative stress and indicated that groups with diminished antioxidant capacity or comorbidities such as atopy, AHR, or obesity may have increased susceptibility to respiratory morbidity associated with O <sub>3</sub> exposure. Generally, these studies were conducted in locations where the 8-h max O <sub>3</sub> concentration ranged from <b>31 to 66 ppb</b> .
Respiratory symptoms and medication use	Young healthy adult subjects exposed in clinical studies to O <sub>3</sub> 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 <sub>3</sub> 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 acute exposure to ambient O <sub>3</sub> and respiratory symptoms (e.g., cough, wheeze, production of phlegm, and shortness of breath) in asthmatic children. Generally, these studies were conducted in locations where the 8-h max O <sub>3</sub> concentration ranged from <b>17 to 66 ppb</b> .

<i>Health Outcome</i>	<i>Conclusions from 2006 O<sub>3</sub> AQCD</i>	<i>Conclusions from 2011 1st Draft ISA</i>
Lung host defenses	Toxicological studies provided extensive evidence that acute O <sub>3</sub> 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 phagocytose microorganisms upon exposure to 80 to 100 ppb O <sub>3</sub> .	Recent studies build on prior evidence that O <sub>3</sub> can affect multiple aspects of innate and acquired immunity, including macrophage function, immune cell proliferation, and natural killer cell function with acute O <sub>3</sub> exposures as low as <b>80 ppb</b> .
Allergic and asthma related responses	Previous toxicological evidence indicated that O <sub>3</sub> exposure skews immune responses toward an allergic phenotype, and enhances the development and severity of asthma-related responses such as AHR.	Further evidence for O <sub>3</sub> -induced allergic skewing is provided by a few recent studies in rodents using exposure concentrations as low as <b>200 ppb</b> .
Hospital admissions, ED visits, and physician visits	Aggregate population time-series studies observed that ambient O <sub>3</sub> concentrations are positively and robustly associated with respiratory-related hospitalizations and asthma ED visits during the warm season.	Strong evidence demonstrated associations of ambient O <sub>3</sub> with respiratory hospital admissions and ED visits in diverse populations across the U.S., Europe, and Canada. Generally, these studies were conducted in locations where the 8-h max O <sub>3</sub> concentration ranged from <b>18 to 60 ppb</b> .
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 <sub>3</sub> exposure and respiratory mortality.	Recent multicity time-series studies and a multicontinent study consistently demonstrated associations between ambient O <sub>3</sub> and respiratory-related mortality visits in diverse populations across the U.S., Europe, and Canada. Generally, these studies were conducted in locations where the 8-h max O <sub>3</sub> concentration ranged from <b>20 to 63 ppb</b> .
Cardiovascular effects	The limited evidence is highly suggestive that O <sub>3</sub> 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 <sub>3</sub> 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
All-cause mortality	The evidence is highly suggestive that O <sub>3</sub> directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.	Likely to be a Causal Relationship
Long-term Exposure to O <sub>3</sub>		
Respiratory effects	The current evidence is suggestive but inconclusive for respiratory health effects from long-term O <sub>3</sub> exposure.	Likely to be a Causal Relationship
New onset asthma	No Studies	Evidence for a relationship between different genetic variants (HMOX, GST, ARG) that, in combination with O <sub>3</sub> exposure, are related to new onset asthma. These results were observed when subjects living in areas where the mean annual 8-h max O <sub>3</sub> concentration was <b>55.2 ppb</b> , compared to those who lived where it was <b>38.4 ppb</b> .
Asthma hospital admissions	No Studies	Chronic O <sub>3</sub> exposure was related to first childhood asthma hospital admissions in a positive concentration-response relationship. Generally, these studies were conducted in locations where the 8-h max O <sub>3</sub> concentration ranged from <b>30 to 41 ppb</b> .

<i>Health Outcome</i>	<i>Conclusions from 2006 O<sub>3</sub> AQCD</i>	<i>Conclusions from 2011 1st Draft ISA</i>
Pulmonary structure and function	Epidemiologic studies observed that reduced lung function growth in children was associated with seasonal exposure to O <sub>3</sub> ; however, cohort studies of annual or multiyear O <sub>3</sub> exposure observed little clear evidence for impacts of longer-term, relatively low-level O <sub>3</sub> exposure on lung function development in children. Animal toxicological studies reported chronic O <sub>3</sub> -induced structural alterations 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 relating effects at exposure levels from <b>30 to 65 ppb</b> . Information from toxicological studies indicates that long-term exposure ( <b>500 ppb</b> ) during gestation or development 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 <sub>3</sub> in inflammatory responses in the airways	Several epidemiologic and toxicology studies (as low as <b>500 ppb</b> ) add to observations of O <sub>3</sub> -induced inflammation and injury.
Allergic responses	Limited epidemiologic evidence supported an association between ambient O <sub>3</sub> and allergic symptoms. Little if any information was available from toxicological studies.	Evidence relates positive outcomes of allergic response and O <sub>3</sub> exposure but with variable strength for the effect estimates; exposure to O <sub>3</sub> may increase total IgE in adult asthmatics. Allergic antibody levels in rodents were increased by exposure to O <sub>3</sub> concentrations as low as <b>200 ppb</b>
Respiratory mortality	Studies of cardio-pulmonary mortality were insufficient to suggest a causal relationship between chronic O <sub>3</sub> exposure and increased risk for mortality in humans	A single study demonstrated that exposure to O <sub>3</sub> (1-h max <b>45 to 60 ppb</b> ) elevated the risk of death from respiratory causes and this effect was robust to the inclusion of PM <sub>2.5</sub>
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 <sub>3</sub> effects.	Suggestive of a Causal Relationship
Central nervous system effects	Toxicological studies report that acute exposures to O <sub>3</sub> 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
Cancer	Little evidence for a relationship between chronic O <sub>3</sub> exposure and increased risk of lung cancer.	Inadequate to infer a Causal Relationship
All-cause mortality	There is little evidence to suggest a causal relationship between chronic O <sub>3</sub> exposure and increased risk for mortality in humans.	Suggestive of a Causal Relationship

## 2.6.1. Respiratory Health Effects

1 Collectively, there is a vast amount of evidence spanning several decades that supports a  
2 causal association between exposure to O<sub>3</sub> and a spectrum of respiratory effects, including  
3 development of the respiratory system; pulmonary structure, inflammation, injury and function;  
4 changes in host defense; new onset asthma and asthma exacerbations; respiratory symptoms; ED  
5 visits and hospital admissions for respiratory diseases; and even death attributable to respiratory  
6 disease (Figure 2-1). The majority of this evidence is derived from studies investigating short-term  
7 exposure (i.e., days to weeks) to O<sub>3</sub>, although more recent evidence demonstrates that long-term  
8 exposure (i.e., months to years) may also be detrimental to the respiratory system.



**Figure 2-1. Snapshot of evidence for the spectrum of respiratory health effects associated with short- and long-term exposure to ozone.**

**Green=Animal Toxicological Studies; Blue=Controlled Human Exposure Studies; Purple=Epidemiologic Studies; AM=Alveolar Macrophage. □**

1 Mechanistic evidence for the effect of O<sub>3</sub> on the respiratory system was initially characterized  
 2 in the 1996 O<sub>3</sub> AQCD, and identified a variety of lung lipid changes which may be further  
 3 metabolized to produce numerous biologically active mediators that can affect host defenses, lung  
 4 function, the immune system and other functions. As summarized in Section 2.3 and fully  
 5 characterized in Chapter 5 key events in the toxicity pathway of O<sub>3</sub> have been identified in humans  
 6 and animal models. They include the formation of secondary oxidation products in the lung,  
 7 activation of neural reflexes, pulmonary injury and inflammation and increased bronchial reactivity.  
 8 In addition, evidence is accumulating that influx of immunomodulatory cells, activation of innate  
 9 and adaptive immunity, induction of AHR and allergic responses, impairment of host defense,  
 10 systemic inflammation and vascular oxidative/nitrosative stress may also be critical to the O<sub>3</sub>  
 11 toxicity pathway (Figure 2-2).

## Mode of Action/Possible Pathways: Respiratory System

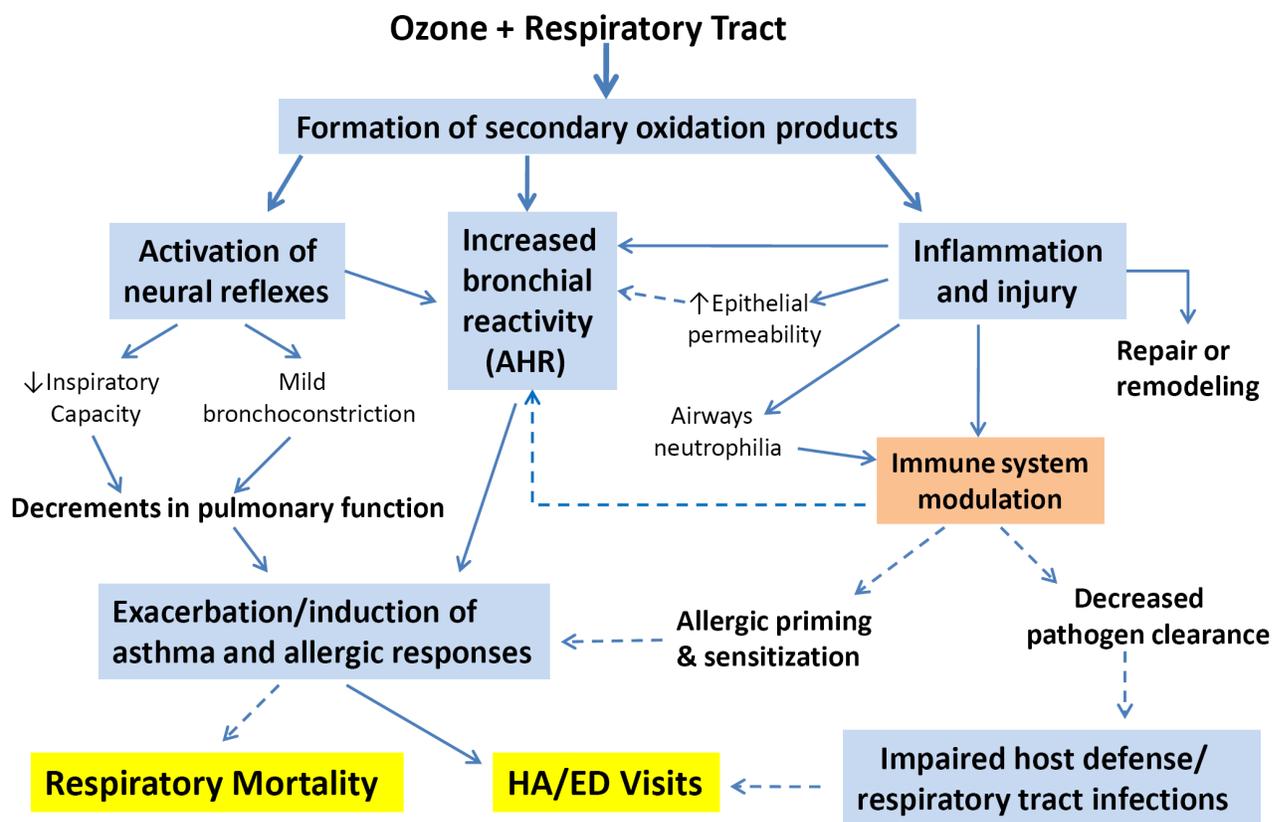


Figure 2-2. Schematic depicting key events in the ozone toxicity pathway. Solid arrows denote pathways for which there is greater certainty. Broken arrows represent pathways of emerging interest.

1           Recent toxicological studies of long-term exposure to O<sub>3</sub> occurring throughout various  
2           lifestages, beginning with prenatal and early life exposures, provide novel evidence for effects on  
3           development of the respiratory system, including ultrastructural changes in bronchiole development,  
4           alterations in placental and offspring cytokines, and increased offspring airway hyper-reactivity  
5           (Section 7.4.7). The strongest evidence for O<sub>3</sub>-induced effects on the developing lung comes from a  
6           series of experiments using infant rhesus monkeys repeatedly exposed to 0.5 ppm O<sub>3</sub> starting at  
7           one month of age. Functional changes in the conducting airways of infant rhesus monkeys exposed  
8           to either O<sub>3</sub> alone or O<sub>3</sub> + antigen were accompanied by a number of cellular and morphological  
9           changes. In addition to these functional and cellular changes, significant structural changes in the  
10          respiratory tract were observed. Importantly, the O<sub>3</sub>-induced structural pathway changes persisted  
11          after recovery in filtered air for six months after cessation of the O<sub>3</sub> exposures. Exposure to O<sub>3</sub> has  
12          also been associated with similar types of alterations in pulmonary structure in all adult laboratory  
13          animal species studied, from rats to monkeys (U.S. EPA, 1996, [017831](#)).

14          In addition to effects on the development and structure of the respiratory tract, there is  
15          extensive evidence for the effect of short-term exposure to O<sub>3</sub> on pulmonary inflammation. Previous  
16          evidence from controlled human exposure studies indicated that O<sub>3</sub> causes an inflammatory response  
17          in the lungs (U.S. EPA, 1996, [017831](#)). This inflammatory response to O<sub>3</sub> was detected after a single  
18          1-h exposure with exercise to O<sub>3</sub> concentrations of 0.3 ppm; the increased levels of some  
19          inflammatory cells and mediators persisted for at least 18 hours. Toxicological studies provided  
20          additional evidence for increases in permeability and inflammation in rabbits at levels as low as  
21          0.1 ppm O<sub>3</sub>. Evidence summarized in the 2006 O<sub>3</sub> AQCD demonstrated that inflammatory responses  
22          were observed subsequent to 6.6 h O<sub>3</sub> exposure to the lowest tested level of 0.08 ppm in healthy  
23          human adults, while animal toxicological studies provided extensive evidence that short-term  
24          (1-3 hours) O<sub>3</sub> exposure as low as 0.1-0.5 ppm could cause lung inflammatory responses. The  
25          limited epidemiologic evidence demonstrated an association between short-term ambient O<sub>3</sub>  
26          exposure and airway inflammation in children (1-h max O<sub>3</sub> of approximately 0.1 ppm). The most  
27          recent epidemiologic studies provide additional supporting evidence by demonstrating associations  
28          of ambient O<sub>3</sub> with mediators of airway inflammation and indicating that groups with diminished  
29          antioxidant capacity or comorbidities such as atopy, AHR, or obesity may have increased  
30          susceptibility to respiratory morbidity associated with O<sub>3</sub> exposure (Sections 6.2.4 and 8.1).

31          The normal inflammatory response in lung tissue is part of host defense that aids in removing  
32          microorganisms or particles that have reached the distal airways and alveolar surface. The 1996 O<sub>3</sub>  
33          AQCD concluded that short-term exposure to elevated concentrations of O<sub>3</sub> resulted in alterations in  
34          these host defense mechanisms in the respiratory system. Specifically, toxicological studies of short-  
35          term exposures as low as 0.1 ppm O<sub>3</sub> were shown to decrease the ability of alveolar macrophages to  
36          ingest particles, and short-term exposures as low as 0.08 ppm for 3 hours prevented mice from  
37          resisting infection with streptococcal bacteria, resulting in mortality. Similarly, alveolar macrophages  
38          removed from the lungs of human subjects after 6.6 hours of exposure to 0.08 and 0.10 ppm O<sub>3</sub>  
39          resulted in a decreased ability to ingest microorganisms, indicating some impairment of host defense

1 capability. These altered host defense mechanisms can lead to susceptibility to respiratory infections,  
2 which are associated with increased risk of asthma when occurring in early life.

3 In addition to pulmonary inflammation and host defenses, recent epidemiologic evidence has  
4 revealed an association between long-term exposure to O<sub>3</sub> and new onset asthma (Section 7.2.1).  
5 Studies have provided evidence for a relationship between different genetic variants (e.g., HMOX,  
6 GST, ARG) that, in combination with O<sub>3</sub> exposure, are related to new onset asthma. This is the first  
7 time that evidence has extended beyond the association of exposure to O<sub>3</sub> and asthma exacerbations  
8 to suggest that long-term exposure to O<sub>3</sub> may play a role in the development of the disease and  
9 contribute to incident cases of asthma.

10 The most commonly observed and strongest evidence for respiratory effects associated with  
11 short-term exposure to O<sub>3</sub> are increased frequency of breathing and decreased tidal volume (i.e.,  
12 rapid, shallow breathing). Previous controlled human exposure studies demonstrated O<sub>3</sub>-induced  
13 decrements in pulmonary function, characterized by alterations in lung volumes and flow and airway  
14 resistance and responsiveness for multihour exposures (up to 7 hours) to O<sub>3</sub> concentrations as low as  
15 0.08 ppm (U.S. EPA, 1996, [017831](#)). A series of mobile laboratory studies of lung function and  
16 respiratory symptoms reported pulmonary function decrements at mean ambient O<sub>3</sub> concentrations  
17 of 0.14 ppm in exercising healthy adolescents and increased respiratory symptoms and pulmonary  
18 function decrements at 0.15 ppm in heavily exercising athletes and at 0.17 ppm in lightly exercising  
19 healthy and asthmatic subjects. Epidemiologic and animal toxicological evidence is coherent with  
20 the results of the controlled human exposure studies, both indicating decrements in lung function  
21 upon O<sub>3</sub> exposure. Combined statistical analysis of six epidemiologic studies in children at summer  
22 camp demonstrated decrements in FEV<sub>1</sub> of 0.50 mL/ppb with previous hour O<sub>3</sub> concentration. For  
23 preadolescent children exposed to 120 ppb (0.12 ppm) ambient O<sub>3</sub>, this amounted to an average  
24 decrement of 2.4-3.0% in FEV<sub>1</sub>. Two key studies of lung function measurements before and after  
25 well-defined outdoor exercise events in adults yielded exposure-response slopes of 0.40 and  
26 1.35 mL/ppb. Animal toxicological studies reported similar respiratory effects in rats at exposures as  
27 low as 0.2 ppm O<sub>3</sub> for 3 hours. The 2006 O<sub>3</sub> AQCD characterized the controlled human exposure  
28 and animal toxicological studies as providing clear evidence of causality for the associations  
29 observed between acute ( $\leq$  24 hours) O<sub>3</sub> exposure and relatively small, but statistically significant  
30 declines in lung function observed in numerous recent epidemiologic studies. Declines in lung  
31 function were particularly noted in children, asthmatics, and adults who work or exercise outdoors.  
32 Recent studies in animals and in vitro models described inflammatory and injury responses mediated  
33 by toll-like receptors (e.g., TLR4, TL2), receptors for TNF or IL-1, multiple signaling pathways  
34 (e.g., p38, JNK, NF $\kappa$ B, MAPK/AP-1), and oxidative stress (Section 6.2.3.3). Recent controlled  
35 human exposure studies examined lower concentration O<sub>3</sub> exposures (40-80 ppb) and demonstrated  
36 that FEV<sub>1</sub>, respiratory symptoms, and inflammatory responses were affected by O<sub>3</sub> exposures of  
37 6.6 hours and in the range of 60 to 80 ppb (Section 6.2.1.2). These studies demonstrated decreases in  
38 FEV<sub>1</sub> in the range of 2.8 to 3.6% with O<sub>3</sub> exposures 6.6 h in duration and as low as 60 ppb in  
39 concentration. Recent epidemiologic studies provide greater insight into subject factors that may

1 increase susceptibility for O<sub>3</sub>-associated respiratory morbidity. It was in these potentially susceptible  
2 populations (e.g., asthmatics with atopy or concurrent respiratory infection, infants with asthmatic  
3 mothers, elderly with AHR or obesity, or groups with diminished antioxidant capacity) that O<sub>3</sub>-  
4 associated decreases in lung function tended to be observed.

5 Ozone exposure has been shown to result in airway hyperresponsiveness (both specific and  
6 non-specific), epithelial permeability, and respiratory tract inflammation. Increased airway  
7 responsiveness is an important consequence of exposure to O<sub>3</sub> because its presence means a change  
8 in airway smooth muscle reactivity and implies that the airways are predisposed to narrowing on  
9 inhalation of a variety of stimuli (e.g., specific allergens, SO<sub>2</sub>, cold air). Specifically, acute (2 or  
10 3 hours) exposure to 0.25 or 0.4 ppm O<sub>3</sub> was found to cause increases in airway responsiveness in  
11 response to allergen challenges among allergic asthmatic subjects who characteristically already had  
12 somewhat increased airway responsiveness at baseline.

13 In addition to alterations in lung volumes and flow, changes in pulmonary function due to  
14 exposure to O<sub>3</sub> may be elicited as respiratory symptoms (e.g., coughing, wheezing, shortness of  
15 breath). The 1996 O<sub>3</sub> AQCD identified an association between respiratory symptoms and increasing  
16 ambient O<sub>3</sub>, particularly among asthmatic children. In the 2006 O<sub>3</sub> AQCD, the evidence was  
17 extended to include young healthy adult subjects that exhibited symptoms of cough and pain on deep  
18 inspiration after exposure to 0.08 ppm O<sub>3</sub> for 6-8 hours during moderate exercise. The increase in the  
19 incidence of cough was found in controlled human exposure studies as low as 0.12 ppm in healthy  
20 adults during 1-3 hours with very heavy exercise and other respiratory symptoms, such as pain on  
21 deep inspiration and shortness of breath, were observed at 0.16-0.18 ppm with heavy and very heavy  
22 exercise. Previous epidemiologic evidence showed significant associations between acute exposure  
23 to ambient O<sub>3</sub> and increases in a wide variety of respiratory symptoms (e.g., cough, wheeze,  
24 production of phlegm, and shortness of breath) in asthmatic children (U.S. EPA, 2006, [088089](#)).  
25 Epidemiologic studies also indicated that acute O<sub>3</sub> exposure is likely associated with increased  
26 asthma medication use in asthmatic children. Similar to what was observed for pulmonary function,  
27 recent epidemiologic studies provided greater insight into subject factors that may increase  
28 susceptibility for O<sub>3</sub>-associated respiratory symptoms. It was in these potentially susceptible  
29 populations (e.g., asthmatics with atopy or concurrent respiratory infection, infants with asthmatic  
30 mothers, elderly with AHR or obesity, or groups with diminished antioxidant capacity) that O<sub>3</sub>-  
31 associated increases in respiratory symptoms tended to be observed. Additionally, recent evidence  
32 provides evidence for an association between long-term exposure to O<sub>3</sub> and respiratory symptoms  
33 (Section 7.2.2).

34 When respiratory symptoms, asthma exacerbations, or other respiratory diseases become too  
35 serious to be cared for at home, they can result in visits to hospital emergency departments (ED) or  
36 hospital admissions. The frequency of these types of ED visits and hospital admissions is associated  
37 with ambient O<sub>3</sub> concentrations. Summertime daily hospital admissions for respiratory causes in  
38 various locations of eastern North America consistently reported a relationship with ambient levels  
39 of O<sub>3</sub> in studies reviewed in the 1996 O<sub>3</sub> AQCD. This association remained even when considering

1 only concentrations below 0.12 ppm O<sub>3</sub>. The 2006 O<sub>3</sub> AQCD concluded that aggregate population  
2 time-series studies demonstrate a positive and robust association between ambient O<sub>3</sub> concentrations  
3 and respiratory-related hospitalizations and asthma ED visits during the warm season. Recent  
4 epidemiologic time-series studies included additional multicity and multicontinent studies in which  
5 short-term increases in ambient O<sub>3</sub> concentrations were consistently associated with increases in  
6 respiratory hospital admissions and ED visits across diverse populations, geographic locations, and  
7 range of O<sub>3</sub> concentrations (Section 6.2.7). There is also recent evidence for an association between  
8 respiratory hospital admissions and long-term exposure to O<sub>3</sub> (Section 7.2.2).

9 Finally, in very serious cases, O<sub>3</sub> exposure may contribute to death from respiratory causes.  
10 Recent evidence from several multicity and multicontinent studies demonstrated associations  
11 between increases in short-term exposure to ambient O<sub>3</sub> concentrations and increases in respiratory  
12 mortality (Section 6.6.2.5). Similarly, a study of long-term exposure to ambient O<sub>3</sub> concentrations  
13 also demonstrated an association between O<sub>3</sub> and increases in respiratory mortality (Section 7.7.1).  
14 Evidence from these new mortality studies is consistent and coherent with the evidence from  
15 epidemiologic, controlled human exposure, and animal toxicological studies for the effects of short-  
16 and long-term exposure to O<sub>3</sub> on respiratory effects. Additionally, the evidence for short- and long-  
17 term respiratory morbidity provides biological plausibility for mortality due to respiratory disease.

18 In summary, recent studies support or build upon the strong body of evidence presented in the  
19 1996 and 2006 O<sub>3</sub> AQCDs that short-term O<sub>3</sub> exposure is causally associated with adverse  
20 respiratory health effects. Recent controlled human exposure studies demonstrated decreases in  
21 FEV<sub>1</sub> in the range of 2.8 to 3.6% with O<sub>3</sub> exposures 6.6 hours in duration and as low as 60 ppb in  
22 concentration. Equally strong evidence demonstrated associations of ambient O<sub>3</sub> with respiratory  
23 hospital admissions and ED visits in diverse populations across the U.S., Europe, and Canada. Most  
24 effect estimates ranged from a 1.4 to 2.9% increase in daily ED visits or hospital admissions and  
25 were observed in locations with mean 1-h max O<sub>3</sub> concentrations between 11 and 60 ppb. Several  
26 multicity and multicontinent studies reported associations between increases in ambient O<sub>3</sub>  
27 concentrations and increases in respiratory mortality. Individual-level epidemiologic studies  
28 provided new evidence for associations of ambient O<sub>3</sub> with mediators of airway inflammation and  
29 oxidative stress and indicated that groups with diminished antioxidant capacity or comorbidities such  
30 as atopy, AHR, or obesity may have increased susceptibility to respiratory morbidity associated with  
31 O<sub>3</sub> exposure. These recent epidemiologic findings provided support for ambient O<sub>3</sub> exposure having  
32 similar effects and modes of action as those observed in studies with experimental exposures. By  
33 demonstrating O<sub>3</sub>-induced airway hyperresponsiveness, activation of neural reflexes (indicative of  
34 decreased pulmonary function), allergic responses, lung injury, impaired host defense, and airway  
35 inflammation, toxicological studies have characterized O<sub>3</sub> modes of action and have provided  
36 biological plausibility for epidemiologic associations of ambient O<sub>3</sub> exposure with lung function and  
37 respiratory symptoms, hospital admissions, ED visits, and mortality. Together, the evidence  
38 integrated across controlled human exposure, epidemiologic, and toxicological studies and across the

1 spectrum of respiratory health endpoints continues to demonstrate that **there is a causal**  
2 **relationship between short-term O<sub>3</sub> exposure and respiratory health effects.**

3 The strongest evidence for a relationship between long-term O<sub>3</sub> exposure and respiratory  
4 morbidity in recent studies demonstrates associations between long-term measures of O<sub>3</sub> exposure  
5 and new-onset asthma in children and increased respiratory symptom effects in asthmatics. While the  
6 evidence may be limited, these U.S. multi-community prospective cohort studies demonstrate that  
7 asthma risk is associated with the important relationships between genetic variability, environmental  
8 O<sub>3</sub> exposure, and behavior. Other recent studies provide coherent evidence for long-term O<sub>3</sub>  
9 exposure and respiratory morbidity effects such as first asthma hospitalization and respiratory  
10 symptoms in asthmatics. Generally, the epidemiologic and toxicological evidence provides a  
11 compelling case that supports the hypothesis that a relationship exists between long-term exposure to  
12 ambient O<sub>3</sub> and measures of respiratory morbidity. Building upon that evidence, the more recent  
13 epidemiologic evidence, combined with toxicological studies in rodents and non-human primates,  
14 provides biologically plausible evidence that **there is likely to be a causal relationship between**  
15 **long-term exposure to O<sub>3</sub> and respiratory morbidity.**

## 2.6.2. Mortality Effects

16 The 2006 O<sub>3</sub> AQCD concluded that the overall body of evidence was highly suggestive that  
17 short-term exposure to O<sub>3</sub> directly or indirectly contributes to non-accidental and cardiopulmonary-  
18 related mortality, but additional research was needed to more fully establish underlying mechanisms  
19 by which such effects occur. The evaluation of new multicity studies that examined the association  
20 between short-term O<sub>3</sub> exposure and mortality found evidence which supports the conclusions of the  
21 2006 O<sub>3</sub> AQCD. These new studies reported consistent positive associations between short-term O<sub>3</sub>  
22 exposure and total (nonaccidental) mortality, with associations being stronger during the warm  
23 season, as well as additional support for associations between O<sub>3</sub> exposure and cardiovascular  
24 mortality being similar or larger in magnitude compared to respiratory mortality. Additionally, these  
25 new studies examined previously identified areas of uncertainty in the O<sub>3</sub>-mortality relationship.  
26 Taken together, the body of evidence indicates that **there is likely to be a causal relationship**  
27 **between short-term exposures to O<sub>3</sub> and all-cause mortality.**

28 The 2006 O<sub>3</sub> AQCD concluded that an insufficient amount of evidence existed “to suggest a  
29 causal relationship between chronic O<sub>3</sub> exposure and increased risk for mortality in humans”  
30 (U.S. EPA, 2006, [088089](#)). Two additional studies have been conducted since the last review, an  
31 ecologic study that finds no association between mortality and O<sub>3</sub>, and a reanalysis of the ACS  
32 cohort that specifically points to a relationship between long-term O<sub>3</sub> exposure and an increased risk  
33 of respiratory mortality. The findings from the reanalysis of the ACS study are consistent and  
34 coherent with the evidence from epidemiologic, controlled human exposure, and animal  
35 toxicological studies for the effects of short- and long-term exposure to O<sub>3</sub> on respiratory effects.  
36 Additionally, the evidence for short- and long-term respiratory morbidity provides biological

1 plausibility for mortality due to respiratory disease. Collectively, the evidence **is suggestive of a**  
2 **causal relationship between long-term O<sub>3</sub> exposures and mortality.**

### 2.6.3. Cardiovascular Health Effects

3 In past O<sub>3</sub> AQCDs the effects of short- and long-term exposure to O<sub>3</sub> on the cardiovascular  
4 system could not be thoroughly evaluated due to the paucity of information available. However,  
5 studies investigating O<sub>3</sub>-induced cardiovascular events have advanced in the last two decades.  
6 Overall, there is limited, mixed evidence for cardiovascular effects in epidemiologic studies. Animal  
7 toxicological studies provide more evidence for O<sub>3</sub> exposure leading to cardiovascular morbidity.  
8 The toxicological studies demonstrate O<sub>3</sub>-induced cardiovascular effects, specifically enhanced  
9 ischemia/reperfusion injury with or without the corresponding development of a systemic oxidative,  
10 proinflammatory environment, disrupted NO-induced vascular reactivity, decreased cardiac function,  
11 and increased HRV. Taking into consideration the positive toxicological studies reported, the  
12 generally limited body of evidence **is suggestive of a causal relationship for both relevant short-**  
13 **and long-term exposures to O<sub>3</sub> and cardiovascular effects.**

### 2.6.4. Central Nervous System Effects

14 In rodents, O<sub>3</sub> exposure has been shown to cause physicochemical changes in the brain  
15 indicative of oxidative stress and inflammation. Recent toxicological studies add to earlier evidence  
16 that short- and long-term exposures to O<sub>3</sub> can produce a range of effects on the central nervous  
17 system and behavior. Previously observed effects, including neurodegeneration, alterations in  
18 neurotransmitters, short- and long-term memory, and sleep patterns, have been further supported by  
19 recent studies. In instances where pathology and behavior are both examined, animals exhibit  
20 decrements in behaviors tied to the brain regions or chemicals found to be affected or damaged. The  
21 single epidemiologic study conducted showed that long-term exposure to O<sub>3</sub> affects memory in  
22 humans as well. Notably, exposure to O<sub>3</sub> levels as low as 0.25 ppm has resulted in progressive  
23 neurodegeneration and deficits in both short- and long-term memory in rodents. Additionally,  
24 changes in the CNS, including biochemical, cellular, and behavioral effects, have been observed in  
25 animals whose sole exposure occurred in utero, at levels as a low as 0.3 ppm. Together the evidence  
26 from studies of short- and long-term exposure to O<sub>3</sub> **is suggestive of a causal relationship between**  
27 **O<sub>3</sub> exposure and adverse CNS effects.**

### 2.6.5. Reproductive and Developmental Effects

28 There is limited though positive toxicological evidence for O<sub>3</sub>-induced developmental effects,  
29 including effects on pulmonary structure and function and central nervous system effects. Limited  
30 epidemiologic evidence exists for an association with O<sub>3</sub> concentration and decreased sperm  
31 concentration. A recent toxicological study provides limited evidence for a possible biological  
32 mechanism (histopathology showing impaired spermatogenesis) for such an association.

1 Additionally, though the evidence for an association between O<sub>3</sub> concentrations and adverse birth  
2 outcomes is generally inconsistent, there are several influential studies that indicate an association  
3 with reduced birth weight and restricted fetal growth. Overall, the evidence **is suggestive of a causal**  
4 **relationship between long-term exposures to O<sub>3</sub> and reproductive and developmental effects.**

### 2.6.6. Cancer and Mutagenicity and Genotoxicity

5 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) reported that evidence did not support ambient  
6 O<sub>3</sub> as a pulmonary carcinogen. Since the 2006 AQCD, very few epidemiologic and toxicological  
7 studies have been published that examine O<sub>3</sub> as a carcinogen, but collectively, study results indicate  
8 that O<sub>3</sub> may contribute to DNA damage. Overall, the evidence **is inadequate to determine if a**  
9 **causal relationship exists between ambient O<sub>3</sub> exposures and cancer.**

## 2.7. Effects on Vegetation and Ecosystems

10 Chapter 9 presents the most policy-relevant information related to this review of the NAAQS  
11 for the effects of O<sub>3</sub> on vegetation and ecosystems. This section integrates the key findings from the  
12 disciplines evaluated in this current assessment of the O<sub>3</sub> scientific literature, which includes plant  
13 physiology, biochemistry, whole plant biology, ecosystems and exposure-response.

14 Ozone effects at small scales, such as the leaf of an individual plant, can result in effects at a  
15 continuum of larger scales. Figure 2-3 is a simplified diagram of the major pathway through which  
16 O<sub>3</sub> enters plants and the major endpoints O<sub>3</sub> may affect from small to large scales. The sections of  
17 Chapter 9 are organized around this paradigm of effects at the cellular and subcellular level followed  
18 by consideration of the whole plant and finally, O<sub>3</sub> impacts on ecosystem-level processes. Ozone  
19 enters leaves through stomata, and can alter stomatal conductance and disrupt CO<sub>2</sub> fixation (Section  
20 9.4). These effects can change rates of leaf gas exchange, growth and reproduction at the individual  
21 plant level (Section 9.5). Those O<sub>3</sub>-induced effects can translate from the individual plant level to the  
22 ecosystem level, and cause changes in ecosystem services, such as C storage, water production,  
23 nutrient cycling, and community composition (Section 9.6). The EPA framework for causal  
24 determinations described in Chapter 1 has been applied to the body of scientific evidence to  
25 collectively examine effects attributed to O<sub>3</sub> exposure (Table 2-4).

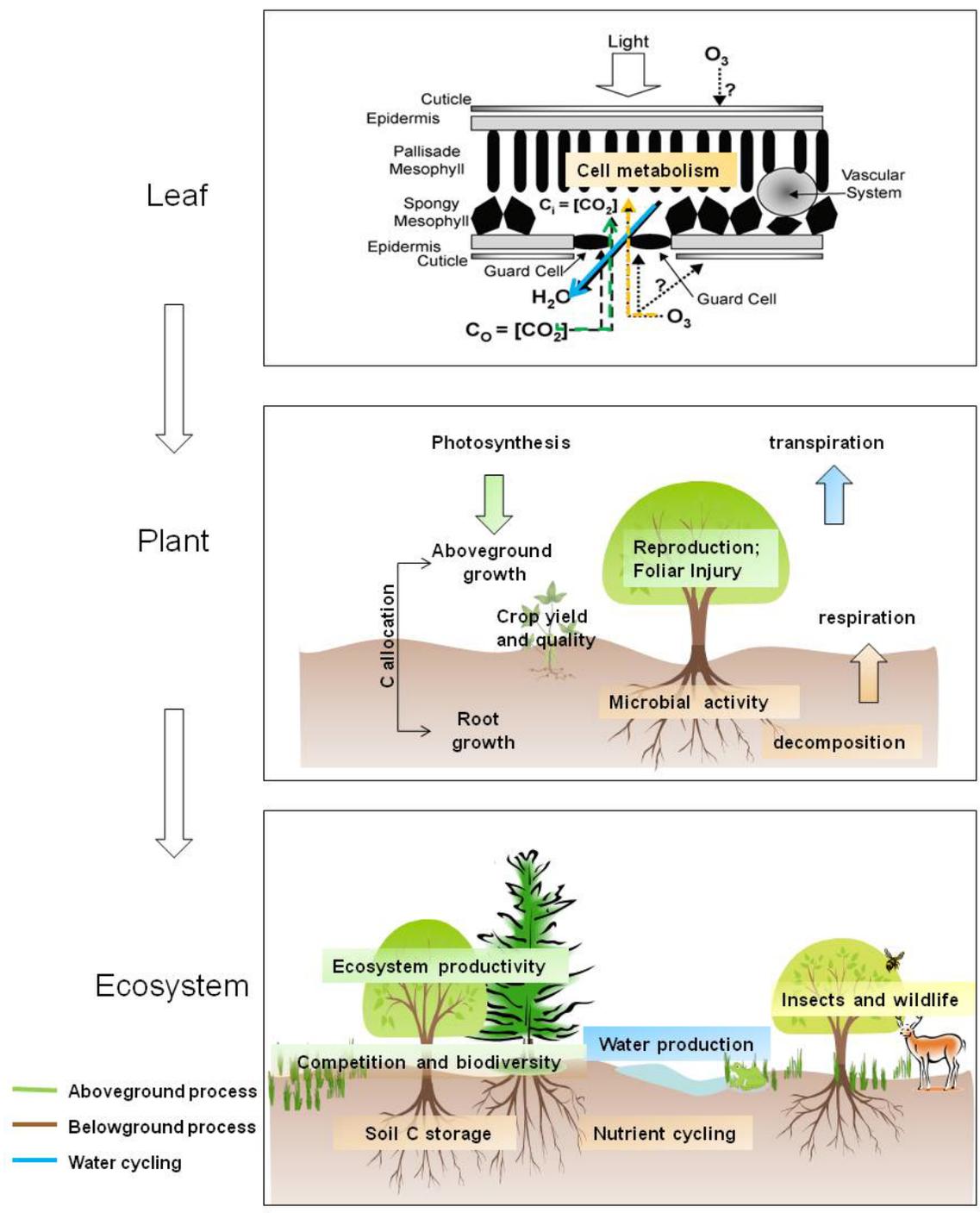


Figure 2-3. The effects of ozone at leaf, plant and ecosystem scales.

**Table 2-4. Summary of ozone causal determinations for vegetation and ecosystem effects**

<b>Vegetation and Ecosystem Effects</b>	<b>Causality Determination</b>
Reduced Vegetation Growth	Causal
Alteration of Vegetation Reproduction	Causal
Visible Foliar Injury Effects on Vegetation	Causal
Alteration of Leaf Gas Exchange in Vegetation	Causal
Reduced Yield and Quality of Agricultural Crops	Causal
Reduced Productivity in Terrestrial Ecosystems	Causal
Reduced Carbon (C) Sequestration in Terrestrial Ecosystems	Likely Causal
Alteration of Terrestrial Ecosystem Water Cycling	Likely Causal
Alteration of Below-ground Biogeochemical Cycles	Causal
Alteration of Terrestrial Community Composition	Likely Causal

### 2.7.1. Mechanisms Governing Response

1 Section 9.4 focuses on the effects of O<sub>3</sub> stress on plants and their responses to that stress on the  
2 molecular, biochemical and physiological levels. Many of the studies focus on the molecular  
3 mechanisms that underlie the observed biochemical and physiological changes observed in many  
4 plant species in response to O<sub>3</sub> exposure. The results support and strengthen those reported in the  
5 2006 O<sub>3</sub> AQCD. The most significant change in this section from the 2006 O<sub>3</sub> AQCD is the emphasis  
6 on molecular mechanisms as new techniques, such as those used in evaluating transcriptomes (total  
7 set of RNA transcripts in a particular cell at a particular time) and proteomes (total set of proteins  
8 expressed in a particular cell at a particular time), have been utilized to perform very comprehensive  
9 analyses of changes in gene transcription and protein expression in plants exposed to O<sub>3</sub>. These  
10 newer molecular studies not only provide very important and wide-ranging information regarding  
11 the many mechanisms of plant responses to O<sub>3</sub>, they also allow for the analysis of interactions  
12 between various biochemical pathways which are induced in response to O<sub>3</sub>. However, many of  
13 these studies are conducted in artificial conditions with model plants which are typically exposed to  
14 very high, short doses of O<sub>3</sub>. Therefore, additional work remains to elucidate whether these plant  
15 responses are transferable to other plant species exposed to more realistic ambient conditions.

16 Ozone is taken up into leaves through open stomata. Once inside the substomatal cavity, O<sub>3</sub> is  
17 thought to rapidly react with the aqueous layer surrounding the cell (apoplast) to form breakdown  
18 products such as H<sub>2</sub>O<sub>2</sub>, superoxide (O<sub>2</sub><sup>-</sup>), hydroxyl radicals (HO<sup>•</sup>) and peroxy radicals (HO<sub>2</sub><sup>•</sup>). These  
19 radicals may play a role in signaling processes and may also interact with sensitive molecules both  
20 outside and inside the cell to cause damage. This process was very comprehensively described in the  
21 2006 O<sub>3</sub> AQCD and is only summarized in this document in Section 9.4.2.

22 As plants have been shown to respond to O<sub>3</sub> exposure very rapidly, this response must result  
23 from a plant's ability to sense the presence of O<sub>3</sub> and/or its breakdown products and then  
24 communicate that information to the nucleus to initiate changes in gene expression. While it remains

1 unclear what the exact mechanism is by which the plant senses the presence of O<sub>3</sub>, whether there are  
2 multiple simultaneous mechanisms by which O<sub>3</sub> can be sensed, and how much variation exists in O<sub>3</sub>  
3 sensing between species and exposure conditions, some progress has been made in the understanding  
4 of this process since the 2006 O<sub>3</sub> AQCD. Experimental evidence described in Section 9.4.3.1  
5 suggests that O<sub>3</sub> and/or its breakdown products may be directly sensed by apoplastic receptor  
6 proteins (although they have not yet been identified). Additionally, a change in cellular redox state  
7 due to plant exposure to O<sub>3</sub> could be the manner in which plants sense the presence of the pollutant.  
8 Once the plant has sensed the presence of the pollutant, there is much evidence to suggest that  
9 mitogen-activated protein kinases (MAPK) play an important role in communicating signals to the  
10 nucleus that result in gene expression changes in response to O<sub>3</sub>. Calcium has also been implicated to  
11 play a role in the signal transduction processes. To summarize, the evidence to date suggests there  
12 may be several mechanisms by which plants sense the presence of O<sub>3</sub> and then communicate this  
13 signal to the nucleus to induce changes in gene expression.

14 New technologies have allowed for the evaluation of changes in the entire transcriptome and  
15 proteome, rather than analyzing the modification of the expression of individual genes and proteins;  
16 the results of these studies are presented in Section 9.4.3.2. While transcriptome and proteome  
17 analyses per se were not previously addressed, the 2006 O<sub>3</sub> AQCD did provide much information  
18 regarding changes in gene expression and protein quantity of individual genes and proteins in  
19 O<sub>3</sub>-treated plants. In the transcriptome and proteome studies described here, O<sub>3</sub> exposure conditions  
20 (concentration, duration of exposure), plant species and sampling times vary significantly; however,  
21 functional classification of the genes and proteins that are either up- or down-regulated by plant  
22 exposure to O<sub>3</sub> exhibit common trends. In summary, genes involved in plant defense, signaling, and  
23 those associated with the synthesis of plant hormones and secondary metabolism are generally up-  
24 regulated in plants exposed to O<sub>3</sub>, while those related to photosynthesis and general metabolism are  
25 typically down-regulated. Proteome studies support these results by demonstrating concomitant  
26 increases or decreases in the proteins encoded by these genes. The transcriptome and proteome  
27 results support and enhance the findings of the 2006 O<sub>3</sub> AQCD.

28 The 2006 O<sub>3</sub> AQCD included a discussion on the role of phytohormones, including salicylic  
29 acid, ethylene and jasmonic acid, in plant response to O<sub>3</sub>. Many additional studies using microarray  
30 technology (used to determine changes in the transcriptome) and a variety of *Arabidopsis* mutants  
31 are described in Section 9.4.3.3 and support the conclusions from the 2006 O<sub>3</sub> AQCD. Transcriptome  
32 analysis has also illuminated the complex interactions that exist between these hormones to better  
33 define plant response to O<sub>3</sub>. To summarize, the results indicate that while ethylene and salicylic acid  
34 are needed to develop O<sub>3</sub>-induced leaf lesions, jasmonic acid acts antagonistically to ethylene and  
35 salicylic acid to limit the spread of the lesions. Abscisic acid, in addition to its role in regulating  
36 stomatal aperture, may also act antagonistically to the jasmonic acid signaling pathway. Nitric oxide  
37 has also been proposed to play a role in regulating O<sub>3</sub>-induced changes in gene expression; however,  
38 its role is not yet well defined. Changes in phytohormones and the interactions between them reveal  
39 some of the complexity of plant responses to an oxidative stressor such as O<sub>3</sub>.

1           Antioxidant metabolites, such as ascorbate and glutathione, and the enzymes that regenerate  
2 them are a critical part of plant defense responses to oxidative stress. The role of ascorbate, which is  
3 located in several cellular compartments and also in the apoplast, was comprehensively evaluated in  
4 the 2006 O<sub>3</sub> AQCD as a first line of defense (due to its location in the apoplast) against oxidative  
5 stress. Ascorbate has also been the focus of studies investigating differences in O<sub>3</sub> tolerance between  
6 plant species or cultivars/genotypes within one species. While the studies evaluated for the current  
7 document support the important role of ascorbate, several studies suggest that ascorbate quantity,  
8 especially in the apoplast, is not the primary factor in determining plant tolerance to O<sub>3</sub>. In summary,  
9 antioxidant metabolites and enzymes increase in quantity in plants exposed to O<sub>3</sub>. In most cases,  
10 there is a correlation between the degree to which these defensive systems are induced and the  
11 ability of the plant to tolerate exposure to O<sub>3</sub>. This up-regulation of antioxidant defenses and the  
12 need to keep antioxidant metabolites in a reduced state requires a significant shift in C metabolism  
13 away from growth and reproduction to sustain the energy needs of the plant for defense.

14           While declines in C fixation as a result of plant exposure to O<sub>3</sub> were extensively described in  
15 the 2006 O<sub>3</sub> AQCD, some recent studies (described in Section 9.4.5.1) of O<sub>3</sub>-induced declines in  
16 photosynthesis have focused also on O<sub>3</sub> effects on the light reactions. Declines in the Fv/Fm ratio (a  
17 measure of the maximum efficiency of the light reactions of photosynthesis) were observed in  
18 several studies using a variety of plant species and exposure conditions. Additionally, O<sub>3</sub> increased  
19 the coefficient of non-photochemical quenching in several species, an indication that defense and  
20 repair mechanisms of a non-photochemical nature are activated in these plants while less absorbed  
21 light is being used to drive photosynthesis. This indicates a shift away from photosynthesis to  
22 defense, resulting in negative impacts on growth and reproduction.

23           Section 9.4.5.2 evaluates the effects of O<sub>3</sub> on respiration. While C assimilation declines in O<sub>3</sub>  
24 exposed plants, respiration is generally up-regulated. These increases in respiration are thought to  
25 result from a plant's greater energy needs for defense (maintaining its antioxidant metabolites in a  
26 reduced state) and repair. The increased energy needs will negatively impact plant growth and  
27 reproduction.

28           Secondary metabolism is most often up-regulated in a variety of species exposed to either  
29 acute or chronic O<sub>3</sub> exposures as a part of a generalized plant defense mechanism. Changes in gene  
30 expression, quantity and activity of enzymes associated with secondary metabolism and alterations  
31 in secondary metabolite quantity have been documented in plants exposed to O<sub>3</sub>. Some secondary  
32 metabolites, such as flavonoids and polyamines, are of particular interest as they are known to have  
33 antioxidant properties. Investigations on the importance of isoprenes in plant response to O<sub>3</sub> have  
34 revealed conflicting results; however, there is some evidence to suggest that they may play a  
35 protective role. In summary, secondary metabolites increase in quantity in O<sub>3</sub>-treated plants as part of  
36 a generalized plant defense response. Some secondary metabolites are of particular importance in  
37 O<sub>3</sub>-treated plants as they may have antioxidant functions. Increased synthesis of secondary  
38 metabolites represents a large energy investment of the plant into defense responses and away from  
39 growth and reproduction.

1 Section 9.4.6 focuses on O<sub>3</sub>-induced changes in stomatal function. Stomata play a critical role  
2 in limiting O<sub>3</sub> uptake into the plant by reducing stomatal aperture. Declines in stomatal conductance  
3 in response to O<sub>3</sub> have been documented for many plant species, and much evidence suggests that  
4 this results from increases in intercellular CO<sub>2</sub> concentration due to reductions in C fixation.  
5 Additionally, sensitivity of some plants to O<sub>3</sub> has been related to a sluggish stomatal response, in  
6 which plants are unable to close their stomata rapidly in response to O<sub>3</sub>. To summarize, stomatal  
7 response to O<sub>3</sub> can help to determine plant sensitivity to the pollutant, and the decreases in stomatal  
8 conductance are thought to be related to declines in C fixation rates. Reduced stomatal conductance  
9 will decrease rates of C assimilation and lead to diminished growth and reproduction in plants.

## 2.7.2. Nature of Effects on Vegetation

10 Ambient O<sub>3</sub> concentrations have long been known to cause visible foliar injury, decreases in  
11 photosynthetic rate, decreases in growth, and decreases in the quality and yield of some plant species  
12 (U.S. EPA, 1978, [040586](#); U.S. EPA, 1984, [029711](#); U.S. EPA, 1996, [080827](#); U.S. EPA, 2006,  
13 [088089](#)). Numerous studies have related O<sub>3</sub> exposure to plant responses, with most research effort  
14 focused on the growth of tree seedlings and the yield of crops as endpoints. The response of a plant  
15 species to O<sub>3</sub> exposure depends upon many factors, including genetic characteristics, biochemical  
16 and physiological status, and previous and current exposure to other stressors. The associated  
17 sections in Section 9.5 focus mainly on studies published since the release of the 2006 O<sub>3</sub> AQCD  
18 (U.S. EPA, 2006, [088089](#)). However, because much O<sub>3</sub> research was conducted prior to the 2006 O<sub>3</sub>  
19 AQCD, the conclusions presented below are collectively based on this ISA as well as the 1978,  
20 1986, 1996, and 2006 AQCDs (U.S. EPA, 1978, [040586](#); U.S. EPA, 1984, [029711](#); U.S. EPA, 1996,  
21 [080827](#); U.S. EPA, 2006, [088089](#)).

### 2.7.2.1. Effects on Woody and Herbaceous Vegetation

#### **Growth and Biomass Allocation**

22 The previous O<sub>3</sub> AQCDs concluded that there is strong and consistent evidence that ambient  
23 concentrations of O<sub>3</sub> decrease growth in numerous plant species across the U.S. Studies published  
24 since the last review continue to support that conclusion (Section 9.5.2.1).

25 A recently published meta-analysis of 263 studies reported that current ambient O<sub>3</sub>  
26 concentrations (~40 ppb) significantly decreased annual total biomass growth of forest species by an  
27 average of 7%, with potentially greater decreases (11 to 17%) in areas that have higher O<sub>3</sub>  
28 concentrations and as background O<sub>3</sub> increases in the future. This meta-analysis demonstrates the  
29 coherence of O<sub>3</sub> effects across numerous studies and species using a variety of experimental  
30 techniques. A study conducted on mature forest trees reported that the cumulative effects of ambient  
31 levels of O<sub>3</sub> decreased seasonal stem growth by 30-50% for most of the species in a high O<sub>3</sub>-year in  
32 comparison to a low O<sub>3</sub>-year.

1 Since the 2006 O<sub>3</sub> AQCD, several studies were published based on the Aspen free-air carbon-  
2 dioxide/O<sub>3</sub> enrichment (FACE) experiment using “free air,” O<sub>3</sub>, and CO<sub>2</sub> exposures in a forest in  
3 Wisconsin. It was found that O<sub>3</sub> caused reductions in total biomass relative to the control in aspen,  
4 paper birch, and sugar maple communities during the first seven years of stand development.  
5 Overall, the studies at the Aspen FACE experiment were consistent with many of the open-top  
6 chamber (OTC) studies that were the foundation of previous O<sub>3</sub> NAAQS reviews. These results  
7 strengthen our understanding of O<sub>3</sub> effects on forests and demonstrate the relevance of the  
8 knowledge gained from trees grown in open-top chamber studies.

9 In recent studies, O<sub>3</sub> was shown to have either negative, non-significant, or positive effects on  
10 root biomass and root:shoot ratio. While the findings of individual studies were mixed, recent meta-  
11 analyses have generally indicated that O<sub>3</sub> reduced C allocated to roots.

12 For some annual species, particularly crops, the endpoint for an assessment of the risk of O<sub>3</sub>  
13 exposure can be defined as yield or growth, e.g., production of grain. For plants grown in mixtures  
14 such as hayfields, and natural or semi-natural grasslands (including native nonagricultural species),  
15 endpoints other than production of biomass may be important. Such endpoints include biodiversity  
16 or species composition, and measures of plant quality. Effects may also result from competitive  
17 interactions among plants in mixed-species communities. Most of the available data on non-crop  
18 herbaceous species are for grasslands with many of the recent studies conducted in Europe.

19 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
20 **and reduced growth of woody and herbaceous vegetation.**

## Reproduction

21 Studies during recent decades have demonstrated O<sub>3</sub> effects on different stages of plant  
22 reproduction (Section 9.5.2.2). Several recent studies published since the 2006 O<sub>3</sub> AQCD further  
23 demonstrate the effects of O<sub>3</sub> on reproductive processes in herbaceous and woody plant species.

24 The impacts of O<sub>3</sub> on reproductive development can occur by influencing (1) age at time of  
25 initial flowering, particularly in long-lived trees that often have long juvenile periods of early growth  
26 without flower and seed production; (2) flower bud initiation and development; (3) pollen  
27 germination and pollen tube growth; and (4) seed, fruit, or cone yields and seed quality.

28 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
29 **and changes in reproduction of vegetation.**

## Visible Foliar Injury

30 Visible foliar injury resulting from exposure to O<sub>3</sub> has been well characterized and  
31 documented over several decades of research on many tree, shrub, herbaceous, and crop species  
32 (U.S. EPA, 1978, [040586](#); U.S. EPA, 1984, [029711](#); U.S. EPA, 1996, [080827](#); U.S. EPA, 2006,  
33 [088089](#)) (Section 9.5.2.3). Ozone-induced visible foliar injury symptoms on certain bioindicator  
34 plant species are considered diagnostic as they have been verified experimentally in exposure-  
35 response studies, using exposure methodologies such as continuous stirred tank reactors (CSTRs),

1 OTCs, and free-air fumigation. Experimental evidence has clearly established a consistent  
2 association of visible injury with O<sub>3</sub> exposure, with greater exposure often resulting in greater and  
3 more prevalent injury. Since the 2006 O<sub>3</sub> AQCD, several multiple-year field surveys of O<sub>3</sub>-induced  
4 visible foliar injury have been conducted at National Wildlife Refuges in Maine, Michigan, New  
5 Jersey, and South Carolina. New sensitive species showing visible foliar injury continue to be  
6 identified from field surveys and verified in controlled exposure studies.

7 The use of biological indicators in field surveys to detect phytotoxic levels of O<sub>3</sub> is a  
8 longstanding and effective methodology. The USDA Forest Service through the Forest Health  
9 Monitoring (FHM) Program (1990-2001) and currently the Forest Inventory and Analysis (FIA)  
10 Program has been collecting data regarding the incidence and severity of visible foliar injury on a  
11 variety of O<sub>3</sub> sensitive plant species throughout the U.S. The network has provided evidence that O<sub>3</sub>  
12 concentrations were high enough to induce visible symptoms on sensitive vegetation. From repeated  
13 observations and measurements made over a number of years, specific patterns of areas experiencing  
14 visible O<sub>3</sub> injury symptoms can be identified.

15 In addition, a study assessed the risk of O<sub>3</sub>-induced visible foliar injury on bioindicator plants  
16 in 244 national parks in support of the National Park Service's Vital Signs Monitoring Network. The  
17 results of the study demonstrated that the risk of visible foliar injury was high in 65 parks (27%),  
18 moderate in 46 parks (19%), and low in 131 parks (54%). Some of the well-known parks with a high  
19 risk of O<sub>3</sub>-induced visible foliar injury include: Gettysburg, Valley Forge, Delaware Water Gap, Cape  
20 Cod, Fire Island, Antietam, Harpers Ferry, Manassas, Wolf Trap Farm Park, Mammoth Cave, Shiloh,  
21 Sleeping Bear Dunes, Great Smoky Mountains, Joshua Tree, Sequoia and Kings Canyon, and  
22 Yosemite.

23 Evidence is sufficient to conclude that **there is a causal relationship between ambient O<sub>3</sub>**  
24 **exposure and the occurrence of O<sub>3</sub>-induced visible foliar injury on sensitive vegetation across**  
25 **the U.S.**

## Gas Exchange

26 There is strong experimental evidence over several decades of research that exposure to O<sub>3</sub>  
27 reduces photosynthesis and alters stomatal conductance in a wide variety of plant species. The mode  
28 of action, as characterized in Section 9.4 and in previous reviews, provides biological plausibility for  
29 O<sub>3</sub> effects on leaf gas exchange.

30 In compiling more than 55 studies, a meta-analysis reported that current O<sub>3</sub> concentrations in  
31 the northern hemisphere are decreasing photosynthesis (11%) and stomatal conductance (13%)  
32 across tree species. It was also found that younger trees less than four years old) were affected less  
33 by O<sub>3</sub> than older trees. Further, the authors also found that decreases in photosynthesis are consistent  
34 with the cumulative uptake of O<sub>3</sub> into the leaf. In contrast, several studies reported that O<sub>3</sub> exposure  
35 may result in loss of stomatal control, incomplete stomatal closure at night and a decoupling of  
36 photosynthesis and stomatal conductance, which may have implications for whole-plant water use  
37 (Section 9.6.3).

1 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
2 **and the alteration of leaf gas exchange in vegetation.**

### 2.7.2.2. Agricultural Crops

#### Yield and Crop Quality

3 The detrimental effect of O<sub>3</sub> on crop production has been recognized since the 1960s and a  
4 large body of research has subsequently stemmed from those initial findings. Previous O<sub>3</sub> AQCDs  
5 have extensively reviewed this body of literature (U.S. EPA, 2006, [088089](#)). Recent experimental  
6 studies of O<sub>3</sub> effects on crops are discussed in Section 9.5.3 and summarized in Tables 9-3 and 9-16.

7 Current O<sub>3</sub> concentrations across the U.S. are high enough to cause yield loss for a variety of  
8 agricultural crops including, but not limited to, soybean, wheat, cotton, potato, watermelon, beans,  
9 turnip, onion, lettuce, and tomato. Continued increases in O<sub>3</sub> concentration may further decrease  
10 yield in these sensitive crops while also initiating yield losses in less sensitive crops. Despite the  
11 well-documented yield losses due to increasing O<sub>3</sub> concentration, there is still a knowledge gap  
12 pertaining to the exact mechanism of O<sub>3</sub>-induced yield loss. Research has linked increasing O<sub>3</sub>  
13 concentration to decreased photosynthetic rates and accelerated senescence, which are related to  
14 yield.

15 Recent modeling research has correlated satellite air-column observations with direct air-  
16 sampling O<sub>3</sub> data and modeled the yield-loss due to O<sub>3</sub> over the continuous tri-state area of Illinois,  
17 Iowa and Wisconsin. This modeling data correlates well with the previous results from FACE-type  
18 experiments and OTC experiments.

19 New research is beginning to consider the mechanism of damage caused by long, lower O<sub>3</sub>  
20 concentration (so-called chronic exposure) compared to short, very high O<sub>3</sub> concentration (so-called  
21 acute exposure). Both types of O<sub>3</sub> exposure cause damage to agricultural crops, but through very  
22 different mechanisms. Until recently, most research on the mechanism of O<sub>3</sub> damage has used acute  
23 exposure studies. It has become clear that the same cellular and biochemical processes involved in  
24 the response to acute O<sub>3</sub> exposure are not involved in response to chronic O<sub>3</sub> exposure, yet both  
25 cause yield-loss in agriculturally important crops.

26 In addition, new research has highlighted the effects of O<sub>3</sub> on crop quality. Increasing O<sub>3</sub>  
27 concentration decreases nutritive quality of grasses, decreases macro- and micro-nutrient  
28 concentrations in fruits and vegetable crops, and decreases cotton fiber quality. These areas of  
29 research require further investigation to determine the mechanism and dose-responses.

30 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
31 **and reduced yield and quality of agricultural crops.**

### 2.7.2.3. Factors That Modify Functional and Growth Response

32 Many biotic and abiotic factors, including insects, pathogens, root microbes and fungi,  
33 temperature, water and nutrient availability, and other air pollutants, as well as elevated CO<sub>2</sub>,

1 influence or alter plant response to O<sub>3</sub>. These modifying factors were comprehensively reviewed in  
2 the 2006 O<sub>3</sub> AQCD. A limited number of studies published since 2006 provide further support for  
3 our understanding of the role of these interactions in modifying O<sub>3</sub>-induced plant responses and are  
4 discussed in Section 9.5.4.

### 2.7.3. Ecosystems and Services

5 Ozone has been found to alter plant physiological processes such as growth, biomass  
6 allocation, reproduction and gas exchange (Section 9.5). Those O<sub>3</sub>-induced effects at the individual  
7 plant scale have the potential to translate to effects at the ecosystem level, and cause changes in  
8 biogeochemical cycling and community composition. Information presented in the associated section  
9 (Section 9.6) was collected at multiple scales, ranging from responses at the population level to the  
10 ecosystem level. The effects of O<sub>3</sub> on ecosystem productivity, C sequestration, water cycling,  
11 nutrient cycling, and community composition are reviewed.

#### 2.7.3.1. Productivity and Carbon Sequestration

12 During the previous NAAQS reviews, there were very few studies that investigated the effect  
13 of O<sub>3</sub> exposure on ecosystem productivity and C sequestration. Recent studies from long-term FACE  
14 experiments provided evidence of the association of O<sub>3</sub> exposure and reduced productivity at the  
15 ecosystem level. Elevated O<sub>3</sub> reduced stand-level biomass by 13-23% at Aspen FACE after 7 years  
16 of O<sub>3</sub> exposure, and annual volume growth by 9.5 m<sup>3</sup>/ha at the Kranzberg Forest (Germany) FACE.  
17 Studies at the leaf and plant scales showed that O<sub>3</sub> reduced photosynthesis and plant growth, which  
18 provided coherence and biological plausibility for the decrease in ecosystem productivity. Results  
19 across different ecosystem models were consistent with the FACE experimental evidence, which  
20 showed that O<sub>3</sub> reduced ecosystem productivity.

21 Although O<sub>3</sub> generally causes negative effects on plant growth, the magnitude of the response  
22 varies among plant communities. For example, O<sub>3</sub> had little impact on white fir, but greatly reduced  
23 growth of ponderosa pine in southern California. Ozone decreased net primary production (NPP) of  
24 most forest types by 7-8% in Mid-Atlantic region, but had small impacts on spruce-fir forest, which  
25 was decreased by only 1%. Among crop species, the estimated yield loss for wheat (7-12%) and  
26 soybean (6-16%) were higher than rice (3-4%) and maize (3-5%).

27 In addition to plant growth, other indicators that are typically estimated by model studies  
28 include net ecosystem CO<sub>2</sub> exchange (NEE), C sequestration, and crop yield. Model simulations  
29 consistently found that O<sub>3</sub> exposure caused negative impacts on those indicators (Section 9.6.2,  
30 Table 9-5), but the severity of these impacts was influenced by multiple interactions of biological  
31 and environmental factors. For example, the largest O<sub>3</sub>-induced crop yield losses occurred in high-  
32 production areas exposed to high O<sub>3</sub> concentrations, such the Midwest and the Mississippi Valley  
33 regions of the U.S.

1 The suppression of ecosystem C sinks results in more CO<sub>2</sub> accumulation in the atmosphere.  
2 Globally, the indirect radiative forcing, reported in Watts/square meter (W/m<sup>2</sup>), caused by O<sub>3</sub>  
3 exposure through lowering ecosystem C sink (0.62-1.09 W/m<sup>2</sup>) could have an even greater impact  
4 on global warming than the direct radiative forcing of O<sub>3</sub> (0.89 W/m<sup>2</sup>). Ozone could also affect  
5 regional C budgets through interacting with multiple factors, such as N deposition, elevated CO<sub>2</sub> and  
6 land use history. Model simulations suggested that O<sub>3</sub> partially offset the growth stimulation caused  
7 by elevated CO<sub>2</sub> and N deposition in both Northeast- and Mid Atlantic-region forest ecosystems of  
8 the U.S.

9 The evidence is sufficient to infer that **there is a causal relationship between O<sub>3</sub> exposure**  
10 **and reduced productivity, and there is likely to be causal relationship between O<sub>3</sub> exposure and**  
11 **reduced carbon sequestration in terrestrial ecosystems.**

### 2.7.3.2. Water Cycling

12 Although the evidence was from a limited number of field and modeling studies, these  
13 findings showed an association of O<sub>3</sub> exposure and the alteration of water cycle at the ecosystem  
14 level. Field studies suggested that peak hourly O<sub>3</sub> exposure increased the rate of water loss from  
15 several tree species, and led to a reduction in the late-season modeled stream flow in three forested  
16 watersheds in eastern Tennessee. Evidence of sluggish stomatal responses during O<sub>3</sub> exposure was  
17 found in their study and several other studies (Section 9.6.3), which provided biological plausibility  
18 for the observed higher water loss at the ecosystem level. However, many experiments, mostly based  
19 on short-term O<sub>3</sub> exposure, found that O<sub>3</sub> generally reduced stomatal conductance. The O<sub>3</sub>-induced  
20 reduction in stomatal aperture is the biological assumption for most process-based models.  
21 Therefore, results of those models normally found that O<sub>3</sub> reduced water loss. For example, one  
22 study found that O<sub>3</sub> damage and N limitation together reduced evapotranspiration and increase  
23 runoff.

24 Although the direction of the response differed among studies, the evidence is sufficient to  
25 conclude that **there is likely to be a causal relationship between O<sub>3</sub> exposure and the alteration**  
26 **of ecosystem water production.**

### 2.7.3.3. Below-Ground Processes

27 Since the 2006 O<sub>3</sub> AQCD, more evidence has shown that although the responses are often  
28 species specific, O<sub>3</sub> altered the quality and quantity of C input to soil, microbial community  
29 composition, and C and nutrient cycling. Biogeochemical cycling of below-ground processes is  
30 driven by C input from plants. Studies at the leaf and plant level have provided biologically plausible  
31 mechanisms, such as reduced photosynthetic rates, increased metabolic cost, and reduced root C  
32 allocation (Section 9.6.4) for the association of O<sub>3</sub> exposure and the alteration of below-ground  
33 processes.

1 Results from Aspen FACE and other experimental studies consistently found that O<sub>3</sub> reduced  
2 litter production and altered C chemistry, such as soluble sugars, soluble phenolics, condensed  
3 tannins, lignin, and macro/micro nutrient concentration in litter. The changes in substrate quality and  
4 quantity could alter microbial metabolism under elevated O<sub>3</sub>, and therefore soil C and nutrient  
5 cycling. Several studies indicated that O<sub>3</sub> generally suppressed soil enzyme activities. However, the  
6 impact of O<sub>3</sub> on litter decomposition was inconsistent and varied among species, sites and exposure  
7 length. Ozone had small impact on dynamics of micro and macro nutrients, except for N. Ozone was  
8 found to reduce N release from leaf litter and decrease gross N mineralization, which could  
9 potentially decrease N availability to plants.

10 Studies from the Aspen FACE experiment suggested that the response of below-ground  
11 C cycle to O<sub>3</sub> exposure, such as litter decomposition, soil respiration and soil C content, changed  
12 over time. For example, in the early part of the experiment (1998-2003), O<sub>3</sub> had no impact on soil  
13 respiration but reduced the formation rates of total soil C under elevated CO<sub>2</sub>. However, after 10-  
14 11 years of exposure, O<sub>3</sub> was found to increase soil respiration but have no significant impact on soil  
15 C formation under elevated CO<sub>2</sub> (Section 9.6.4.1).

16 The evidence is sufficient to infer that **there is a causal relationship between O<sub>3</sub> exposure**  
17 **and the alteration of below-ground biogeochemical cycles.**

#### 2.7.3.4. Community Composition

18 In the 2006 O<sub>3</sub> AQCD, the impact of O<sub>3</sub> exposure on species competition and community  
19 composition was assessed. Ozone was found to cause a significant decline in ponderosa and Jeffrey  
20 pine in the San Bernardino Mountains in southern California. Ozone-exposure also tended to shift  
21 the grass-legume mixtures in favor of grass species (U.S. EPA, 2006, [088089](#)). Since the 2006 O<sub>3</sub>  
22 AQCD, more evidence has shown that O<sub>3</sub> exposure changed the competitive interactions and led to  
23 loss of O<sub>3</sub> sensitive species or genotypes. Studies at plant level found that the severity of O<sub>3</sub> damage  
24 on growth, reproduction and foliar injury varied among species (Section 9.6.5), which provided the  
25 biological plausibility for the alteration of community composition. Additionally, research since the  
26 last review has shown that O<sub>3</sub> can alter community composition and diversity of soil microbial  
27 communities.

28 The decline of conifer forests under O<sub>3</sub> exposure was continually observed in several regions.  
29 Ozone damage was believed to be an important causal factor in the dramatic decline of sacred fir in  
30 the valley of Mexico, as well as cembran pine in southern France and Carpathian Mountains. Results  
31 from the Aspen FACE site indicated that O<sub>3</sub> could alter community composition of broadleaf forests  
32 as well. At the Aspen FACE site, O<sub>3</sub> reduced growth and increased mortality of a sensitive aspen  
33 clone, while the O<sub>3</sub> tolerant clone emerged as the dominant clone in the pure aspen community. In  
34 the mixed aspen-birch and aspen-maple communities, O<sub>3</sub> reduced the competitive capacity of aspen  
35 compared to birch and maple.

36 The tendency for O<sub>3</sub>-exposure to shift the biomass of grass-legume mixtures in favor of grass  
37 species, was reported in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) and has been generally

1 confirmed by recent studies. However, in a high elevation mature/species-rich grass-legume pasture,  
2 O<sub>3</sub> fumigation showed no significant impact on community composition.

3 Ozone exposure not only altered community composition of plant species, but also  
4 microorganisms. The shift in community composition of bacteria and fungi has been observed in  
5 both natural and agricultural ecosystems, although no general patterns could be identified.

6 The evidence is sufficient to conclude that **there is likely to be a causal relationship between**  
7 **O<sub>3</sub> exposure and the alteration of community composition.**

#### 2.7.4. Air Quality Indices

8 Exposure indices are metrics that quantify exposure as it relates to measured plant damage  
9 (i.e., reduced growth). They are summary measures of monitored ambient O<sub>3</sub> concentrations over  
10 time intended to provide a consistent metric for reviewing and comparing exposure-response effects  
11 obtained from various studies. No new information is available since 2006 that alters the basic  
12 conclusions put forth in the 2006 and 1996 O<sub>3</sub> AQCDs (U.S. EPA, 1996, [080827](#); U.S. EPA, 2006,  
13 [088089](#)). These AQCDs focused on the research used to develop various exposure indices to help  
14 quantify effects on growth and yield in crops, perennials, and trees (primarily seedlings). The  
15 performance of indices was compared through regression analyses of earlier studies designed to  
16 support the estimation of predictive O<sub>3</sub> exposure-response models for growth and/or yield of crops  
17 and tree (seedling) species.

18 The main conclusions from the 1996 and 2006 O<sub>3</sub> AQCDs (U.S. EPA, 1996, [080827](#);  
19 U.S. EPA, 2006, [088089](#)) regarding an index based on ambient exposure are still valid. These key  
20 conclusions can be restated as follows:

- 21       ▪ O<sub>3</sub> effects in plants are cumulative;
- 22       ▪ higher O<sub>3</sub> concentrations appear to be more important than lower concentrations in  
23       eliciting a response;
- 24       ▪ plant sensitivity to O<sub>3</sub> varies with time of day and plant development stage; and
- 25       ▪ exposure indices that cumulate hourly O<sub>3</sub> concentrations and preferentially weight the  
26       higher concentrations have better statistical fits to growth/yield response data than do the  
27       mean and peak indices.

28 Various weighting functions have been used, including threshold-weighted (e.g., SUM06) and  
29 continuous sigmoid-weighted (e.g., W126) functions. Based on statistical goodness-of-fit tests, these  
30 cumulative, concentration-weighted indices could not be differentiated from one another using data  
31 from previous exposure studies. Additional statistical forms for O<sub>3</sub> exposure indices are summarized  
32 in Section 9.7 of this ISA. The majority of studies published since the 2006 O<sub>3</sub> AQCD (2006,

1 [088089](#)) do not change earlier conclusions, including the importance of peak concentrations, and the  
2 duration and occurrence of O<sub>3</sub> exposures in altering plant growth and yield.

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

#### 2.7.4.1. Modeled Ozone Deposition or "Flux"

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

#### 2.7.4.2. Night-Time Exposures

19 A 12-h (8:00 a.m. to 8:00 p.m.) daylight period for a W126 cumulating exposure was proposed  
20 in 2007 and 2009 following the release of the 2006 O<sub>3</sub> AQCD and was based primarily on evidence  
21 that the conditions for uptake of O<sub>3</sub> into the plant occur mainly during the daytime hours. Plants have  
22 the highest stomatal conductance during the daytime and atmospheric turbulent mixing is greatest  
23 then as well (U.S. EPA, 2006, [088089](#)). Recent reviews of the literature reported that a large number  
24 of species had varying degrees of nocturnal stomatal conductance. In general, stomatal conductance  
25 at night is at a much lower rate compared to daytime conductance. For significant nocturnal stomatal  
26 flux and O<sub>3</sub> effects to occur, specific conditions must exist. A susceptible plant with nocturnal  
27 stomatal conductance and low defense must be growing in an area with relatively high night-time O<sub>3</sub>  
28 and appreciable nocturnal turbulence. It is unclear how many areas there are in the U.S. where these  
29 conditions occur. More information is needed in these locations in order to assess the local O<sub>3</sub>  
30 patterns, micrometeorology and responses of potentially vulnerable plant species.

#### 2.7.5. Exposure-Response

31 None of the information on effects of O<sub>3</sub> on vegetation published since the 2006 O<sub>3</sub> AQCD has  
32 modified the assessment of quantitative exposure-response relationships that was presented in that

1 document (U.S. EPA, 2006, [088089](#)). This assessment updates the 2006 exposure-response models  
2 by computing them using the W126 metric, cumulated over 90 days. Almost all of the experimental  
3 research on the effects of O<sub>3</sub> on growth or yield of plants published since 2006 used only two levels  
4 of exposure. In addition, hourly O<sub>3</sub> concentration data that would allow calculations of exposure  
5 using the W126 scale are generally unavailable. However, two long-term experiments, one with a  
6 crop species (soybean), one with a tree species (aspen), have produced data that can be used to  
7 validate the exposure-response models presented in the 2006 O<sub>3</sub> AQCD, and methodology used to  
8 derive them.

9 Quantitative characterization of exposure-response in the 2006 O<sub>3</sub> AQCD was based on  
10 experimental data generated for that purpose by the National Crop Loss Assessment Network  
11 (NCLAN) and EPA National Health and Environmental Effects Research Laboratory, Western  
12 Ecology Division (NHEERL-WED) projects, using OTCs to expose crops and trees seedling to O<sub>3</sub>.  
13 In recent years, yield and growth results for two of the species that had provided extensive exposure-  
14 response information in those projects have become available from studies that used FACE  
15 technology, which is intended to provide conditions much closer to natural environments. The robust  
16 methods that were used previously with exposure measured as SUM06 were applied to the NCLAN  
17 and NHEERL-WED data with exposure measured as W126, in order to derive single-species median  
18 models for soybean and aspen from studies involving different genotypes, years, and locations. The  
19 resulting models were used to predict the change in yield of soybean and biomass of aspen between  
20 the two levels of exposure reported in current FACE experiments. Results from these new  
21 experiments were exceptionally close to predictions from the models. The accuracy of model  
22 predictions for two widely different plant species provides support for the validity of the  
23 corresponding multiple-species models for crops and trees in the NCLAN and NHEERL-WED  
24 projects. However, variability among species in those projects indicates that the range of sensitivity  
25 is likely quite wide. This was confirmed by a recent experiment with cottonwood in a naturally  
26 occurring gradient of exposure, which established the occurrence of species with responses  
27 substantially more severe under currently existing conditions than are predicted by the median model  
28 for multiple species.

29 Results from several meta-analyses have provided approximate values for responses of yield  
30 of soybean, wheat, rice and other crops under broad categories of exposure, relative to charcoal-  
31 filtered air. Additional reports have summarized yield data for six crop species under various broad  
32 comparative exposure categories, and reviewed 263 studies that reported effects on tree biomass.  
33 However, these analyses have proved difficult to compare with exposure-response models, especially  
34 given that exposure was not expressed on the same W126 scale.

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

1 Atmospheric O<sub>3</sub> plays an important role in the Earth's energy budget by interacting with  
2 incoming solar radiation and outgoing infrared radiation. Tropospheric O<sub>3</sub> makes up only a small  
3 portion of the total column of O<sub>3</sub>, but it has important incremental effects on the overall radiation  
4 budget. Chapter 10 assesses the specific role of tropospheric O<sub>3</sub> in the earth's radiation budget and  
5 how perturbations in tropospheric O<sub>3</sub> might affect climate through its role as a greenhouse gas  
6 (Section 10.2), and health, ecology and welfare through its role in shielding the earth's surface from  
7 solar ultraviolet radiation (Section 10.3).

### 2.8.1. Tropospheric Ozone as a Greenhouse Gas

8 Tropospheric O<sub>3</sub> is a major greenhouse gas, and increases in its abundance may contribute to  
9 climate change according to the 2007 climate assessment by the Intergovernmental Panel on Climate  
10 Change (IPCC). Models calculate that the global burden of tropospheric O<sub>3</sub> has doubled since the  
11 preindustrial era, while observations indicate that in some regions O<sub>3</sub> may have increased by factors  
12 as great as 4 or 5. These increases are tied to the rise in emissions of O<sub>3</sub> precursors from human  
13 activity, mainly fossil fuel consumption and agricultural processes. The impact on climate of the O<sub>3</sub>  
14 change since preindustrial times has been estimated to be about 25-40% of anthropogenic CO<sub>2</sub>  
15 impact and about 75% of anthropogenic CH<sub>4</sub> impact according to the IPCC, ranking it third in  
16 importance among the greenhouse gases.

17 The metric frequently used to estimate the potential climate impact of O<sub>3</sub> is called radiative  
18 forcing (RF). RF is a change in the radiative balance at the tropopause or at the top of the  
19 atmosphere when a perturbation is introduced in the earth-atmosphere-ocean system. The units of RF  
20 are energy flux per unit area, or W/m<sup>2</sup>, and positive values indicate warming while negative values  
21 indicate cooling. The IPCC estimates a radiative forcing of 0.35 W/m<sup>2</sup> for the change in tropospheric  
22 O<sub>3</sub> since the preindustrial era, compared to 1.66 W/m<sup>2</sup> for CO<sub>2</sub> and 0.48 W/m<sup>2</sup> for CH<sub>4</sub>. The error  
23 bars encompassing the tropospheric O<sub>3</sub> radiative forcing estimate range from 0.25 to 0.65 W/m<sup>2</sup>,  
24 making it relatively more uncertain than the long-lived greenhouse gases. Despite these  
25 uncertainties, **there is a causal relationship between tropospheric O<sub>3</sub> and radiative forcing.**

26 RF does not take into account the climate feedbacks that could amplify or dampen the actual  
27 surface temperature response. Quantifying the change in surface temperature requires a complex  
28 climate simulation in which all important feedbacks are accounted for. As these processes are not  
29 well understood or easily modeled, the surface temperature response to a given RF is highly  
30 uncertain and can vary greatly among models and from region to region within the same model.  
31 Despite these uncertainties, **there is likely to be a causal relationship between tropospheric O<sub>3</sub>  
32 and climate change.**

## 2.8.2. Tropospheric Ozone and UV-B related effects

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

9           Adverse human health effects associated with solar UV-B radiation exposure include  
10 erythema, skin cancer, ocular damage, and immune system suppression. A potential human health  
11 benefit of increased UV-B exposure involves the UV-induced production of vitamin D which may  
12 help reduce the risk of metabolic bone disease, type I diabetes, mellitus, and rheumatoid arthritis,  
13 and may provide beneficial immunomodulatory effects on multiple sclerosis, insulin-dependent  
14 diabetes mellitus, and rheumatoid arthritis.

15           Adverse ecosystem and materials damage effects are also associated with solar UV-B radiation  
16 exposure. Terrestrial ecosystem effects from increased UV-B radiation include reduced plant  
17 productivity and plant cover, changes in biodiversity, susceptibility to infection, and increases in  
18 natural UV protective responses. In general, however, these effects are small for moderate UV-B  
19 increases at mid-latitudes. Aquatic ecosystem effects from increased UV-B radiation include  
20 sensitivity in growth, immune response, and behavioral patterns of aquatic organisms.  
21 Biogeochemical cycles, particularly the carbon cycle, can also be influenced by increased UV-B  
22 radiation with effects ranging from UV-induced increases in CO<sub>2</sub> uptake through soil respiration to  
23 UV-induced release of CO<sub>2</sub> through photodegradation of above-ground plant litter. Changes in solar  
24 UV radiation may also have effects on carbon cycling and CO<sub>2</sub> uptake in the oceans as well as  
25 release of dissolved organic matter from sediment and algae. Finally, materials damage from  
26 increased UV-B radiation include UV-induced photodegradation of wood and plastics.

27           There is a lack of published studies that critically examine the incremental health or welfare  
28 effects (adverse or beneficial) attributable specifically to changes in UV-B exposure resulting from  
29 perturbations in tropospheric O<sub>3</sub> concentrations. While the effects are expected to be small, they  
30 cannot yet be critically assessed within reasonable uncertainty. Overall, the evidence **is inadequate**  
31 **to determine if a causal relationship exists between tropospheric O<sub>3</sub> and UV-B related health**  
32 **and welfare effects.**

## 2.9. Summary of Causal Determinations for Health Effects and Welfare Effects

1 This chapter has provided an overview of the underlying evidence used in making the causal  
 2 determinations for the health and welfare effects of O<sub>3</sub>. This review builds upon the conclusions of  
 3 the previous AQCDs for O<sub>3</sub> (U.S. EPA, 1978, [040586](#); U.S. EPA, 1984, [029711](#); U.S. EPA, 1996,  
 4 [017831](#); U.S. EPA, 1996, [080827](#); U.S. EPA, 2006, [088089](#)).

5 The evaluation of the epidemiologic, toxicological, and controlled human exposure studies  
 6 published since the completion of the 2006 O<sub>3</sub> AQCD have provided additional evidence for O<sub>3</sub>-  
 7 related health outcomes. Table 2-5 provides an overview of the causal determinations for all of the  
 8 health outcomes evaluated. Causal determinations for O<sub>3</sub> and welfare effects are included in  
 9 Table 2-6, while causal determinations for climate change and UV-B effects are in Table 2-7.  
 10 Detailed discussions of the scientific evidence and rationale for these causal determinations are  
 11 provided in subsequent chapters of this ISA.

**Table 2-5. Summary of ozone causal determinations by exposure duration and health outcome**

Health Outcome	Conclusions from 2006 O <sub>3</sub> AQCD	Conclusions from 2011 1st Draft ISA
Short-Term Exposure to O <sub>3</sub>		
Respiratory effects	The overall evidence supports a <b>causal relationship</b> between acute ambient O <sub>3</sub> exposures and increased respiratory morbidity outcomes.	Causal Relationship
Cardiovascular effects	The limited evidence is <b>highly suggestive</b> that O <sub>3</sub> 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 <b>exposures to O<sub>3</sub> are associated with</b> alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration.	Suggestive of a Causal Relationship
All-cause mortality	The evidence is <b>highly suggestive</b> that O <sub>3</sub> directly or indirectly contributes to non-accidental and cardiopulmonary-related mortality.	Likely to be a Causal Relationship
Long-term Exposure to O <sub>3</sub>		
Respiratory effects	The current evidence is <b>suggestive</b> but inconclusive for respiratory health effects from long-term O <sub>3</sub> exposure.	Likely to be a Causal Relationship
Cardiovascular Effects	<b>No studies</b> from previous review	Suggestive of a Causal Relationship
Reproductive and developmental effects	<b>Limited evidence</b> 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 <sub>3</sub> effects.	Suggestive of a Causal Relationship
Central nervous system effects	Toxicological studies report that <b>acute exposures to O<sub>3</sub> are associated with</b> alterations in neurotransmitters, motor activity, short and long term memory, sleep patterns, and histological signs of neurodegeneration.	Suggestive of a Causal Relationship
Cancer	<b>Little evidence</b> for a relationship between chronic O <sub>3</sub> exposure and increased risk of lung cancer.	Inadequate to infer a Causal Relationship
Mortality	There is <b>little evidence to suggest a causal relationship</b> between chronic O <sub>3</sub> exposure and increased risk for mortality in humans.	Suggestive of a Causal Relationship

**Table 2-6. Summary of ozone causal determination for welfare effects**

Vegetation and Ecosystem Effects	Conclusions from 2006 O <sub>3</sub> AQCD	Conclusions from 2011 1st Draft ISA
Reduced Vegetation Growth	Data published since the 1996 AQCD strengthen previous conclusions that there is strong evidence that current ambient O <sub>3</sub> concentrations <b>cause</b> decreased growth and biomass accumulation in annual, perennial and woody plants, including agronomic crops, annuals, shrubs, grasses, and trees.	Causal Relationship
Alteration of Vegetation Reproduction	For several decades, studies have <b>demonstrated O<sub>3</sub> effects</b> on different stages of reproduction.	Causal Relationship
Visible Foliar Injury Effects on Vegetation	Data published since the 1996 AQCD strengthen previous conclusions that there is strong evidence that current ambient O <sub>3</sub> concentrations <b>cause</b> impaired aesthetic quality of many native plants and trees by increasing foliar injury.	Causal Relationship
Alteration of Leaf Gas Exchange in Vegetation	<b>Ozone exposure reduces photosynthesis</b> , and the mechanisms of this reduction are better understood as a result of the research since the 1996 AQCD.	Causal Relationship
Reduced Yield and Quality of Agricultural Crops	Data published since the 1996 AQCD strengthen previous conclusions that there is strong evidence that current ambient O <sub>3</sub> concentrations <b>cause</b> decreased yield and/or nutritive quality in a large number of agronomic and forage crops.	Causal Relationship
Reduced Productivity in Terrestrial Ecosystems	There is <b>evidence that O<sub>3</sub> is an important stressor of ecosystems</b> and that the effects of O <sub>3</sub> on individual plants and processes are scaled up through the ecosystem, affecting net primary productivity.	Causal Relationship
Reduced Carbon (C) Sequestration in Terrestrial Ecosystems	<b>Limited studies</b> from previous review	Likely to be a Causal Relationship
Alteration of Terrestrial Ecosystem Water Cycling	Ecosystem water quantity <b>may be affected</b> by O <sub>3</sub> exposure at the landscape level.	Likely to be a Causal Relationship
Alteration of Below-ground Biogeochemical Cycles	Ozone-sensitive species have <b>well known responses to O<sub>3</sub> exposure</b> , 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. <b>Significant changes in plant community composition resulting directly from O<sub>3</sub> exposure have been demonstrated.</b>	Likely to be a Causal Relationship

**Table 2-7. Summary of ozone causal determination for climate change and UV-B effects**

Effects	Conclusions from 2006 O <sub>3</sub> AQCD	Conclusions from 2011 1st Draft ISA
Radiative Forcing	Climate forcing by O <sub>3</sub> 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 <sub>3</sub> await further advances in monitoring and chemical transport modeling, the overall body of scientific evidence <b>suggests</b> that high concentrations of O <sub>3</sub> on the regional scale <b>could have a discernable influence on climate</b> , leading to surface temperature and hydrological cycle changes.	Likely to be a Causal Relationship
UV-B Related Health and Welfare Effects	UV-B has <b>not been studied in sufficient detail</b> to allow for a credible health benefits assessment. In conclusion, the effect of changes in surface-level O <sub>3</sub> concentrations on UV-induced health outcomes cannot yet be critically assessed within reasonable uncertainty.	Inadequate to Determine if a Causal Relationship Exists

# References

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# Chapter 3. Atmospheric Chemistry and Ambient Concentrations

## 3.1. Introduction

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

10 The material in this chapter is organized as follows. Section 3.2 outlines the physical and  
11 chemical processes involved in O<sub>3</sub> formation and removal. Section 3.3 describes the latest methods  
12 used to model global O<sub>3</sub> concentrations, and Section 3.4 describes the application of some of those  
13 methods for estimating background concentrations of O<sub>3</sub>. Section 3.5 includes a comprehensive  
14 description of available O<sub>3</sub> monitoring techniques and monitoring networks, while Section 3.6  
15 presents information on the spatial and temporal variability of O<sub>3</sub> concentrations across the U.S. and  
16 their associations with other pollutants using available monitoring data.

## 3.2. Physical and Chemical Processes

17 O<sub>3</sub> in the troposphere is a secondary pollutant formed by photochemical reactions of precursor  
18 gases and is not directly emitted from specific sources. Ozone and other oxidants, such as PAN and  
19 H<sub>2</sub>O<sub>2</sub> form in polluted areas by atmospheric reactions involving two main classes of precursor  
20 pollutants: VOCs and NO<sub>x</sub>. Carbon monoxide (CO) is also important for O<sub>3</sub> formation in polluted  
21 areas and in the remote troposphere. The formation of O<sub>3</sub>, other oxidants and oxidation products  
22 from these precursors is a complex, nonlinear function of many factors including (1) the intensity  
23 and spectral distribution of sunlight; (2) atmospheric mixing; (3) concentrations of precursors in the  
24 ambient air and the rates of chemical reactions of these precursors; and (4) processing on cloud and  
25 aerosol particles. Information contained in this chapter briefly describes these processes and  
26 numerical models that incorporate these processes to calculate O<sub>3</sub> concentrations.

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1 Ozone is present not only in polluted urban atmospheres, but throughout the troposphere, even  
 2 in remote areas of the globe. The same basic processes involving sunlight-driven reactions of  $\text{NO}_x$ ,  
 3 VOCs and CO contribute to  $\text{O}_3$  formation throughout the troposphere. These processes also lead to  
 4 the formation of other photochemical products, such as PAN,  $\text{HNO}_3$ , and  $\text{H}_2\text{SO}_4$ , and to other  
 5 compounds, such as HCHO and other carbonyl compounds.  
 6 The processes responsible for producing summertime  $\text{O}_3$  episodes are fairly well understood,  
 7 and were covered in detail in the previous  $\text{O}_3$  AQCD (U.S. EPA, 2006, [088089](#)). This section focuses  
 8 on topics that form the basis for discussions in later chapters and for which there is substantial new  
 9 information since the previous AQCD. A schematic overview of the major photochemical cycles  
 10 influencing  $\text{O}_3$  in the troposphere and the stratosphere is given in Figure 3-1.

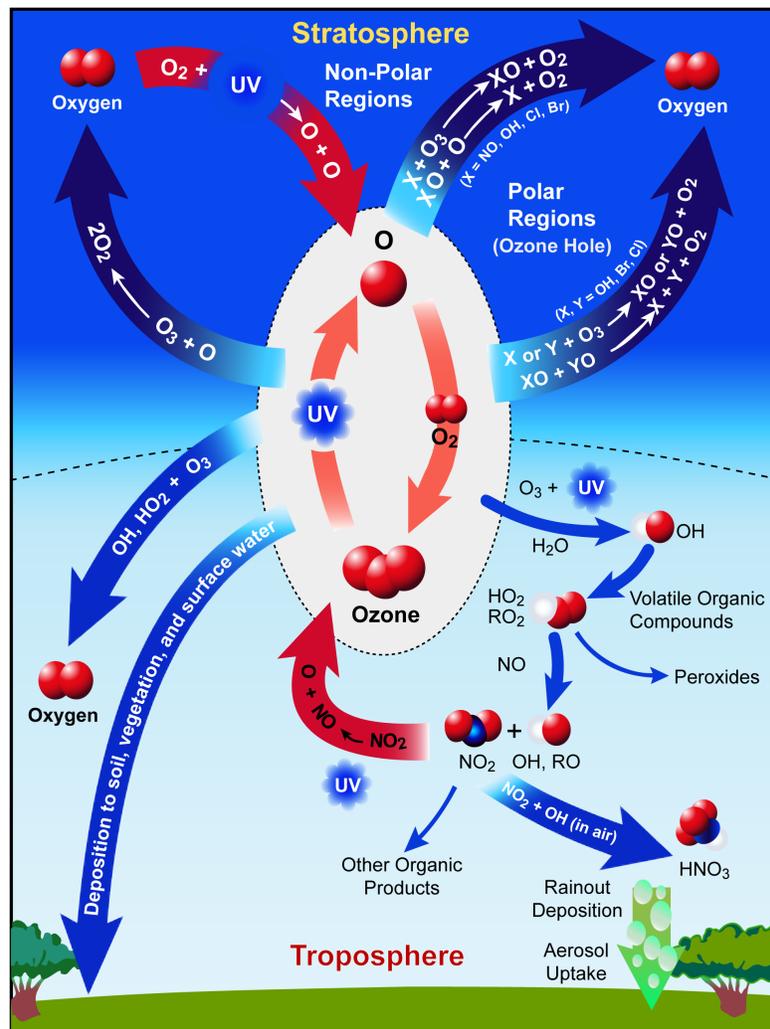


Figure 3-1. Schematic overview of photochemical processes influencing stratospheric and tropospheric ozone.

1 Major episodes of high O<sub>3</sub> concentrations in the eastern U.S. and in Europe are associated with  
2 slow moving high pressure systems. High pressure systems during the warmer seasons are associated  
3 with the sinking of air, resulting in warm, generally cloudless skies, with light winds. The sinking of  
4 air results in the development of stable conditions near the surface which inhibit or reduce the  
5 vertical mixing of O<sub>3</sub> precursors. The combination of inhibited vertical mixing and light winds  
6 minimizes the dispersal of pollutants emitted in urban areas, allowing their concentrations to build  
7 up. Photochemical activity involving these precursors is enhanced because of higher temperatures  
8 and the availability of sunlight. In the eastern U.S., O<sub>3</sub> and other secondary pollutants are determined  
9 by meteorological and chemical processes extending typically over spatial scales of several hundred  
10 thousand square kilometers (e.g., Civerolo et al., 2003, [053985](#); Rao et al., 2003, [054094](#)). Ozone  
11 episodes are thus best regarded as regional in nature. The conditions conducive to formation of high  
12 O<sub>3</sub> can persist for several days. These conditions have been described in greater detail in the 1996  
13 and 2006 O<sub>3</sub> AQCDs (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)). The transport of  
14 pollutants 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 higher frequency  
16 and duration of days with high O<sub>3</sub> concentrations. However, orographic lifting over the San Gabriel  
17 Mountains results in O<sub>3</sub> transport from Los Angeles to areas hundreds of kilometers downwind (e.g.,  
18 in Colorado and Utah) (Langford et al., 2009, [491703](#)). Ozone concentrations in southern urban  
19 areas (such as Houston, TX and Atlanta, GA) tend to decrease with increasing wind speed. In  
20 northern U.S. cities (such as Chicago, IL; New York, NY; Boston, MA; and Portland, ME), the  
21 average O<sub>3</sub> concentrations over the metropolitan areas increase with wind speed, indicating that  
22 transport of O<sub>3</sub> and its precursors from upwind areas is important (Husar and Renard, 1998, [052413](#);  
23 Schichtel and Husar, 2001, [016669](#)).

24 Aircraft observations indicate that there can be substantial differences in mixing ratios of key  
25 species between the surface and the overlying atmosphere (Berkowitz and Shaw, 1997, [047593](#);  
26 Fehsenfeld et al., 1996, [047803](#)). In particular, mixing ratios of O<sub>3</sub> can be higher in the lower free  
27 troposphere (aloft) than in the planetary boundary layer (PBL) during multiday O<sub>3</sub> episodes  
28 (Taubman et al., 2004, [052228](#); Taubman et al., 2006, [087582](#)). Convective processes and small scale  
29 turbulence transport O<sub>3</sub> and other pollutants both upward and downward throughout the planetary  
30 boundary layer and the free troposphere. During the day, convection driven by heating of the earth's  
31 surface results in a deeper planetary boundary layer (PBL) with vertically well mixed O<sub>3</sub> and  
32 precursors. As solar heating of the surface decreases going into night, the daytime boundary layer  
33 collapses leaving behind O<sub>3</sub> and its precursors in a residual layer above a shallow nighttime  
34 boundary layer. Pollutants in the residual layer have now become essentially part of the free  
35 troposphere, as shown in AX2.3.2 of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). Winds in the  
36 free troposphere tend to be stronger than those closer to the surface and so are capable of  
37 transporting pollutants over long distances. Thus, O<sub>3</sub> and its precursors can be transported vertically  
38 by convection into the upper part of the mixed layer on one day, then transported overnight as a layer

1 of elevated mixing ratios, and then entrained into a growing convective boundary layer downwind  
2 and brought back down to the surface.

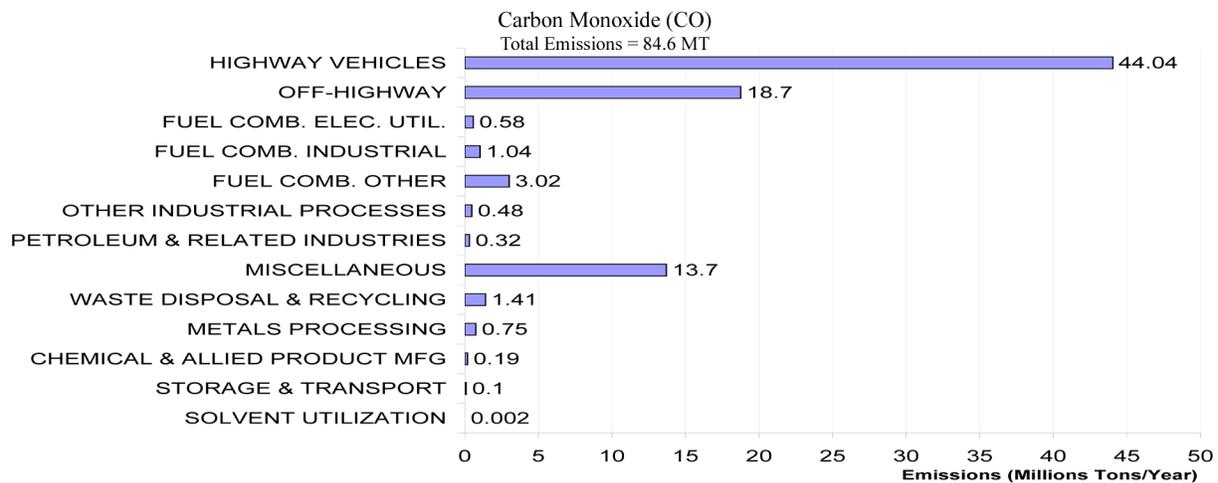
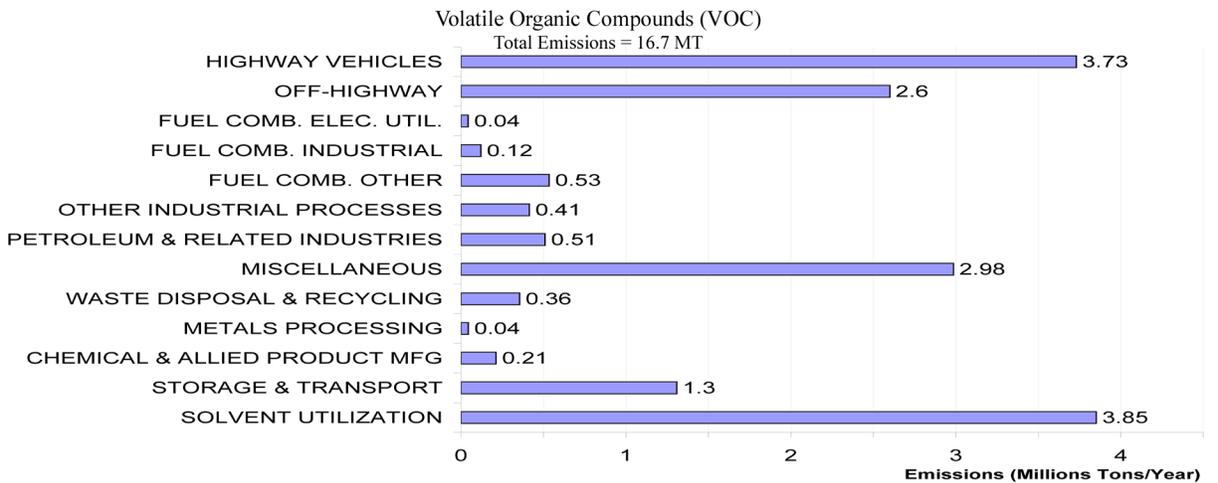
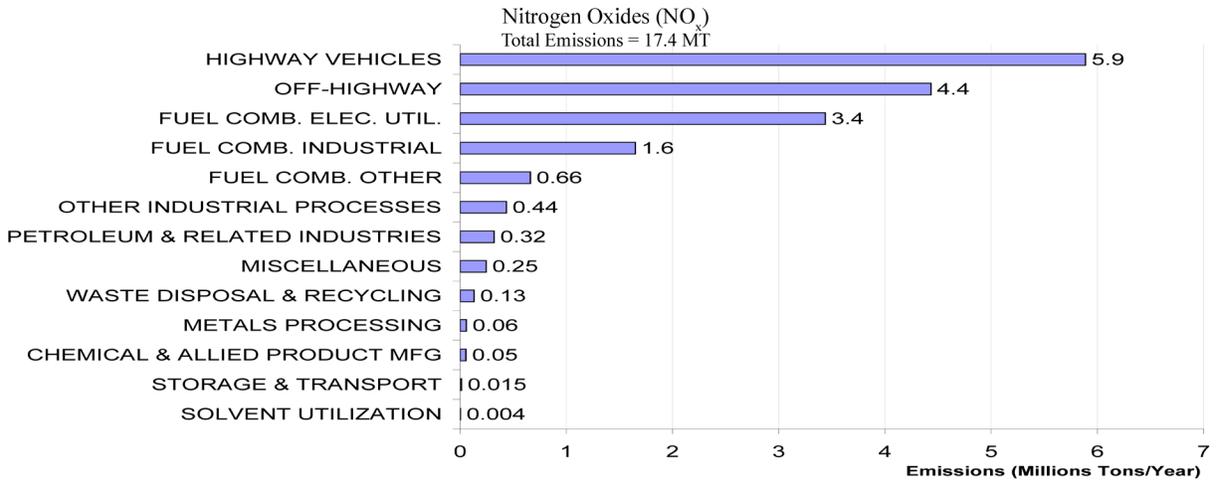
3 High O<sub>3</sub> concentrations showing large diurnal variations at the surface in southern New  
4 England were associated with the presence of such layers (Berkowitz et al., 1998, [081467](#)). Winds  
5 several hundred meters above the ground can bring pollutants from the west, even though surface  
6 winds are from the southwest during periods of high O<sub>3</sub> in the eastern U.S. (Blumenthal et al., 1997,  
7 [052278](#)). These considerations suggest that in many areas of the U.S., O<sub>3</sub> and its precursors can be  
8 transported over hundreds if not thousands of square kilometers.

9 Nocturnal low level jets (LLJs) are an efficient means for transporting pollutants that have  
10 been entrained into the residual boundary layer over hundreds of kilometers (U.S. EPA, 2006,  
11 [088089](#), Annex AX2.3.3). LLJs are most prevalent in the central U.S. extending northward from  
12 eastern Texas, and along the Atlantic states extending southwest to northeast. LLJs have also been  
13 observed off the coast of California. Turbulence associated with LLJs brings pollutants to the surface  
14 and results in secondary O<sub>3</sub> maxima during the early morning in many locations (Corsmeier et al.,  
15 1997, [047620](#)). Stratospheric intrusions and intercontinental transport of O<sub>3</sub> are also important and  
16 are covered in Section 3.4 in relation to policy relevant background concentrations.

### 3.2.1. Sources of Precursors Involved in Ozone Formation

17 Emissions of O<sub>3</sub> precursor compounds (NO<sub>x</sub>, VOCs, and CO) can be divided into natural and  
18 anthropogenic source categories. Natural sources can be further divided into biogenic from  
19 vegetation, microbes, and animals, and abiotic from biomass burning, lightning, and geogenic  
20 sources. However, the distinction between natural and anthropogenic sources is often difficult to  
21 make in practice, as human activities directly or indirectly affect emissions from what would have  
22 been considered natural sources during the preindustrial era. Thus, emissions from plants and  
23 animals used in agriculture have been referred to as anthropogenic or biogenic in different  
24 applications. Wildfire emissions can be considered natural, except that forest management practices  
25 can lead to buildup of fuels on the forest floor, thereby altering the frequency and severity of forest  
26 fires.

27 Estimates of emissions for NO<sub>x</sub>, VOCs, and CO (U.S. EPA, 2008, [665052](#)) are shown in  
28 Figure 3-2 to provide a general indication of the relative importance of the different sources in the  
29 U.S. as a whole. The magnitudes of the sources are strongly location and time dependent and so  
30 should not be used to apportion sources of exposure. Shown in Figure 3-2 are Tier 1 categories. The  
31 miscellaneous category can be quite large compared to total emissions, especially for CO and VOCs.  
32 The miscellaneous category includes agriculture and forestry, wildfires, prescribed burns, and a  
33 much more modest contribution from structural fires.



Source: U.S. EPA (2008, [665052](#))

**Figure 3-2. Estimated anthropogenic emissions of ozone precursors for 2005 including NO<sub>x</sub> (top), VOCs (middle), and CO (bottom) in the U.S. in million metric tons (MT) per year.**

1 Anthropogenic NO<sub>x</sub> emissions are associated with combustion processes. Most emissions are  
2 in the form of NO, which is formed at high combustion temperatures from atmospheric nitrogen (N<sub>2</sub>)  
3 and oxygen (O<sub>2</sub>) and from fuel nitrogen (N). According to the 2005 National Emissions Inventory  
4 (2005 NEI)(U.S. EPA, 2008, [665052](#)), the largest sources of NO<sub>x</sub> are on- and off-road mobile  
5 sources and electric power generation plants. Emissions of NO<sub>x</sub> therefore are highest in areas having  
6 a high density of power plants and in urban regions having high traffic density. Dallman and Harley  
7 (2010, [665390](#)) compared NO<sub>x</sub> emissions estimates from the National Emissions Inventory, mobile  
8 sector data (U.S. EPA, 2008, [665052](#)) with an alternative method based on fuel consumption and  
9 found reasonable agreement in total U.S. anthropogenic emissions between the two techniques (to  
10 within about 5%). However, emissions from on-road diesel engines in the fuel based inventory  
11 constituted 46% of total mobile source NO<sub>x</sub> compared to 35% in the EPA inventory. As a result,  
12 emissions from on-road diesel engines in the fuel based approach are even larger than electric power  
13 generation as estimated in the 2005 NEI, and on-road diesel engines might represent the largest  
14 single NO<sub>x</sub> source category. Differences between the two techniques are largely compensated by  
15 differences in emissions from on-road gasoline engines. Uncertainties in the fuel consumption  
16 inventory ranged from 3% for on-road gasoline engines to 20% for marine sources, and in the EPA  
17 inventory uncertainties ranged from 16% for locomotives to 30% for off-road diesel engines. It  
18 should be noted that the on-road diesel engine emissions estimate by Dallman and Harley (2010,  
19 [665390](#)) is still within the uncertainty of the EPA estimate (22%).

20 Major natural sources of NO<sub>x</sub> in the U.S. include lightning, soils, and wildfires; stratospheric  
21 intrusions can also be important under certain conditions in many locations. Uncertainties in natural  
22 NO<sub>x</sub> emissions are much larger than for anthropogenic NO<sub>x</sub> emissions. Fang et al. (2010, [665391](#))  
23 estimated lightning generated NO<sub>x</sub> of ~0.6 MT for July 2004. This value is ~40% of the  
24 anthropogenic emissions for the same period, but Fang et al. estimated that ~98% is formed in the  
25 free troposphere and so contributions to the surface NO<sub>x</sub> burden are low because most of this NO<sub>x</sub> is  
26 oxidized to NO<sub>z</sub> species during downward transport into the planetary boundary layer. The  
27 remaining 2% is formed within the planetary boundary layer. Both nitrifying and denitrifying  
28 organisms in the soil can produce NO<sub>x</sub>, mainly in the form of NO. Emission rates depend mainly on  
29 fertilization amount and soil temperature and moisture. Nationwide, about 60% of the total NO<sub>x</sub>  
30 emitted by soils is estimated to occur in the central corn belt of the U.S. Spatial and temporal  
31 variability in soil NO<sub>x</sub> emissions leads to considerable uncertainty in emissions estimates. However,  
32 these emissions are relatively low, only ~0.97 MT/year, or about 6% of anthropogenic NO<sub>x</sub>  
33 emissions. The oxidation of ammonia (NH<sub>3</sub>) emitted mainly by livestock and soils, leads to the  
34 formation of a small amount of NO.

35 Hundreds of VOCs, containing mainly 2 to ~12 carbon (C) atoms, are emitted by evaporation  
36 and combustion processes from a large number of anthropogenic sources. The two largest  
37 anthropogenic source categories in the U.S. EPA's emissions inventories are industrial processes and  
38 transportation. Emissions of VOCs from highway vehicles account for roughly two-thirds of the  
39 transportation-related emissions. The accuracy of VOC emission estimates is difficult to determine,

1 both for stationary and mobile sources. Evaporative emissions, which depend on temperature and  
2 other environmental factors, compound the difficulties of assigning accurate emission factors. In  
3 assigning VOC emission estimates to the mobile source category, models are used that incorporate  
4 numerous input parameters (e.g., type of fuel used, type of emission controls, age of vehicle), each  
5 of which has some degree of uncertainty.

6 On the U.S. and global scales, emissions of VOCs from vegetation are much larger than those  
7 from anthropogenic sources. Emissions of VOCs from anthropogenic sources in the 2005 NEI were  
8 ~17 MT/year (including wildfires, which constitute ~1/6 of that total), but were 29 MT/year from  
9 biogenic sources. Uncertainties in both biogenic and anthropogenic VOC emission inventories  
10 prevent determination of the relative contributions of these two categories, at least in many areas.  
11 Vegetation emits significant quantities of VOCs, such as terpenoid compounds (isoprene, 2-methyl-  
12 3-buten-2-ol, monoterpenes), compounds in the hexanal family, alkenes, aldehydes, organic acids,  
13 alcohols, ketones, and alkanes. The major chemicals emitted by plants are isoprene (40%), other  
14 terpenoid and sesqui-terpenoid compounds (25%) and the remainder consists of assorted oxygenated  
15 compounds and hydrocarbons according to the 2005 NEI. Coniferous forests represent the largest  
16 source on a nationwide basis because of their extensive land coverage. Most biogenic emissions  
17 occur during the summer because of their dependence on temperature and incident sunlight.  
18 Biogenic emissions are also higher in southern states than in northern states for these reasons and  
19 because of species variations. The uncertainty in natural emissions is about 50% for isoprene under  
20 midday summer conditions and could be as much as a factor of ten higher for some compounds  
21 (Guenther et al., 2000, [025002](#)). In EPA's regional modeling efforts, biogenic emissions of VOCs are  
22 estimated using the BEIS model (U.S. EPA, 2010, [677538](#)) with data from the Biogenic Emissions  
23 Landcover Database (BELD) and annual meteorological data. However, other emissions models are  
24 used such as MEGAN (Model of Emissions of Gases and Aerosols from Nature) (Guenther et al.,  
25 2006, [607080](#)), especially in global modeling efforts.

26 Anthropogenic CO is emitted primarily by incomplete combustion of carbon-containing fuels.  
27 In general, any increase in fuel O<sub>2</sub> content, burn temperature, or mixing time in the combustion zone  
28 will tend to decrease production of CO relative to CO<sub>2</sub>. CO emissions from large fossil-fueled power  
29 plants are typically very low since the boilers at these plants are tuned for highly efficient  
30 combustion with the lowest possible fuel consumption. Additionally, by allowing time for the  
31 furnace flue gases to mix with air and be oxidized by OH to CO<sub>2</sub> in the hot gas stream before the OH  
32 concentrations drop as the flue gases cool, the CO-to-CO<sub>2</sub> ratio in these emissions is shifted toward  
33 CO<sub>2</sub>. Nationally, on-road mobile sources constituted ~26% of total CO emissions in the 2005 NEI.  
34 When emissions from non-road vehicles are included, it can be seen from Figure 3-2 that all mobile  
35 sources accounted for ~73% of total anthropogenic CO emissions in the U.S.

36 Analyses by Harley et al. (2005, [088154](#)) and Parrish (2006, [090352](#)) are consistent with the  
37 suggestion in Pollack et al. (2004, [184461](#)) that the EPA MOBILE6 vehicle emissions model  
38 (U.S. EPA, 2010, [677539](#)) overestimates vehicle CO emissions by a factor of ~2. Field  
39 measurements by Bishop and Stedman (2008, [194670](#)) were in accord with Parrish's (2006, [090352](#))

1 findings that the measured trends of CO and NO<sub>x</sub> concentrations from mobile sources in the U.S.  
2 indicated that modeled CO emission estimates were substantially too high. Hudman et al. (2008,  
3 [191253](#)) found that the NEI overestimated anthropogenic CO emissions by 60% for the eastern U.S.  
4 during the period July 1-August 15, 2004 using aircraft observations of CO from the International  
5 Consortium for Atmospheric Research on Transport and Transformation (ICARTT) campaign  
6 (Fehsenfeld et al., 2006, [190531](#)) and results from a tropospheric chemistry model (GEOS-Chem).  
7 Improvements in emissions technologies not correctly represented in MOBILE emission models  
8 have been suggested as one cause for this discrepancy. For example, Pokharel et al. (2002, [052473](#);  
9 2003, [053740](#)) demonstrated substantial decrements in the CO fraction of tailpipe exhaust in several  
10 U.S. cities and Burgard et al. (2006, [193222](#)) documented improvements in emission from heavy-  
11 duty on-road diesel engines. Some of the largest errors in the MOBILE models are addressed in the  
12 successor model, MOVES (U.S. EPA, 2011, [677540](#)).

13 Estimates of biogenic CO emissions in the 2005 NEI are made in a manner similar to that for  
14 VOCs. National biogenic emissions, excluding fires, were estimated to contribute ~7% and wildfires  
15 added another ~16% to the national CO emissions total. Photodecomposition of organic matter in  
16 oceans, rivers, lakes, and other surface waters, and from soil surfaces also releases CO (Goldstein  
17 and Galbally, 2007, [193247](#)). However, soils can act as a CO source or a sink depending on soil  
18 moisture, UV flux reaching the soil surface, and soil temperature (Conrad and Seiler, 1985, [029520](#)).  
19 Soil uptake of CO is driven by anaerobic bacteria (Inman et al., 1971, [010972](#)). Emissions of CO  
20 from soils appear to occur by abiotic processes, such as thermodecomposition or  
21 photodecomposition of organic matter. In general, warm and moist conditions found in most soils  
22 favor CO uptake, whereas hot and dry conditions found in deserts and some savannas favor the  
23 release of CO (King, 1999, [002828](#)).

### 3.2.2. Gas Phase Reactions Leading to Ozone Formation

24 Photochemical processes involved in O<sub>3</sub> formation have been extensively reviewed in a  
25 number of books (Finlayson-Pitts and Pitts, 1986, [035054](#); Jacob, 1999, [091122](#); Jacobson, 2002,  
26 [090667](#); Seinfeld and Pandis, 1998, [018352](#)) and in the previous O<sub>3</sub> AQCDs (U.S. EPA, 1996,  
27 [017831](#); U.S. EPA, 2006, [088089](#)).

28 The photochemical formation of O<sub>3</sub> in the troposphere proceeds through the oxidation of NO  
29 to nitrogen dioxide (NO<sub>2</sub>) by organic (RO<sub>2</sub>) or hydro-peroxy (HO<sub>2</sub>) radicals. The photolysis of NO<sub>2</sub>  
30 yields NO and a ground-state oxygen atom, O(<sup>3</sup>P), which then reacts with molecular oxygen to form  
31 O<sub>3</sub>. Free radicals oxidizing NO to NO<sub>2</sub> are formed during the oxidation of VOCs (U.S. EPA, 2006,  
32 [088089](#), Annex AX2.2.2).

33 The term VOC refers to all carbon-containing gas-phase compounds in the atmosphere, both  
34 biogenic and anthropogenic in origin, excluding CO and CO<sub>2</sub>. Classes of organic compounds  
35 important for the photochemical formation of O<sub>3</sub> include alkanes, alkenes, aromatic hydrocarbons,  
36 carbonyl compounds (e.g., aldehydes and ketones), alcohols, organic peroxides, and halogenated  
37 organic compounds (e.g., alkyl halides). This array of compounds encompasses a wide range of

1 chemical properties and lifetimes: isoprene has an atmospheric lifetime of approximately an hour,  
2 whereas methane has an atmospheric lifetime of about a decade.

3 In urban areas, compounds representing all classes of VOCs and CO are important for O<sub>3</sub>  
4 formation. In nonurban vegetated areas, biogenic VOCs emitted from vegetation tend to be the most  
5 important. In the remote troposphere, methane (CH<sub>4</sub>) and CO are the main carbon-containing  
6 precursors to O<sub>3</sub> formation. The oxidation of VOCs is initiated mainly by reaction with hydroxyl  
7 (OH) radicals. The primary source of OH radicals in the atmosphere is the reaction of electronically  
8 excited O atoms, O(<sup>1</sup>D), with water vapor. O(<sup>1</sup>D) is produced by the photolysis of O<sub>3</sub> in the Hartley  
9 bands. In polluted areas, the photolysis of aldehydes (e.g., HCHO), HONO and H<sub>2</sub>O<sub>2</sub> can also be  
10 significant sources of OH or HO<sub>2</sub> radicals that can rapidly be converted to OH (Eisele et al., 1997,  
11 [057210](#)). Ozone can oxidize alkenes and, at night, when they are most abundant, NO<sub>3</sub> radicals also  
12 oxidize alkenes. In coastal environments and other selected environments, atomic Cl and Br radicals  
13 can also initiate the oxidation of VOCs (U.S. EPA, 2006, [088089](#), Annex AX2.2.3). It should also be  
14 emphasized that the reactions of oxygenated VOCs are important components of O<sub>3</sub> formation  
15 (U.S. EPA, 2006, [088089](#), Annex AX2.2.9). They may be present in ambient air not only as the result  
16 of the atmospheric oxidation of hydrocarbons but also by direct emissions. For example, motor  
17 vehicles and some industrial processes emit formaldehyde (Rappenglück et al., 2009, [629680](#)) and  
18 vegetation emits methanol.

19 There are a large number of oxidized N-containing compounds in the atmosphere including  
20 NO, NO<sub>2</sub>, NO<sub>3</sub>, HNO<sub>2</sub>, HNO<sub>3</sub>, N<sub>2</sub>O<sub>5</sub>, HNO<sub>4</sub>, PAN and its homologues, other organic nitrates, such as  
21 alkyl nitrates, isoprene nitrates and particulate nitrate. Collectively these species are referred to as  
22 NO<sub>y</sub>. Oxidized nitrogen compounds are emitted to the atmosphere mainly as NO which rapidly  
23 interconverts with NO<sub>2</sub> and so NO and NO<sub>2</sub> are often “lumped” together into their own group or  
24 family, which is referred to as NO<sub>x</sub>. NO<sub>x</sub> can be oxidized to reservoir and termination species (PAN  
25 and its homologues, organic nitrates, HNO<sub>3</sub>, HNO<sub>4</sub> and particulate nitrate). These reservoir and  
26 termination species are referred to as NO<sub>z</sub>. The major reactions involving interconversions of  
27 oxidized N species were covered in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#), Annex AX2.2.4).  
28 Mollner et al. (2010, [665393](#)) identified pernitrous acid (HOONO), an unstable isomer of nitric acid  
29 as a product of the major gas phase reaction forming HNO<sub>3</sub>. However, since pernitrous acid is  
30 unstable, it is not a reservoir for NO<sub>x</sub>. This finding stresses the importance of identifying products in  
31 addition to measuring the rate of disappearance of reactants in kinetic studies.

32 The photochemical cycles by which the oxidation of hydrocarbons leads to O<sub>3</sub> production are  
33 best understood by considering the oxidation of methane, structurally the simplest VOC. The CH<sub>4</sub>  
34 oxidation cycle serves as a model for the chemistry of the relatively clean or unpolluted troposphere  
35 (although this is a simplification because vegetation releases large quantities of complex VOCs, such  
36 as isoprene, into the atmosphere). In the polluted atmosphere, the underlying chemical principles are  
37 the same, as discussed in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#), Annex AX2.2.5). The  
38 conversion of NO to NO<sub>2</sub> occurring with the oxidation of VOCs is accompanied by the production of

1 O<sub>3</sub> and the efficient regeneration of the OH radical, which in turn can react with other VOCs as  
2 shown in Figure 3-1.

3 The oxidation of alkanes and alkenes in the atmosphere has been treated in depth in the 1996  
4 O<sub>3</sub> AQCD (U.S. EPA, 1996, [017831](#)) and was updated in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006,  
5 [088089](#), Annex AX2.2.6 and AX2.2.7). In contrast to simple hydrocarbons containing one or two C  
6 atoms, detailed kinetic information about the gas phase oxidation pathways of many anthropogenic  
7 hydrocarbons (e.g., aromatic compounds such as benzene and toluene), biogenic hydrocarbons (e.g.,  
8 isoprene, the monoterpenes), and their intermediate oxidation products (e.g., epoxides, nitrates, and  
9 carbonyl compounds) is lacking. Reaction with OH radicals represents the major loss process for  
10 alkanes. Reaction with chlorine (Cl) atoms is an additional sink for alkanes. Stable products of  
11 alkane photooxidation are known to include carbonyl compounds, alkyl nitrates, and  
12 d-hydroxycarbonyls. Major uncertainties in the atmospheric chemistry of the alkanes concern the  
13 chemistry of alkyl nitrate formation; these uncertainties affect the amount of NO-to-NO<sub>2</sub> conversion  
14 occurring and, hence, the amounts of O<sub>3</sub> formed during photochemical degradation of the alkanes.

15 The reaction of OH radicals with aldehydes produced during the oxidation of alkanes forms  
16 acyl (R'CO) radicals, and acyl peroxy radicals (R'C(O)-O<sub>2</sub>) are formed by the further addition of O<sub>2</sub>.  
17 As an example, the oxidation of ethane (C<sub>2</sub>H<sub>5</sub>-H) yields acetaldehyde (CH<sub>3</sub>-CHO). The reaction of  
18 CH<sub>3</sub>-CHO with OH radicals yields acetyl radicals (CH<sub>3</sub>-CO). The acetyl radicals will then  
19 participate with O<sub>2</sub> in a termolecular recombination reaction to form acetyl peroxy radicals, which  
20 can then react with NO to form CH<sub>3</sub> + CO<sub>2</sub> or they can react with NO<sub>2</sub> to form PAN. PAN acts as a  
21 temporary reservoir for NO<sub>2</sub>. Upon the thermal decomposition of PAN, either locally or elsewhere,  
22 NO<sub>2</sub> is released to participate in the O<sub>3</sub> formation process again.

23 Alkenes react in ambient air with OH, NO<sub>3</sub>, and Cl radicals and with O<sub>3</sub>. All of these reactions  
24 are important atmospheric transformation processes, and all proceed by initial addition to the  
25 >C = C< bonds. Major products of alkene photooxidation include carbonyl compounds.  
26 Hydroxynitrates and nitratocarbonyls, and decomposition products from the energy-rich biradicals  
27 formed in alkene-O<sub>3</sub> reactions are also produced. Major uncertainties in the atmospheric chemistry of  
28 the alkenes concern the products and mechanisms of their reactions with O<sub>3</sub>, especially the yields of  
29 free radicals that participate in O<sub>3</sub> formation. Examples of oxidation mechanisms of complex alkanes  
30 and alkenes can be found in comprehensive texts such as Seinfeld and Pandis (1998, [018352](#)). Apart  
31 from the effects of the oxidation of isoprene on production of free radicals and O<sub>3</sub> formation,  
32 isoprene nitrates appear to play an important role as NO<sub>x</sub> reservoirs over the eastern U.S. (see for  
33 example Perring et al. (2009, [616370](#))). Their decomposition leads to the recycling of NO<sub>x</sub>, which  
34 can participate in the O<sub>3</sub> formation process again as was the case with decomposition of PAN and the  
35 even more unstable pernitrous acid.

36 The oxidation of aromatic hydrocarbons constitutes an important component of the chemistry  
37 of O<sub>3</sub> formation in urban atmospheres (U.S. EPA, 2006, [088089](#), Annex AX2.2.8). Virtually all of the  
38 important aromatic hydrocarbon precursors emitted in urban atmospheres are lost through reaction  
39 with the hydroxyl radical. Loss rates for these compounds vary from slow (i.e., benzene) to moderate

1 (e.g., toluene), to very rapid (e.g., xylene and trimethylbenzene isomers). However, the mechanism  
2 for the oxidation of aromatic hydrocarbons following reaction with OH is poorly understood, as is  
3 evident from the poor mass balance of the reaction products. The mechanism for the oxidation of  
4 toluene has been studied most thoroughly, and there is general agreement on the initial steps in the  
5 mechanism. However, at present there is no promising approach for resolving the remaining issues  
6 concerning the later steps. The oxidation of aromatic hydrocarbons also leads to particle formation  
7 that could remove gas-phase constituents that participate in O<sub>3</sub> formation.

8 Adequate analytical techniques needed to identify and quantify key intermediate species are  
9 not available for many compounds. In addition, methods to synthesize many of the suspected  
10 intermediate compounds are not available so that laboratory studies of their reaction kinetics cannot  
11 be performed. Similar considerations apply to the oxidation of biogenic hydrocarbons besides  
12 isoprene. These considerations are important because oxidants, other than O<sub>3</sub>, that are formed from  
13 the chemistry described above could exert effects on human health and perhaps also on vegetation  
14 (Doyle et al., 2004, [088404](#); Doyle et al., 2007, [596377](#); Sexton et al., 2004, [087831](#)). Gas phase  
15 oxidants include PAN, H<sub>2</sub>O<sub>2</sub>, CH<sub>3</sub>OOH and other organic hydroperoxides.

16 Ozone is lost through a number of gas phase reactions and deposition to surfaces. The reaction  
17 of O<sub>3</sub> with NO to produce NO<sub>2</sub> mainly results in the recycling of O<sub>3</sub> downwind via the  
18 recombination of O(<sup>3</sup>P) with O<sub>2</sub> to re-form O<sub>3</sub>. By itself, this reaction does not lead to a net loss of  
19 O<sub>3</sub> unless the NO<sub>2</sub> is converted to stable end products such as HNO<sub>3</sub>. Ozone reacts with unsaturated  
20 hydrocarbons and with hydrogen (H) containing free radicals (OH, HO<sub>2</sub>).

21 Perhaps the most recent field study aimed at obtaining a better understanding of atmospheric  
22 chemical processes was the Second Texas Air Quality Field Study (TexAQS-II) conducted in  
23 Houston in August and September 2006 (see overview by Olaguer et al., 2009, [200191](#)). The  
24 TexAQS-II Radical and Aerosol Measurement Project (TRAMP) found evidence for the importance  
25 of short-lived radical sources such as HCHO and HONO in increasing O<sub>3</sub> productivity. During  
26 TRAMP, daytime HCHO pulses as large as 32 ppb were observed and attributed to industrial  
27 activities upwind in the Houston Ship Channel (HSC) and HCHO peaks as large as 52 ppb were  
28 detected by in-situ surface monitors in the HSC. Primary HCHO produced in flares from local  
29 refineries and petrochemical facilities could increase peak O<sub>3</sub> by ~30 ppb (Webster et al., 2007,  
30 [104266](#)). Other findings from TexAQS-II included significant concentrations of HONO during the  
31 day, with peak concentrations approaching 1 ppb at local noon. These concentrations are well in  
32 excess of current air quality model predictions using gas phase mechanisms alone (e.g., Sarwar et al.,  
33 2008, [618491](#)) and multiphase processes are needed to account for these observations. Olaguer et al.  
34 (2009, [200191](#)) also noted that using measured HONO brings modeled O<sub>3</sub> concentrations into much  
35 better agreement with observations and could result in the production of an additional 10 ppb O<sub>3</sub>.  
36 Large nocturnal vertical gradients indicating a surface or near-surface source of HONO, and large  
37 concentrations of night-time radicals (~30 ppt HO<sub>2</sub>) were also found during TRAMP.

### 3.2.3. Multiphase Processes

1 In addition to reactions occurring in the gas phase, reactions occurring on the surfaces of or  
2 within cloud droplets and airborne particles also occur. Their collective surface area is huge,  
3 implying that collisions with gas phase species occur on very short time scales. In addition to  
4 hydrometeors (e.g., cloud and fog droplets and snow and ice crystals) there are also potential  
5 reactions involving atmospheric particles of varying composition (e.g., wet [deliquesced] inorganic  
6 particles, mineral dust, carbon chain agglomerates and organic carbon particles) to consider.  
7 Multiphase reactions are involved in the formation of a number of species such as particulate nitrate,  
8 and gas phase HONO that can act to both increase and reduce the rate of O<sub>3</sub> formation in the polluted  
9 troposphere. Data collected in Houston as part of TexAQS-II summarized by Olaguer et al. (2009,  
10 [200191](#)) indicate that concentrations of HONO are much higher than can be explained by gas phase  
11 chemistry and by tailpipe emissions; and that the photolysis of HONO formed in multiphase  
12 reactions in addition to the other sources can help narrow the discrepancy between observed and  
13 predicted production of O<sub>3</sub>. However, removal of HO<sub>x</sub> and NO<sub>x</sub> onto hydrated particles will reduce  
14 the production of O<sub>3</sub>.

15 Multi-phase processes have been associated with the release of gaseous halogen compounds  
16 from marine aerosol, mainly in marine and coastal environments. However, Thornton et al., (2010,  
17 [386870](#)) found production rates of gaseous nitryl chloride near Boulder, CO from reaction of N<sub>2</sub>O<sub>5</sub>  
18 with particulate Cl<sup>-</sup>, similar to those found in coastal and marine environments. ClNO<sub>2</sub> readily  
19 photolyzes to yield Cl. They also found that substantial quantities of N<sub>2</sub>O<sub>5</sub> are recycled through  
20 ClNO<sub>2</sub> back into NO<sub>x</sub> instead of forming HNO<sub>3</sub> (a stable reservoir for reactive nitrogen compounds).  
21 The oxidation of hydrocarbons by Cl radicals released from the marine aerosol could lead to the  
22 rapid formation of peroxy radicals and higher rates of O<sub>3</sub> production in selected coastal environments  
23 and in continental environments. It should be noted that in addition to production from marine  
24 aerosol, reactive halogen species are also produced by the oxidation of halogenated organic  
25 compounds (e.g., CH<sub>3</sub>Cl, CH<sub>3</sub>Br and CH<sub>3</sub>I). The atmospheric chemistry of halogens is complex  
26 because Cl, Br and I containing species can react among themselves and with hydrocarbons and  
27 other species and could also be important for O<sub>3</sub> destruction, as has been noted for the lower  
28 stratosphere (McElroy et al., 1986, [019501](#); Yung et al., 1980, [057212](#)). For example, the reactions of  
29 Br and Cl containing radicals deplete O<sub>3</sub> in selected environments such as the Arctic during the  
30 spring (e.g., Barrie et al., 1988, [053377](#)), the tropical marine boundary layer (e.g., Dickerson et al.,  
31 1999, [053394](#)), and inland salt flats and salt lakes (e.g., Stutz et al., 2002, [051882](#)). Mahajan et al.  
32 (2010, [665392](#)) found that I and Br species acting together resulted in O<sub>3</sub> depletion that was much  
33 larger than would have been expected if they acted individually and did not interact with each other  
34 (see U.S. EPA, 2006, [088089](#), section AX2.2.10.3 for more detailed descriptions of these processes).  
35 It should be stressed that knowledge of multiphase processes is still evolving and there are still many  
36 questions that remain to be answered. However, it is becoming clear that multiphase processes are  
37 important for O<sub>3</sub> chemistry.

1 Reactions of O<sub>3</sub> with monoterpenes have been shown to produce oxidants in the aerosol phase,  
2 principally as components of ultrafine particles. These reactions involving ambient O<sub>3</sub> and terpene-  
3 related compounds from cleaning products, air fresheners and wood products, can also occur in  
4 indoor air as was discussed in the previous O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). Docherty et al.  
5 (2005, [087613](#)) found evidence for the substantial production of organic hydroperoxides in  
6 secondary organic aerosol (SOA) resulting from the reaction of monoterpenes with O<sub>3</sub>. Analysis of  
7 the SOA formed in their environmental chamber indicated that the SOA consisted mainly of organic  
8 hydroperoxides. In particular, they obtained yields of 47% and 85% of organic peroxides from the  
9 oxidation of  $\alpha$ - and  $\beta$ -pinene. The hydroperoxides then react with aldehydes in particles to form  
10 peroxyhemiacetals, which can either rearrange to form other compounds such as alcohols and acids  
11 or revert back to the hydroperoxides. The aldehydes are also produced in large measure during the  
12 ozonolysis of the monoterpenes. Monoterpenes also react with OH radicals resulting in the  
13 production of more lower-molecular-weight products than in the reaction with monoterpenes and O<sub>3</sub>.  
14 Bonn et al. (2004, [053770](#)) estimated that hydroperoxides lead to 63% of global SOA formation from  
15 the oxidation of terpenes. The oxidation of anthropogenic aromatic hydrocarbons by OH radicals  
16 could also produce organic hydroperoxides in SOA (Johnson et al., 2004, [087659](#)). Recent  
17 measurements show that the abundance of oxidized SOA exceeds that of more reduced hydrocarbon  
18 like organic aerosol in Pittsburgh (Zhang et al., 2005, [157185](#)) and in about 30 other cities across the  
19 Northern Hemisphere (Zhang et al., 2007, [101119](#)). Based on aircraft and ship-based sampling of  
20 organic aerosols over coastal waters downwind of northeastern U.S. cities, de Gouw et al. (2008,  
21 [191757](#)) reported that 40-70% of measured organic mass was water soluble and estimated that  
22 approximately 37% of SOA is attributable to aromatic precursors, using PM yields estimated for  
23 NO<sub>x</sub>-limited conditions. Reactions of O<sub>3</sub> on the surfaces of particles, in particular those with humic  
24 acid like composition, are instrumental in the processing of SOA and the release of  
25 low-molecular-weight products such as HCHO (D'Anna et al., 2009, [628847](#)). However, direct  
26 reactions of O<sub>3</sub> and atmospheric particles appear to be too slow to represent a major O<sub>3</sub> sink in the  
27 troposphere (D'Anna et al., 2009, [628847](#)).

### 3.2.4. Temperature and Chemical Precursor Relationships

28 As might be expected based on the temperature dependence of many reactions involved in the  
29 production and destruction of O<sub>3</sub> and the temperature dependence of emissions processes such as  
30 evaporation of hydrocarbon precursors and the emissions of biogenically important precursors such  
31 as isoprene, ambient concentrations of O<sub>3</sub> also show temperature dependence. Bloomer et al. (2009,  
32 [628855](#)) determined the sensitivity of O<sub>3</sub> to temperature at rural sites in the eastern U.S. They found  
33 that O<sub>3</sub> increased on average at rural (CASTNET) sites by ~3.2 ppbv/°C before 2002, and after 2002  
34 by ~2.2 ppbv/°C. This change in sensitivity was largely the result of reductions in NO<sub>x</sub> emissions  
35 from power plants. These results are in accord with model predictions by Wu et al. (2008, [629684](#))  
36 showing that the sensitivity of O<sub>3</sub> to temperature decreases with decreases in precursor emissions.

1 However, this study was basically confined to the eastern U.S., but results from Phoenix, AZ showed  
2 basically no sensitivity of O<sub>3</sub> to temperature (U.S. EPA, 2006, [088089](#)).

3 The warmer months of the year are generally regarded as being the most conducive to O<sub>3</sub>  
4 concentrations that are of concern for human health. However, Schnell et al. (2009, [180146](#)) reported  
5 observations of high O<sub>3</sub> concentrations (maximum 1-h avg of 140 ppb; maximum 8-h avg of  
6 120 ppb) in the Jonah-Pinedale gas fields in Wyoming during winter at temperatures of -17°C.  
7 Potential factors contributing to these anomalously high concentrations include a highly reflective  
8 snow surface, emissions of short-lived radical reservoirs (e.g., HONO and HCHO) and a very  
9 shallow, stable boundary layer trapping these emissions (Schnell et al., 2009, [180146](#)). Multiphase  
10 processes might also be involved in the production of these short-lived reservoirs. At a temperature  
11 of -17°C, the production of hydroxyl radicals (by the photolysis of O<sub>3</sub> yielding O<sup>1</sup>D followed by the  
12 reaction, O(<sup>1</sup>D) + H<sub>2</sub>O, needed to initiate hydrocarbon oxidation) is severely limited, suggesting that  
13 another source of free radicals is needed. Radicals can be produced by the photolysis of molecules  
14 such as HONO and HCHO which photolyze in optically thin regions of the solar spectrum. A similar  
15 issue, in part due to the under-prediction of free radicals, has arisen in the Houston airshed where  
16 chemistry transport models under-predict O<sub>3</sub> (Olague et al., 2009, [200191](#)).

17 Rather than varying directly with emissions of its precursors, O<sub>3</sub> changes in a nonlinear  
18 fashion with the concentrations of its precursors. At the low NO<sub>x</sub> concentrations found in remote  
19 continental areas to rural and suburban areas downwind of urban centers (low-NO<sub>x</sub> regime), the net  
20 production of O<sub>3</sub> typically increases with increasing NO<sub>x</sub>. At the high NO<sub>x</sub> concentrations found in  
21 downtown metropolitan areas, especially near busy streets and roadways and in power plant plumes,  
22 there is scavenging (titration) of O<sub>3</sub> by reaction with NO (high-NO<sub>x</sub> regime). In between these two  
23 regimes, there is a transition stage in which O<sub>3</sub> shows only a weak dependence on NO<sub>x</sub>  
24 concentrations.

25 In the low-NO<sub>x</sub> regime, the overall effect of the oxidation of VOCs is to generate (or at least  
26 not consume) free radicals, and O<sub>3</sub> production varies directly with NO<sub>x</sub>. In the high-NO<sub>x</sub> regime,  
27 NO<sub>2</sub> scavenges OH radicals which would otherwise oxidize VOCs to produce peroxy radicals, which  
28 in turn would oxidize NO to NO<sub>2</sub>. In this regime, O<sub>3</sub> production is limited by the availability of free  
29 radicals. The production of free radicals is in turn limited by the availability of solar UV radiation  
30 capable of photolyzing O<sub>3</sub> (in the Hartley bands) or aldehydes and/or by the abundance of VOCs  
31 whose oxidation produce more radicals than they consume. There are a number of ways to refer to  
32 the chemistry in these two chemical regimes. Sometimes the terms VOC-limited and NO<sub>x</sub>-limited  
33 are used. However, there are difficulties with this usage because (1) VOC measurements are not as  
34 abundant as they are for nitrogen oxides; (2) rate coefficients for reaction of individual VOCs with  
35 free radicals vary over an extremely wide range; and (3) consideration is not given to CO nor to  
36 reactions that can produce free radicals without involving VOCs. The terms NO<sub>x</sub>-limited and  
37 NO<sub>x</sub>-saturated (e.g., Jaegle et al., 2001, [057250](#)) will be used wherever possible to more adequately  
38 describe these two regimes. However, the terminology used in original articles will also be used  
39 here.

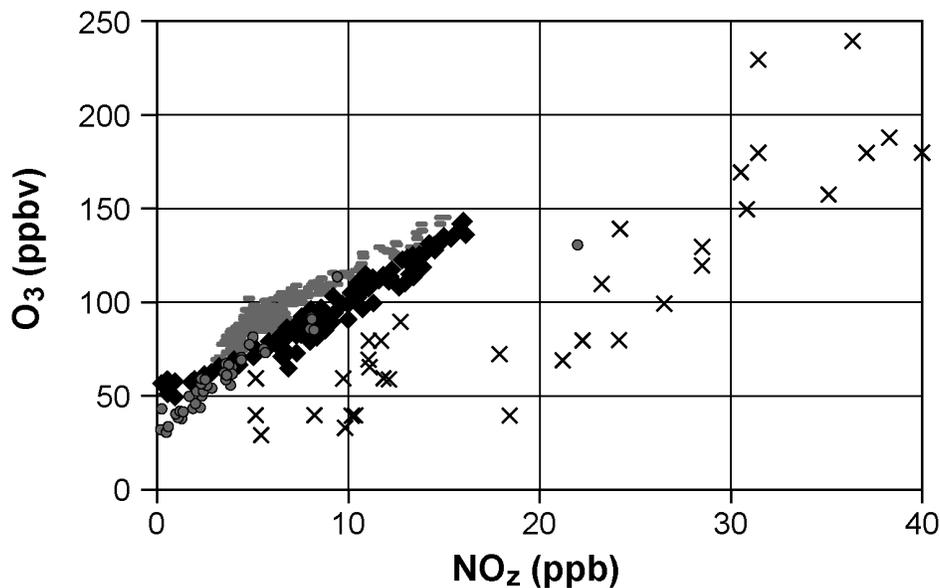
1 The chemistry of OH radicals, which are responsible for initiating the oxidation of  
2 hydrocarbons, shows behavior similar to that for O<sub>3</sub> with respect to NO<sub>x</sub> concentrations (e.g.,  
3 Hameed et al., 1979, [029458](#); Poppe et al., 1993, [044229](#); Zimmermann and Poppe, 1993, [052378](#)).  
4 These considerations introduce a high degree of uncertainty into attempts to relate changes in O<sub>3</sub>  
5 concentrations to emissions of precursors. There are no definitive rules governing the concentrations  
6 of NO<sub>x</sub> at which the transition from NO<sub>x</sub>-limited to NO<sub>x</sub>-saturated conditions occurs. The transition  
7 between these two regimes is highly spatially and temporally dependent and depends also on the  
8 nature and abundance of the hydrocarbons that are present.

9 Trainer et al. (1993, [038672](#)) and Olszyna et al. (1994, [038832](#)) have shown that O<sub>3</sub> and NO<sub>y</sub>  
10 are highly correlated in rural areas in the eastern U.S. Trainer et al. (1993, [038672](#)) also showed that  
11 O<sub>3</sub> concentrations correlate even better with NO<sub>z</sub> than with NO<sub>y</sub>, as may be expected because NO<sub>z</sub>  
12 represents the amount of NO<sub>x</sub> that has been oxidized, forming O<sub>3</sub> in the process. NO<sub>z</sub> is equal to the  
13 difference between measured total reactive nitrogen (NO<sub>y</sub>) and NO<sub>x</sub> and represents the summed  
14 products of the oxidation of NO<sub>x</sub>. NO<sub>z</sub> is composed mainly of HNO<sub>3</sub>, PAN and other organic  
15 nitrates, particulate nitrate, and HNO<sub>4</sub>. Trainer et al. (1993, [038672](#)) also suggested that the slope of  
16 the regression line between O<sub>3</sub> and NO<sub>z</sub> can be used to estimate the rate of O<sub>3</sub> production per NO<sub>x</sub>  
17 oxidized (also known as the O<sub>3</sub> production efficiency [OPE]). Ryerson et al. (1998, [048310](#); 2001,  
18 [016249](#)) used measured correlations between O<sub>3</sub> and NO<sub>z</sub> to identify different rates of O<sub>3</sub> production  
19 in plumes from large point sources. A number of studies in the planetary boundary layer over the  
20 continental U.S. have found that the OPE ranges typically from 1 to nearly 10. However, it may be  
21 higher in the upper troposphere and in certain areas, such as the Houston-Galveston area in Texas.  
22 Observations indicate that the OPE depends mainly on the abundance of NO<sub>x</sub>.

23 Various techniques have been proposed to use ambient NO<sub>x</sub> and VOC measurements to derive  
24 information about the dependence of O<sub>3</sub> production on their concentrations. For example, it has been  
25 suggested that O<sub>3</sub> formation in individual urban areas could be understood in terms of measurements  
26 of ambient NO<sub>x</sub> and VOC concentrations during the early morning (e.g., NRC, 1991, [038041](#)). In  
27 this approach, the ratio of summed (unweighted) VOC to NO<sub>x</sub> is used to determine whether  
28 conditions were NO<sub>x</sub>-limited or VOC-limited. This procedure is inadequate because it omits many  
29 factors that are important for O<sub>3</sub> production such as the impact of biogenic VOCs (which are  
30 typically not present in urban centers during early morning); important differences in the ability of  
31 individual VOCs to generate free radicals (rather than just total VOC) and other differences in O<sub>3</sub>  
32 forming potential for individual VOCs (Carter, 1995, [052288](#)); and changes in the VOC to NO<sub>x</sub> ratio  
33 due to photochemical reactions and deposition as air moves downwind from urban areas (Milford et  
34 al., 1994, [038669](#)).

35 Photochemical production of O<sub>3</sub> generally occurs simultaneously with the production of  
36 various other species such as HNO<sub>3</sub>, organic nitrates, and other oxidants such as hydrogen peroxide.  
37 The relative rate of production of O<sub>3</sub> and other species varies depending on photochemical  
38 conditions, and can be used to provide information about O<sub>3</sub>-precursor sensitivity. Sillman (1995,  
39 [052346](#)) and Sillman and He (2002, [052350](#)) identified several secondary reaction products that

1 show different correlation patterns for  $\text{NO}_x$ -limited and  $\text{NO}_x$ -saturated conditions. The most  
 2 important correlations are for  $\text{O}_3$  versus  $\text{NO}_Y$ ,  $\text{O}_3$  versus  $\text{NO}_Z$ ,  $\text{O}_3$  versus  $\text{HNO}_3$ , and  $\text{H}_2\text{O}_2$  versus  
 3  $\text{HNO}_3$ . The correlations between  $\text{O}_3$  and  $\text{NO}_Y$ , and  $\text{O}_3$  and  $\text{NO}_Z$  are especially important because  
 4 measurements of  $\text{NO}_Y$  and  $\text{NO}_X$  are more widely available than for VOCs. Measured  $\text{O}_3$  versus  $\text{NO}_Z$   
 5 (Figure 3-3) shows distinctly different patterns in different locations. In rural areas and in urban  
 6 areas such as Nashville, TN,  $\text{O}_3$  is highly correlated with  $\text{NO}_Z$ . By contrast, in Los Angeles, CA,  $\text{O}_3$   
 7 is not as highly correlated with  $\text{NO}_Z$ , and the rate of increase of  $\text{O}_3$  with  $\text{NO}_Z$  is lower and the  $\text{O}_3$   
 8 concentrations for a given  $\text{NO}_Z$  value are generally lower. The different  $\text{O}_3$  versus  $\text{NO}_Z$  relations in  
 9 Nashville, TN and Los Angeles, CA reflects the difference between  $\text{NO}_x$ -limited conditions in  
 10 Nashville versus an approach to  $\text{NO}_x$ -saturated conditions in Los Angeles.



Source: adapted with permission of American Geophysical Union from Trainer et al. (1993, [038672](#)), Sillman et al. (1998, [052223](#)), and Sillman and He (2002, [052350](#))

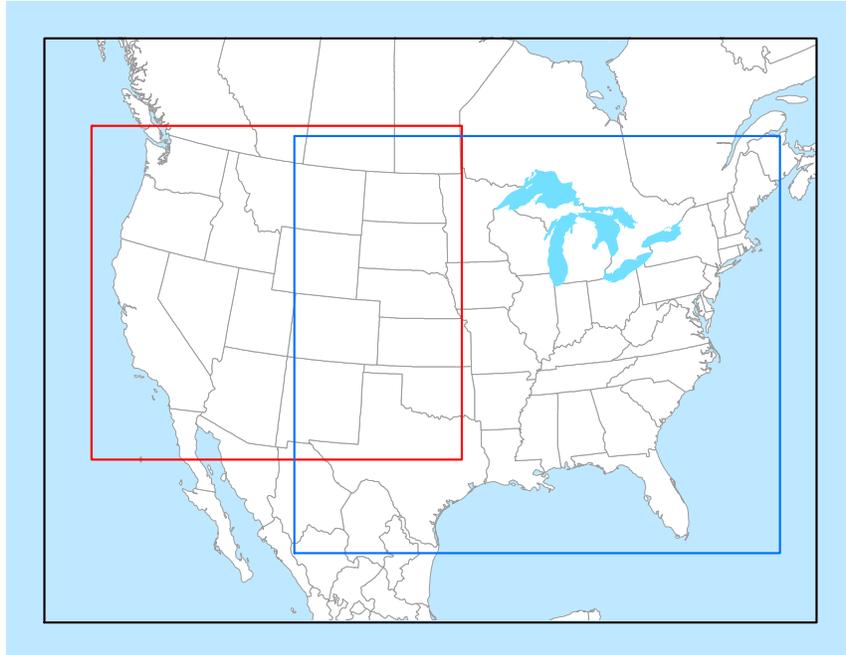
**Figure 3-3. Measured concentrations of ozone and  $\text{NO}_Z$  ( $\text{NO}_Y$ – $\text{NO}_X$ ) during the afternoon at rural sites in the eastern U.S. (grey circles) and in urban areas and urban plumes associated with Nashville, TN (gray dashes); Paris, France (black diamonds); and Los Angeles, CA (Xs).**

11 The difference between  $\text{NO}_x$ -limited and  $\text{NO}_x$ -saturated regimes is also reflected in  
 12 measurements of  $\text{H}_2\text{O}_2$ .  $\text{H}_2\text{O}_2$  production is highly sensitive to the abundance of free radicals and is  
 13 thus favored in the  $\text{NO}_x$ -limited regime. Measurements in the rural eastern U.S. (Jacob et al., 1995,  
 14 [052308](#)), Nashville, TN (Sillman et al., 1998, [052223](#)), and Los Angeles, CA (Sakugawa and Kaplan,  
 15 1989, [044129](#)), show large differences in  $\text{H}_2\text{O}_2$  concentrations between likely  $\text{NO}_x$ -limited and  
 16  $\text{NO}_x$ -saturated locations.

### 3.3. Atmospheric Modeling

1 Chemistry-transport models (CTMs) have been widely used to compute the interactions  
2 among atmospheric pollutants and their transformation products, and the transport and deposition of  
3 pollutants. They have also been widely used to improve our basic understanding of atmospheric  
4 chemical processes and to develop control strategies. To do this, CTMs solve a set of coupled, non-  
5 linear partial differential equations, or continuity equations, for relevant chemical species. Jacobson  
6 (2005, [684174](#)) described the governing partial differential equations, different coordinate systems in  
7 use, and the finite difference approximations used to solve the equations numerically. Because of  
8 limitations imposed by the complexity and spatial-temporal scales of relevant physical and chemical  
9 processes, the CTMs must include parameterizations of these processes, which include atmospheric  
10 transport; the transfer of solar radiation through the atmosphere; chemical reactions; and removal to  
11 the surface by turbulent motions and precipitation. Development of parameterizations for use in  
12 CTMs requires data for three dimensional wind fields, temperatures, humidity, cloudiness, and solar  
13 radiation; emissions data for primary (i.e., directly emitted from sources) species such as NO<sub>x</sub>, SO<sub>2</sub>,  
14 NH<sub>3</sub>, VOCs, and primary PM; and chemical reactions.

15 The domains of CTMs extend from a few 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 on the  
17 Community Multi-scale Air Quality modeling system (CMAQ) (Byun and Ching, 1999, [156314](#);  
18 Byun and Schere, 2006, [090560](#)). CMAQ's horizontal domain typically extends over North America  
19 with efforts underway to extend it over the entire Northern Hemisphere. Note that CTMs can be  
20 'nested' within each other as shown in Figure 3-4 which shows domains for CMAQ (version 4.6.1);  
21 additional details on the model configuration and application are found in (U.S. EPA, 2009, [191774](#)).  
22 The figure shows the outer domain (36 km horizontal grid spacing) and two 12 km spatial resolution  
23 (east and west) sub-domains. The upper boundary for CMAQ is typically set at 100 hPa, which is  
24 located on average at about 16 km altitude, although in some recent applications the upper boundary  
25 has been set at 50 hPa. These domains and grid spacings are quite common and can also be found in  
26 a number of other models.

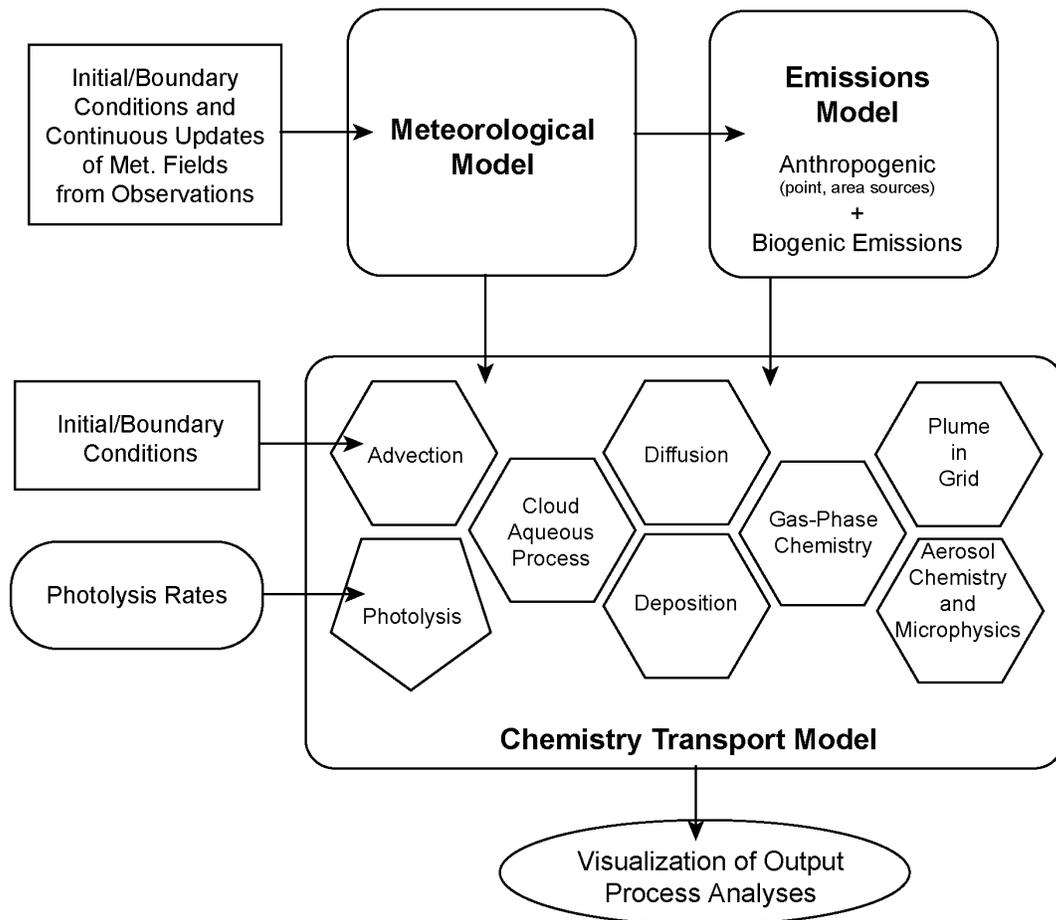


**Figure 3-4. Sample CMAQ modeling domains: 36 km-grid-spacing; outer parent domain in black; 12 km western U.S. (WUS) domain in red; 12 km eastern U.S. (EUS) domain in blue.**

1           The main components of a CTM such as EPA’s CMAQ are summarized in Figure 3-5. The  
 2 capabilities of a number of CTMs designed to study local- and regional-scale air pollution problems  
 3 were summarized by Russell and Dennis (2000, [035563](#)) and in the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
 4 2006, [088089](#)). CMAQ is most often driven by the MM5 mesoscale meteorological model (Seaman,  
 5 2000, [035562](#)), though it may be driven by other meteorological models including the Weather  
 6 Research Forecasting (WRF) model and the Regional Atmospheric Modeling System (RAMS)  
 7 (ATMET, 2011, [677541](#)). With the realization of the importance of intercontinental transport and the  
 8 need to consider exchange among different media, the domains of models such as RAMS have been  
 9 extended and interactions with other geophysical compartments such as land and ocean have been  
 10 considered. For example, the Ocean- Land- Atmosphere Model (OLAM) was developed to extend  
 11 the capability of RAMS to the global scale (Walko and Avissar, 2008, [665033](#)).

12           Simulations of pollution episodes over regional domains have been performed with a  
 13 horizontal resolution down to 1 km; see the application and general survey results reported in Ching  
 14 et al. (2006, [090300](#)). However, simulations at such high resolution require better parameterizations  
 15 of meteorological processes such as boundary layer fluxes, deep convection, and clouds (Seaman,  
 16 2000, [035562](#)). Finer spatial resolution is necessary to resolve features such as urban heat island  
 17 circulation; sea, bay, and land breezes; mountain and valley breezes; and the nocturnal low-level jet,

1 all of which can affect pollutant concentrations. Other major air quality systems used for regional  
 2 scale applications include the Comprehensive Air Quality Model with extensions (CAMx)  
 3 (ENVIRON, 2005, [677542](#)) and the Weather Research and Forecast model with Chemistry  
 4 (WRF/Chem) (NOAA, 2010, [677543](#)).



**Figure 3-5. Main components of a comprehensive atmospheric chemistry modeling system, such as the U.S. EPA's Community Model for Air Quality (CMAQ) System.**

5 CMAQ and other grid-based or Eulerian air quality models subdivide the modeling domain  
 6 into a three-dimensional array of grid cells. Spatial derivatives in the species continuity equations are  
 7 cast in finite-difference form over this grid and a system of equations for the concentrations of all the  
 8 chemical species in the model are solved numerically at each grid point. Time-dependent continuity  
 9 or mass conservation equations are solved for each species in each grid cell including terms for  
 10 transport, chemical production and destruction, and emissions and deposition (if relevant). Chemical  
 11 processes are simulated with ordinary differential equations, and transport processes are simulated  
 12 with partial differential equations. Because of a number of factors such as the different time scales

1 inherent in different processes, the coupled, nonlinear nature of the chemical process terms, and  
2 computer storage limitations, not all of the terms in the equations are solved simultaneously in three  
3 dimensions. Instead, operator splitting, in which terms in the continuity equation involving  
4 individual processes are solved sequentially, is used.

5 The most common approach to setting up the horizontal domain is to nest a finer grid within a  
6 larger domain of coarser resolution. However, there are other strategies such as the stretched grid and  
7 the adaptive grid. In a stretched grid, the grid's resolution continuously varies throughout the  
8 domain, thereby eliminating any potential problems with the sudden change from one resolution to  
9 another at the boundary. Caution should be exercised in using such a formulation because certain  
10 parameterizations like those for convection might be valid on a relatively coarse grid scale but may  
11 not be valid on finer scales. Adaptive grids are not fixed at the start of the simulation, but instead  
12 adapt to the needs of the simulation as it evolves. They have the advantage that they can resolve  
13 processes at relevant spatial scales. However, they can be very slow if the situation to be modeled is  
14 complex. Additionally, if adaptive grids are used for separate meteorological, emissions, and  
15 photochemical models, there is no reason a priori why the resolution of each grid should match, and  
16 the gains realized from increased resolution in one model will be wasted in the transition to another  
17 model. The use of finer horizontal resolution in CTMs will necessitate finer-scale inventories of land  
18 use and better knowledge of the exact paths of roads, locations of factories, and, in general, better  
19 methods for locating sources and estimating their emissions.

20 The vertical resolution of these CTMs is variable and usually configured to have more layers  
21 in the PBL and fewer higher up. Because the height of the boundary layer is of critical importance in  
22 simulations of air quality, improved resolution of the boundary layer height would likely improve air  
23 quality simulations. Additionally, current CTMs do not adequately resolve fine-scale features such as  
24 the nocturnal low-level jet in part because little is known about the nighttime boundary layer.

25 The meteorological fields are produced either by other numerical prediction models such as  
26 those used for weather forecasting (e.g., MM5, WRF), and/or by assimilation of satellite data. The  
27 flow of information shown in Figure 3-5 has most often been unidirectional in the sense that  
28 information flows into the CTM (large box) from outside; feedbacks on the meteorological fields and  
29 on boundary conditions (i.e., out of the box) have not been included. However, CTMs now have the  
30 capability to consider these feedbacks as well; see, for example, Binkowski et al. (2007, [090563](#)) and  
31 the Weather Research and Forecast model with Chemistry (WRF/Chem).

32 Because of the large number of chemical species and reactions that are involved in the  
33 oxidation of realistic mixtures of anthropogenic and biogenic hydrocarbons, condensed mechanisms  
34 must be used in atmospheric models. These mechanisms can be tested by comparison with smog  
35 chamber data. However, the existing chemical mechanisms often neglect many important processes  
36 such as the formation and subsequent reactions of long-lived carbonyl compounds, the incorporation  
37 of the most recent information about intermediate compounds, and heterogeneous reactions  
38 involving cloud droplets and aerosol particles.

1 The initial conditions, or starting concentration fields of all species computed by a model, and  
2 the boundary conditions, or concentrations of species along the horizontal and upper boundaries of  
3 the model domain throughout the simulation, must be specified at the beginning of the simulation.  
4 Both initial and boundary conditions can be estimated from models or data or, more generally, model  
5 + data hybrids. Because data for vertical profiles of most species of interest are very sparse, results  
6 of model simulations over larger, usually global, domains are often used. As might be expected, the  
7 influence of boundary conditions depends on the lifetime of the species under consideration and the  
8 time scales for transport from the boundaries to the interior of the model.

9 Chemical kinetics mechanisms representing the important reactions occurring in the  
10 atmosphere are used in CTMs to estimate the rates of chemical formation and destruction of each  
11 pollutant simulated as a function of time. The Master Chemical Mechanism (MCM, 2010, [677544](#)) is  
12 viewed as a benchmark database providing as near an explicit treatment of chemical reactions in the  
13 troposphere as is possible. The MCM currently includes over 12,600 reactions and 4,500 species.  
14 However, mechanisms that are this comprehensive are still computationally too demanding to be  
15 incorporated into CTMs for regulatory use. Simpler treatments of tropospheric chemistry have been  
16 assembled by combining chemical species into mechanisms that group together compounds with  
17 similar chemistry. It should be noted that because of different approaches to the lumping of organic  
18 compounds into surrogate groups for computational efficiency, chemical mechanisms can produce  
19 different results under similar conditions. Jimenez et al. (2003, [156611](#)) provided brief descriptions  
20 of the features of the main mechanisms in use and compared concentrations of several key species  
21 predicted by seven chemical mechanisms in a box-model simulation over 24 hours. There are several  
22 of these mechanisms (CB04, CB05, SAPRC) that have been incorporated into CMAQ (see for  
23 example, Luecken et al., 2008, [190084](#)) and Fuentes et al. (2007, [191251](#)) for RACM2. The CB  
24 mechanism is currently undergoing extension (CB06) to include, among other things, longer-lived  
25 species to better simulate chemistry in the remote and upper troposphere. These mechanisms were  
26 developed primarily for homogeneous gas phase reactions and treat multi-phase chemical reactions  
27 in a very cursory manner, if at all. As an example of the effects of their neglect, models such as  
28 CMAQ could have difficulties with capturing the regional nature of O<sub>3</sub> episodes, in part because of  
29 uncertainty in the chemical pathways converting NO<sub>x</sub> to HNO<sub>3</sub> and recycling of NO<sub>x</sub> (e.g.,  
30 Godowitch et al., 2008, [139006](#); Hains et al., 2008, [137411](#)). Much of this uncertainty also involves  
31 multi-phase processes as described by, for example, Thornton et al. (2010, [386870](#)).

32 CMAQ and other CTMs incorporate processes and interactions of aerosol-phase chemistry  
33 (Binkowski and Roselle, 2003, [191769](#); Gaydos et al., 2007, [139738](#); Zhang and Wexler, 2008,  
34 [191770](#)). There have also been several attempts to study the feedbacks of chemistry on atmospheric  
35 dynamics using meteorological models like MM5 and WRF (Grell et al., 2000, [048047](#); Liu et al.,  
36 2001, [048201](#); Lu et al., 1997, [048202](#); Park et al., 2001, [044169](#)). This coupling is necessary to  
37 accurately simulate feedbacks which may be caused by the heavy aerosol loading found in forest fire  
38 plumes (Lu et al., 1997, [048202](#); Park et al., 2001, [044169](#)) or in heavily polluted areas. Photolysis

1 rates in CMAQ can now be calculated interactively with model produced O<sub>3</sub>, NO<sub>2</sub>, and aerosol fields  
2 (Binkowski et al., 2007, [090563](#)).

3 Spatial and temporal characterizations of anthropogenic and biogenic precursor emissions  
4 must be specified as inputs to a CTM. Emissions inventories have been compiled on grids of varying  
5 resolution for many hydrocarbons, aldehydes, ketones, CO, NH<sub>3</sub>, and NO<sub>x</sub>. Emissions inventories  
6 for many species require the application of algorithms for calculating the dependence of emissions  
7 on physical variables, such as temperature, and to convert the inventories into formatted emission  
8 files which can be used by a CTM. For example, preprocessing of emissions data for CMAQ often is  
9 done by the Sparse-Matrix Operator Kernel Emissions (SMOKE) system (CEMPD, 2011, [677545](#)).  
10 For many species, information concerning the temporal variability of emissions is lacking, so long-  
11 term annual averages are used in short-term, episodic simulations. Annual emissions estimates are  
12 often modified by the emissions model to produce emissions more characteristic of the time of day  
13 and season. Significant errors in emissions can occur if inappropriate time dependence is used.  
14 Additional complexity arises in model calculations because different chemical mechanisms can  
15 include different species, and inventories constructed for use with one mechanism must be adjusted  
16 to reflect these differences in another.

17 Each of the model components described above has associated uncertainties; and the relative  
18 importance of these uncertainties varies with the modeling application. The largest errors in  
19 photochemical modeling are still thought to arise from the meteorological and emissions inputs to  
20 the model (Russell and Dennis, 2000, [035563](#)). While the effects of poorly specified boundary  
21 conditions propagate through the model's domain, the effects of these errors remain undetermined.  
22 Because many meteorological processes occur on spatial scales smaller than the model's vertical or  
23 horizontal grid spacing and thus are not calculated explicitly, parameterizations of these processes  
24 must be used. These parameterizations introduce additional uncertainty. Because the chemical  
25 production (and loss) terms in the continuity equations for individual species are numerically  
26 coupled, the chemical calculations must be performed iteratively until calculated concentrations  
27 converge to within some preset criterion. The number of iterations and the convergence criteria  
28 chosen also can introduce error.

29 The performance of CTMs must be evaluated by comparison with field data as part of a cycle  
30 of model evaluations and subsequent improvements (e.g., NRC Committee on Models in the  
31 Regulatory Decision Process, 2007, [632611](#)). However, they are too demanding of computational  
32 time to have the full range of their sensitivities examined by using Monte Carlo techniques (NRC  
33 Committee on Models in the Regulatory Decision Process, 2007, [632611](#)). Models of this  
34 complexity are evaluated by comparison with field observations for O<sub>3</sub> and other species.  
35 Evaluations of the performance of CMAQ are given in Arnold et al. (2003, [087579](#)), Eder and Yu  
36 (2005, [089229](#)), Appel et al. (2005, [089227](#)), and Fuentes and Raftery (2005, [087580](#)). Discrepancies  
37 between model predictions and observations can be used to point out gaps in current understanding  
38 of atmospheric chemistry and to spur improvements in parameterizations of atmospheric chemical  
39 and physical processes. Model evaluation does not merely involve a straightforward comparison

1 between model predictions and the concentration field of the pollutant of interest. Such comparisons  
2 may not be meaningful because it is difficult to determine if agreement between model predictions  
3 and observations truly represents an accurate treatment of physical and chemical processes in the  
4 CTM or the effects of compensating errors in complex model routines (in other words, a model  
5 evaluator would want to know if they had the right answer for the right reasons). Ideally, each of the  
6 model components (emissions inventories, chemical mechanism, meteorological driver) should be  
7 evaluated individually. However, this is rarely done in practice. In addition to comparisons between  
8 concentrations of calculated and measured species, comparisons of correlations between measured  
9 primary VOCs and NO<sub>x</sub> and modeled VOCs and NO<sub>x</sub> are especially useful for evaluating results  
10 from chemistry-transport models. Likewise, comparisons of correlations between measured species  
11 and modeled species can be used to provide information about the chemical state of the atmosphere  
12 and to evaluate model representations (including: O<sub>3</sub> production from NO<sub>x</sub>; O<sub>3</sub>-NO<sub>x</sub>-VOC  
13 sensitivity; and the general accuracy of photochemical representations). A CTM that demonstrates  
14 the accuracy of both its computed VOC and NO<sub>x</sub> in comparison with ambient measurements, and  
15 the spatial and temporal relations among the critical secondary species associated with O<sub>3</sub>, has a  
16 higher probability of representing O<sub>3</sub>-precursor relations correctly than one that does not.

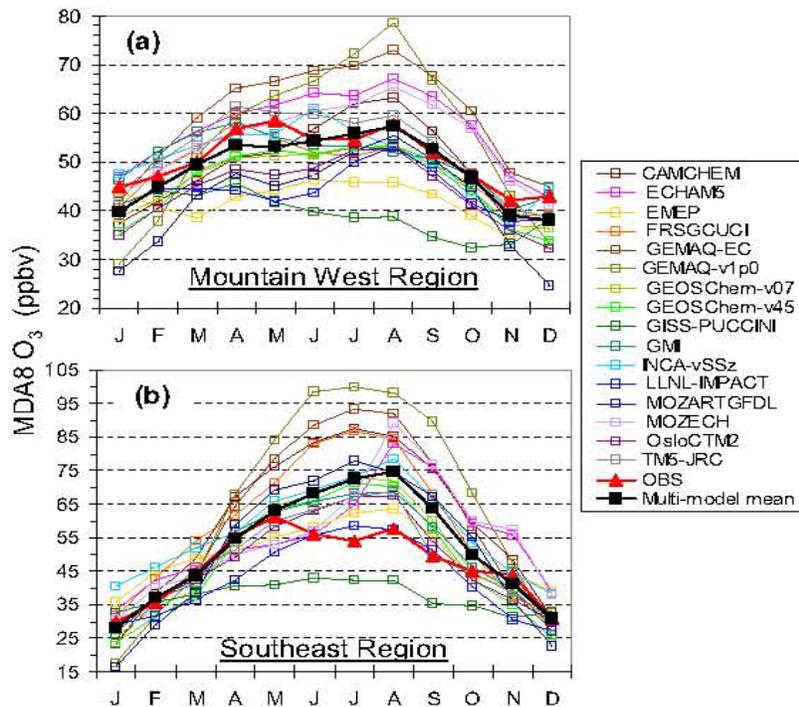
17 The above techniques are sometimes referred to as “static” in the sense that individual model  
18 variables are compared to observations. It is also crucial to understand the (dynamic) response to  
19 changes in inputs and to compare the model responses to those that are observed. These tests might  
20 involve changes in some natural forcing or in emissions from an anthropogenic source. As an  
21 example, techniques such as the direct decoupled method (DDM) (Dunker, 1981, [040504](#); Dunker et  
22 al., 2002, [665029](#)) could be used in this regard. However, the observational basis for comparing a  
23 model's response is largely unavailable for many problems of interest, in large part because  
24 meteorological conditions are also changing while the emissions are changing. As a result, methods  
25 such as DDM are used mainly to address the effectiveness of emissions controls.

### 3.3.1. Global Scale CTMs

26 With recognition of the global nature of many air pollution problems, global scale CTMs have  
27 been applied to regional scale pollution problems (e.g., NRC Committee on the Significance of  
28 International Transport of Air Pollutants, 2009, [202867](#)). Global-scale CTMs are used to address  
29 issues associated with global change, to characterize long-range transport of air pollutants, and to  
30 provide boundary conditions for the regional-scale models. The upper boundaries of global scale  
31 CTMs extend anywhere from the tropopause (~8 km at the poles to ~16 km in the tropics) to the  
32 mesopause at ~80 km, in order to obtain more realistic boundary conditions for problems involving  
33 stratospheric dynamics and chemistry. The global-scale CTMs consider the same processes shown in  
34 Figure 3-5 for the regional scale models. In addition, many of the same issues that have arisen for the  
35 regional models have also arisen for the global scale models (see Emmerson and Evans, 2009,  
36 [605119](#)). For example, predictions of HNO<sub>3</sub> were found to be too high and predictions of PAN were  
37 found to be too low over the U.S. during summer in the MOZART model (Fang et al., 2010,

1 [665391](#)). Similar findings were obtained in a box model of upper tropospheric chemistry (Henderson  
2 et al., 2010, [674771](#)).

3 The GEOS-Chem model is a community global scale CTM that has been widely used to study  
4 issues associated with the intra- and inter-hemispheric transport of pollution and global change  
5 (Harvard University, 2010, [677546](#)). Comparisons of the capabilities of GEOS-Chem and several  
6 other models to simulate intra-hemispheric transport of pollutants are given in a number of articles  
7 (e.g., Fiore et al., 2009, [665030](#); Reidmiller et al., 2009, [644826](#)). Reidmiller et al. (2009, [644826](#))  
8 showed comparisons among 18 global models and their ensemble average to spatially and monthly  
9 averaged observations of O<sub>3</sub> at CASTNET sites (see Figure 3-6). These results show that the  
10 multi-model ensemble agrees much better with the observations than do most of the individual  
11 models. The GEOS-Chem model was run for two grid spacings, 4°×4.5° and 2°×2.5° with very  
12 similar results that lie close to the ensemble average. In general, the model ensemble and the two  
13 GEOS-Chem simulations are much closer to the observations in the Mountain West than in the  
14 Southeast. In particular, there are sizable over-predictions by most of the models in the Southeast  
15 during summer, the time when major O<sub>3</sub> episodes occur.



Source: Used with permission from Copernicus Publications, Reidmiller et al. (2009, [644826](#))

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

1 The issue of overestimating O<sub>3</sub> is not limited to global models. Godowitch et al. (2008,  
2 [139006](#)), Gilliland et al. (2008, [606585](#)) and Nolte et al. (2008, [679712](#)) found positive O<sub>3</sub> biases in  
3 regional models over the eastern U.S., as well, which they largely attributed to uncertainties in  
4 temperature, relative humidity and planetary boundary layer height. Agreement between monthly  
5 average values is expected to be better than with daily values because of a number of factors  
6 including the increasing uncertainty of emissions at finer time resolution. Kasibhatla and Chameides  
7 (2000, [052237](#)) found that the accuracy of simulations improved in their simulations as the averaging  
8 time of both the simulation and the observations increased.

9 Simulations of the effects of long-range transport at particular locations must be able to link  
10 multiple horizontal resolutions from the global to the local scale. Because of limitations on  
11 computational resources, global simulations are not made at the same horizontal resolutions found in  
12 the regional scale models, i.e., down to 1-4 km resolution on a side. They are typically conducted  
13 with a horizontal grid spacing of 1°-2° of latitude and longitude (or roughly 100-200 km at mid-  
14 latitudes). Some models such as GEOS-Chem have the capability to include nested models at a  
15 resolution of 0.5°×0.667° (e.g., Wang et al., 2009, [622281](#)) and efforts are underway to achieve even  
16 higher spatial resolution. Another approach is to nest regional models within GEOS-Chem. Caution  
17 must be exercised with nesting different models because of differences in chemical mechanisms and  
18 numerical schemes, and in boundary conditions between the outer and inner models. As an example  
19 of these issues, surface O<sub>3</sub> concentrations that are too high have been observed in models in which  
20 CMAQ was nested inside of GEOS-Chem (see e.g., Lam and Fu, 2010, [665031](#) for one way to  
21 address this issue). The high O<sub>3</sub> was the result of stratospheric O<sub>3</sub> intruding into the CMAQ domain,  
22 followed by too rapid downward mixing of this O<sub>3</sub> in CMAQ. Ozone has large vertical gradients in  
23 the upper troposphere that must be preserved if its downward transport is to be simulated correctly.  
24 Errors in parameterizations of vertical transport (e.g., vertical velocities, diffusivities) leading to too  
25 rapid mixing may be involved. It is also highly likely that using a vertical resolution in CMAQ that  
26 is too coarse is involved, coupled with using fewer layers in CMAQ than in the driving MM5 or  
27 WRF meteorological model. As a result of the above factors, O<sub>3</sub> gradients are eliminated and O<sub>3</sub> is  
28 mixed too rapidly in the upper troposphere. Efforts are also being made to extend the domain of  
29 CMAQ over the Northern Hemisphere. In this approach, the same numerical schemes are used for  
30 transporting 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 governing  
32 processes are accurately described. Consequently, there is a crucial need for observations at the  
33 appropriate scales to evaluate the scientific understanding represented by the models.

### 3.4. Policy Relevant Background Concentrations

34 The background concentrations of O<sub>3</sub> that are useful for risk and policy assessments informing  
35 decisions about the NAAQS are referred to as PRB concentrations. PRB concentrations have  
36 historically been defined by EPA as those concentrations that would occur in the U.S. in the absence

1 of anthropogenic emissions in continental North America (CNA) defined here as the U.S., Canada,  
2 and Mexico. For this document, PRB concentrations include contributions from natural sources  
3 everywhere in the world and from anthropogenic sources outside CNA. Background concentrations  
4 so defined, facilitate separation of pollution that can be controlled by U.S. regulations or through  
5 international agreements with neighboring countries from those that are judged to be generally  
6 uncontrollable by the U.S. Over time, consideration of potential broader ranging international  
7 agreements may lead to alternative determinations in which O<sub>3</sub> precursor source contributions should  
8 be considered by EPA as part of PRB.

9 Contributions to PRB O<sub>3</sub> include photochemical reactions involving natural emissions of  
10 VOCs, NO<sub>x</sub>, and CO as well as the long-range transport of O<sub>3</sub> and its precursors from outside CNA  
11 and the STE of O<sub>3</sub>. These sources have the greatest potential for producing the highest PRB  
12 concentrations, and therefore are discussed in greater detail below. Natural sources of O<sub>3</sub> precursors  
13 include biogenic emissions, wildfires, and lightning. Biogenic emissions from agricultural activities  
14 in CNA are not considered in the formation of PRB O<sub>3</sub>. Definitions of background and approaches to  
15 derive background concentrations were reviewed in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#))  
16 and Reid et al. (2008, [665032](#)).

### 3.4.1. Contributions from Anthropogenic Emissions Outside North America

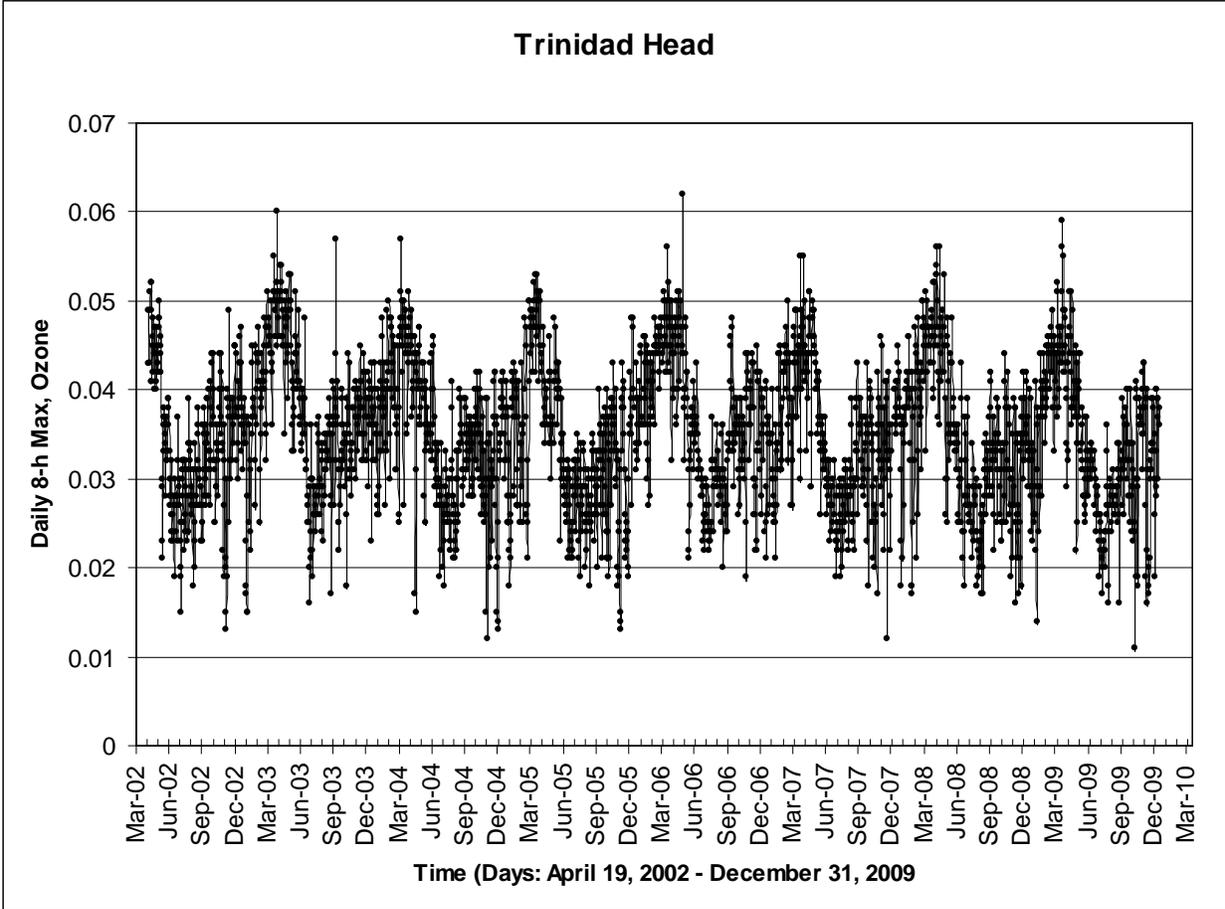
17 In addition to emissions from North America, emissions from Eurasia have contributed to the  
18 global burden of O<sub>3</sub> in the atmosphere and to the U.S. (e.g., NRC Committee on the Significance of  
19 International Transport of Air Pollutants, 2009, [202867](#) and references therein). Because the mean  
20 tropospheric lifetime of O<sub>3</sub> is 30-35 days (Hsu and Prather, 2009, [629687](#)), O<sub>3</sub> can be transported  
21 from continent to continent and around the globe in the Northern Hemisphere and O<sub>3</sub> produced by  
22 U.S. emissions can be recirculated around northern mid-latitudes back to the U.S. High elevation  
23 sites are most susceptible to the intercontinental transport of pollution especially during spring. An  
24 O<sub>3</sub> concentration of ~85 ppb was observed at Mt. Bachelor Observatory, OR (elevation 2,700 m) on  
25 April 22, 2006 with a number of occurrences of O<sub>3</sub> >60 ppb from mid-April to mid-May of 2006.  
26 Calculations using GEOS-Chem, a global-scale, chemistry-transport model, indicate that Asia  
27 contributed 9 ± 3 ppb to a modeled mean concentration of 53 ± 9 ppb O<sub>3</sub> at Mt. Bachelor during the  
28 same period compared to measured concentrations of 54 ± 10 ppb (Zhang et al., 2008, [624402](#)).  
29 Zhang et al. (2008, [624402](#)) also calculated a contribution of 5 to 7 ppb to surface O<sub>3</sub> over the  
30 western U.S. during that period from Asian anthropogenic emissions. They also estimated an  
31 increase in NO<sub>x</sub> emissions of ~ 44% from Asia from 2001 to 2006 resulting in an increase of 1-2 ppb  
32 in O<sub>3</sub> over North America.

33 Cooper et al. (2010, [380093](#)) analyzed all available O<sub>3</sub> measurements in the free troposphere  
34 above western North America at altitudes of 3-8 km (above sea level) during April and May of 1995  
35 to 2008 (i.e., times when intercontinental transport is most prominent). They derived a trend of 0.63  
36 ± 0.34 ppb/year in median O<sub>3</sub> concentrations with indication of a similar rate of increase since 1984.

1 Back trajectories that were likely to have been strongly and recently influenced by North American  
2 emissions were filtered out, resulting in a trend of  $0.71 \pm 0.45$  ppb/year. Considering only trajectories  
3 with an Asian origin resulted in a trend of  $0.80 \pm 0.34$  ppb/year. These results suggest that local  
4 North American emissions were not responsible for the measured O<sub>3</sub> increases. This O<sub>3</sub> could have  
5 been produced from natural and anthropogenic precursors in Asia and Europe with some  
6 contribution from North American emissions that have circled the globe. Cooper et al. (2010,  
7 [380093](#)) also found that it is unlikely that the trends in tropospheric O<sub>3</sub> are associated with trends in  
8 stratospheric intrusions. Note, however, that these results relate to O<sub>3</sub> trends above ground level and  
9 not to surface O<sub>3</sub>. Model results (e.g., Zhang et al., 2008, [624402](#)) show that surface O<sub>3</sub> contributions  
10 from Asia are much smaller than those derived in the free troposphere because of dilution and  
11 chemical destruction during downward transport to the surface.

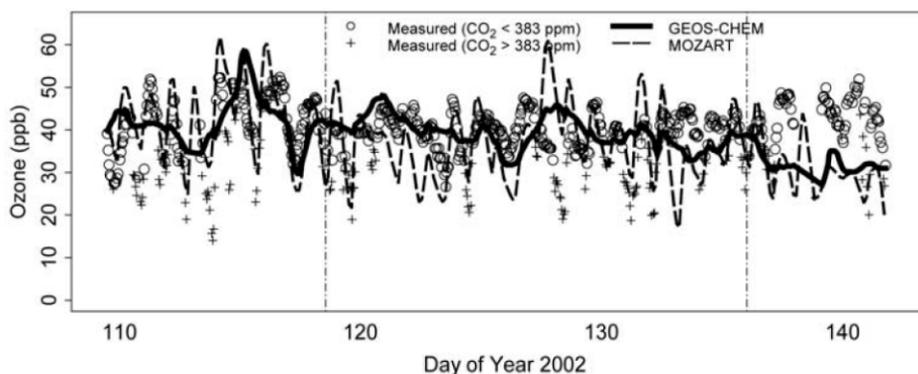
12 There are limited cases where PRB conditions are observable at lower elevations, for example  
13 at Trinidad Head, CA at times during spring (Goldstein et al., 2004, [087780](#); Oltmans et al., 2008,  
14 [615534](#)). Figure 3-7 shows the time series of daily maximum 8-h avg O<sub>3</sub> concentrations measured at  
15 Trinidad Head from April 18, 2002 through December 31, 2009. The data show pronounced seasonal  
16 variability with spring maxima and summer minima. Springtime concentrations typically range from  
17 40 to 50 ppb with a number of occurrences >50 ppb. The two highest daily maxima were 60 and  
18 62 ppb. The data also show much lower concentrations during summer, with concentrations typically  
19 ranging between 20 and 30 ppb. Oltmans et al. (2008, [615534](#)) examined the time series of O<sub>3</sub> and  
20 back trajectories reaching Trinidad Head. They found that springtime maxima (April-May) were  
21 largely associated with back trajectories passing over the Pacific Ocean and most likely entraining  
22 emissions from Asia, with minimal interference from local sources. However, Parrish et al. (2009,  
23 [616076](#)) noted that only considering trajectories coming from a given direction is not sufficient for  
24 ruling out local continental influences, as sea breeze circulations are complex phenomena involving  
25 vertical mixing and entrainment of long-shore components. They found that using a wind speed  
26 threshold, in addition to a criterion for wind direction, allowed for determination of background  
27 trajectories not subject to local influence; as judged by measurements of chemical tracers such as  
28 CO<sub>2</sub>, MTBE and radon. By applying the two criteria for wind speed and direction, they found that  
29 Trinidad Head met these criteria only 30% of the time during spring. Goldstein et al. (2004, [087780](#))  
30 used CO<sub>2</sub> as an indicator of exchange with the local continental environment and found that O<sub>3</sub>  
31 concentrations were higher by about 2-3 ppb when filtered against local influence indicating higher  
32 O<sub>3</sub> in air arriving from over the Pacific (see Figure 3-8). At Trinidad Head during spring, O<sub>3</sub> is more  
33 likely to be titrated by local emissions of NO<sub>x</sub> than to be photochemically produced (Parrish et al.,  
34 2009, [616076](#)). At other times of the year, Trinidad Head is less strongly affected by air passing over  
35 Asia and many trajectories have long residence times over the semi-tropical and tropical Pacific  
36 Ocean, where O<sub>3</sub> concentrations are much lower than they are at mid-latitudes. The application of  
37 the Trinidad Head data to PRB conditions would require the use of screening procedures adopted by  
38 Parrish et al. (2009, [616076](#)) and the application of photochemical models to determine the extent

- 1 either of titration of O<sub>3</sub> by fresh NO<sub>x</sub> emissions and the extent of local production of O<sub>3</sub> from these
- 2 emissions.



Source: Used with permission from Elsevier Ltd., Oltmans et al. (2008, [615534](#)) and NOAA Climate Monitoring Diagnostics Laboratory for data from 2008-2009

**Figure 3-7. Time series of daily maximum 8-h avg ozone concentrations (ppm) measured at Trinidad Head, CA, from April 18, 2002 through December 31, 2009.**



**Observations:  $38 \pm 7$  ppb (unfiltered)**  
 **$41 \pm 5$  ppb (filtered against local influence)**  
**GEOS-Chem model:  $39 \pm 5$  ppb**  
**MOZART-2 global model:  $37 \pm 9$  ppb**

Source: Used with permission from American Geophysical Union, Goldstein et al. (2004, [087780](#))

**Figure 3-8. Time series of measured ozone and model calculated ozone at Trinidad Head, CA, during April and May, 2002.**

1 Parrish et al. (2009, [616076](#)) also examined data obtained at other marine boundary layer sites  
 2 on the Pacific Coast. These include Olympic NP, Redwood NP, Point Arena, and Point Reyes. Using  
 3 data from these sites, they derived trends in  $O_3$  of 0.46 ppb/year (with a 95% confidence interval of  
 4 0.13 ppb/year) during spring and 0.34 ppb/year (0.09 ppb/year) for the annual mean  $O_3$  increase in  
 5 air arriving from over the Pacific during the past two decades. Although  $O_3$  data are available from  
 6 the Channel Islands, Parrish et al. (2009, [616076](#)) noted that these data are not suitable for  
 7 determining background influence because of the likelihood of circulating polluted air from the  
 8 South Coast Basin.

### 3.4.2. Contributions from the Stratosphere

9 As noted in the 2006  $O_3$  AQCD (U.S. EPA, 2006, [088089](#)), stratospheric air rich in  $O_3$  is  
 10 transported to the troposphere. Ozone is produced naturally by photochemical reactions in the  
 11 stratosphere as shown in Figure 3-1 in Section 3.2. Some of this  $O_3$  is transported downward into the  
 12 troposphere throughout the year, with maximum contributions during late winter and early spring  
 13 mainly in a process known as tropopause folding. These folds occur basically behind every cold  
 14 front, bringing stratospheric air with them. The tropopause should not be interpreted as a material  
 15 surface through which there is no exchange. Rather these folds should be thought of as regions in  
 16 which mixing of tropospheric and stratospheric air is occurring (Shapiro, 1980, [047756](#)). This  
 17 imported stratospheric air contributes to the natural background of  $O_3$  in the troposphere, especially  
 18 in the free troposphere during winter and spring. STE also occurs during other seasons including  
 19 summer. Thompson et al., (2007, [090796](#)) found that roughly 20-25% of tropospheric  $O_3$  over  
 20 northeastern North America during July-August 2004 was of stratospheric origin. This  $O_3$  can be

1 mixed into the PBL where it can either be destroyed or transported to the surface. Yang et al. (2010,  
2 [628857](#)) estimated that roughly 20% of free tropospheric O<sub>3</sub> above coastal California in 2005 and  
3 2006 was stratospheric in origin. Some of this O<sub>3</sub> could also contribute to O<sub>3</sub> at the surface.

4 It should be noted that there is considerable uncertainty in the magnitude and distribution of  
5 this potentially important source of tropospheric O<sub>3</sub>. Stratospheric intrusions that reach the surface  
6 are rare. Much more common are intrusions which penetrate only to the middle and upper  
7 troposphere. However, O<sub>3</sub> transported to the upper and middle troposphere can still affect surface  
8 concentrations through various exchange mechanisms that mix air from the free troposphere with air  
9 in the PBL. Substantial photochemical production of O<sub>3</sub> in the troposphere also begins in late winter  
10 and early spring; therefore, it cannot be assumed that O<sub>3</sub> present at these times is only stratospheric  
11 in origin. The basic atmospheric dynamics and thermodynamics of stratospheric-tropospheric  
12 exchange were outlined in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#), Annex AX2.3.1).

13 Several instances of STE producing high concentrations of O<sub>3</sub> around Denver and Boulder,  
14 CO were analyzed by Langford et al. (2009, [491703](#)). Several likely instances of STE, including one  
15 of the cases analyzed by Langford et al. (2009, [491703](#)) were also cited in the 2006 O<sub>3</sub> AQCD  
16 (U.S. EPA, 2006, [088089](#), Annex AX3, Section AX3.9). Clear examples of STE have also been  
17 observed in southern Quebec province by Hocking et al. (2007, [608032](#)), in accord with previous  
18 estimates by Wernli et al. (2002, [052425](#)) and James et al. (2003, [043286](#)).

### 3.4.2.1. *Other Natural Sources of Precursors to PRB Ozone Formation*

19 Biomass burning consists of wildfires and the intentional burning of vegetation to clear new  
20 land for agriculture and for population resettlement; to control the growth of unwanted plants on  
21 pasture land; to manage forest resources with prescribed burning; to dispose of agricultural and  
22 domestic waste; and as fuel for cooking, heating, and water sterilization. Globally, most wildfires  
23 may be ignited directly as the result of human activities, leaving only 10-30% initiated by lightning  
24 (Andreae, 1991, [078147](#)). However, because fire management practices suppress natural wildfires,  
25 the buildup of fire fuels increases the susceptibility of forests to more severe but less frequent fires in  
26 the future. Thus there is considerable uncertainty in attributing the fraction of wildfire emissions to  
27 human activities because the emissions from naturally occurring fires that would have been present  
28 in the absence of fire suppression practices are not known. Contributions to NO<sub>x</sub>, CO and VOCs  
29 from wild fires and prescribed fires are considered as precursors to PRB O<sub>3</sub> formation.

30 Biomass burning also exhibits strong seasonality and interannual variability (van der Werf et  
31 al., 2006, [157084](#)), with most biomass burned during the local dry season. This is true for both  
32 prescribed burns and wildfires. The unusually warm and dry weather in central Alaska and western  
33 Yukon in the summer of 2004, for example, contributed to the burning of 11 million acres there.  
34 Subsequent modeling by Pfister et al. (2005, [093009](#)) showed that the CO contribution from these  
35 fires in July 2004 was 33.1 (± 5.5) MT that summer, or in the range of the total U.S. anthropogenic  
36 CO emissions during the same period. In addition to emissions from forest fires in the U.S.,  
37 emissions from forest fires in other countries can be transported to the U.S., for example from boreal

1 forest fires in Canada (Mathur, 2008, [156742](#)), Siberia (Generoso et al., 2007, [155786](#)) and tropical  
2 forest fires in the Yucatan Peninsula and Central America (Wang et al., 2006, [157109](#)).

3 Estimates of biogenic VOC and CO emissions are made using the BEIS model with data from  
4 the Biogenic Emissions Landcover Database (BELD) and annual meteorological data. VOC  
5 emissions from vegetation were described in Section 3.2. As noted earlier, NO<sub>x</sub> is produced by  
6 lightning. Kaynak et al. (2008, [486686](#)) found contributions of 2 to 3 ppb PRB O<sub>3</sub> centered mainly  
7 over the southeastern U.S. during summer. Although total column estimates of lightning-produced  
8 NO<sub>x</sub> are large compared to anthropogenic NO<sub>x</sub> during summer, lightning-generated NO<sub>x</sub> does not  
9 contribute substantially to the NO<sub>x</sub> burden in the continental boundary layer. This is because only  
10 2% of NO<sub>x</sub> production by lightning occurs within the boundary layer and most occurs in the free  
11 troposphere (Fang et al., 2010, [665391](#)). In addition, much of the NO<sub>x</sub> produced in the free  
12 troposphere is converted to more oxidized N species during downward transport. However, Fang et  
13 al. (2010, [665391](#)) estimate these NO<sub>x</sub> oxidation products contribute ~1/3 to wet deposition by total  
14 oxidized N species over the U.S.

### 3.4.3. Estimating PRB Concentrations

15 There are two approaches to estimating PRB concentrations that have been considered in  
16 previous assessments. The first involves using measurements and the second the use of chemistry-  
17 transport models. Section 3.9 of the 2006 O<sub>3</sub> AQCD, (U.S. EPA, 2006, [088089](#)), noted that estimates  
18 of PRB concentrations cannot be obtained solely by examining measurements of O<sub>3</sub> obtained at  
19 relatively remote monitoring sites in the U.S. (AX3.2.3) because of the long-range transport from  
20 anthropogenic source regions within North America. The 2006 O<sub>3</sub> AQCD also noted that it is  
21 impossible to determine sources of O<sub>3</sub> without ancillary data that could be used as tracers of sources  
22 or to calculate photochemical production and loss rates. As further noted by Reid et al. (2008,  
23 [665032](#)), the use of monitoring data is essentially limited to the edges of the domain of interest. This  
24 is because PRB O<sub>3</sub> entering from outside North America can only be destroyed over North America  
25 either through chemical reactions or by deposition to the surface. Within North America, PRB O<sub>3</sub> is  
26 only produced by interactions between natural sources and between North American natural sources  
27 and precursors from other continents. PRB O<sub>3</sub> as defined above is different from the baseline O<sub>3</sub>  
28 defined by Chan and Vet (2010, [679710](#)). Their baseline O<sub>3</sub> refers to “O<sub>3</sub> measured at a given site in  
29 the absence of strong local influences”. The current definition of PRB implies that only CTMs can  
30 be used to estimate the range of PRB concentrations. A further advantage to using models is that the  
31 entire range of O<sub>3</sub> concentrations in different environments can be used to evaluate model  
32 performance. However, there may be specific instances such as stratospheric intrusions that occur on  
33 spatial scales too fine to be resolved by the current generation of global CTMs.

34 Estimates of PRB concentrations in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) were based  
35 on output from the GEOS-Chem model (Fiore et al., 2003, [051226](#)). The GEOS-Chem model  
36 estimates indicate that PRB O<sub>3</sub> concentrations in eastern U.S. surface air are generally 15-35 ppb  
37 from June through August. PRB concentrations decline from spring to summer. PRB O<sub>3</sub>

1 concentrations may be higher, especially at high altitude sites during the spring, due to enhanced  
2 contributions from (1) pollution sources outside North America; and (2) stratospheric O<sub>3</sub> exchange.  
3 Only one model (GEOS-Chem (Harvard University, 2010, [677581](#))) was documented in the  
4 literature for calculating PRB O<sub>3</sub> concentrations (see Fiore et al., 2003, [051226](#)). The simulated  
5 monthly mean concentrations in different quadrants of the U.S. are typically within 5 ppbv of  
6 observations at CASTNET sites, with no significant bias, except in the Southeast in summer when  
7 the model is 8-12 ppbv too high. This bias might be due to excessive background O<sub>3</sub> transported in  
8 from the Gulf of Mexico and the tropical Atlantic Ocean or to inaccuracies in emissions inventories  
9 within the U.S. The time series comparisons for specific sites show that the model simulates the day-  
10 to-day variability of O<sub>3</sub> and reveals no further bias. These evaluations focused on the afternoon hours  
11 (1:00 p.m. to 5:00 p.m. local time), when surface measurements are representative of a deep mixed  
12 layer that can be resolved with the model. At night, surface O<sub>3</sub> depletion often takes place by titration  
13 or deposition under local, stably stratified conditions, but such conditions cannot be simulated with  
14 confidence by a global model. The issue is not only one of vertical resolution (the lowest layers in  
15 GEOS-Chem extend to 20, 50, 100, 200, and 400 m above the local surface) but also of horizontal  
16 resolution (2°×2.5°).

17 The model reproduced the occurrences of relatively high O<sub>3</sub> at remote sites previously  
18 reported by Lefohn et al. (2001, [016253](#)), and shows that these can generally be explained by North  
19 American pollution. Goldstein et al. (2005, [087880](#)) presented comparisons of GEOS-Chem and  
20 MOZART global model results with observations at Trinidad Head, CA, during April-May 2002.  
21 The observations, filtered to remove local influence, averaged 41 ± 5 ppbv, as compared to GEOS-  
22 Chem (39 ± 5 ppbv) and MOZART (37 ± 9 ppbv). Neither model was successful at reproducing the  
23 weak day-to-day structure in the observations, but they showed no bias in the simulation of  
24 occasional >50 ppbv days (see Figure 3-8).

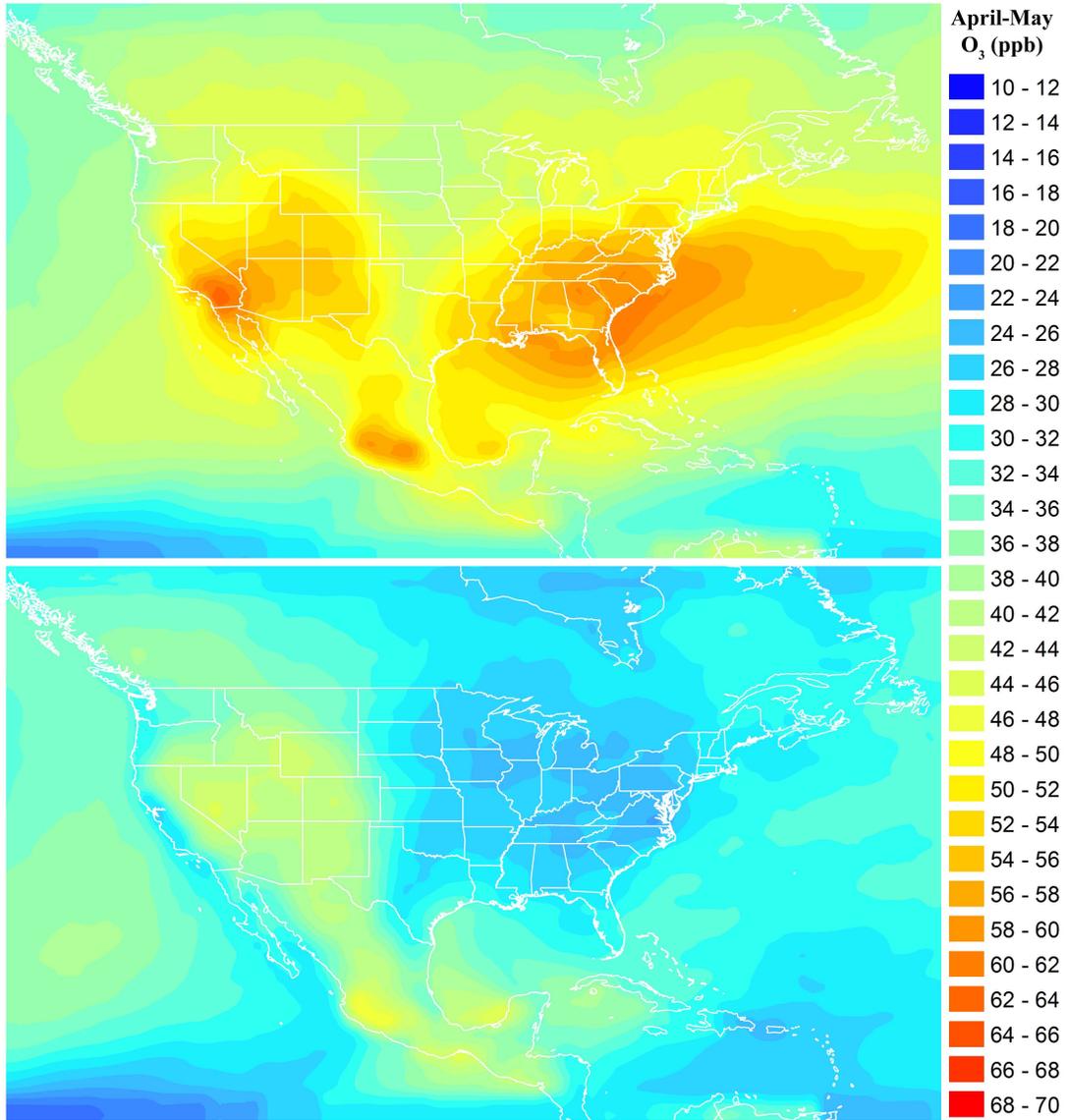
25 Although many of the features of the day-to-day variability in O<sub>3</sub> at relatively remote  
26 monitoring sites in the U.S. are simulated reasonably well by Fiore et al. (2003, [051226](#)),  
27 uncertainties in the calculation of the temporal variability of O<sub>3</sub> originating from different sources on  
28 shorter time scales must be recognized. The uncertainties stem in part from an underestimate in the  
29 seasonal variability in the STE of O<sub>3</sub> (Fusco and Logan, 2003, [051229](#)), the geographical variability  
30 of this exchange, and the variability in the exchange between the free troposphere and the PBL in the  
31 model. In addition, the relatively coarse spatial resolution in that version of GEOS-Chem (2°×2.5°)  
32 limited the ability to provide separate estimates for cities located close to each other, and so only  
33 regional estimates were provided for the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) based on the  
34 results of Fiore et al. (2003, [051226](#)).

35 Wang et al. (2009, [622281](#)) recomputed PRB concentrations for 2001 using GEOS-Chem at  
36 higher spatial resolution (1°×1°) and not only for afternoon hours but for the daily maximum 8-h O<sub>3</sub>  
37 concentration (the base and PRB results for the 2001 model year simulation are shown in Figure 3-9  
38 for spring and Figure 3-10 for summer). These GEOS-Chem calculations represents the latest results  
39 documented in the literature. However, all models undergo continuous updating of inputs,

1 parameterizations of physical and chemical processes, and inputs and improvements in model  
2 resolution. Inputs that might be considered most relevant include emissions inventories and  
3 meteorological fields. However, the model's results may not be particularly sensitive to changes in  
4 model inputs, especially in the current context. For example, as noted above, increases in Asian  
5 emissions only accounted for an increase of 1-2 ppb in background O<sub>3</sub> even though Asian emissions  
6 have increased by about 44% from 2001 to 2006. To the extent that results from an updated model  
7 become available, they will be presented and used in the next draft of the ISA. In that case, the  
8 results shown here are to be viewed more as illustrating the type of calculations that will ultimately  
9 be used for informing NAAQS setting.

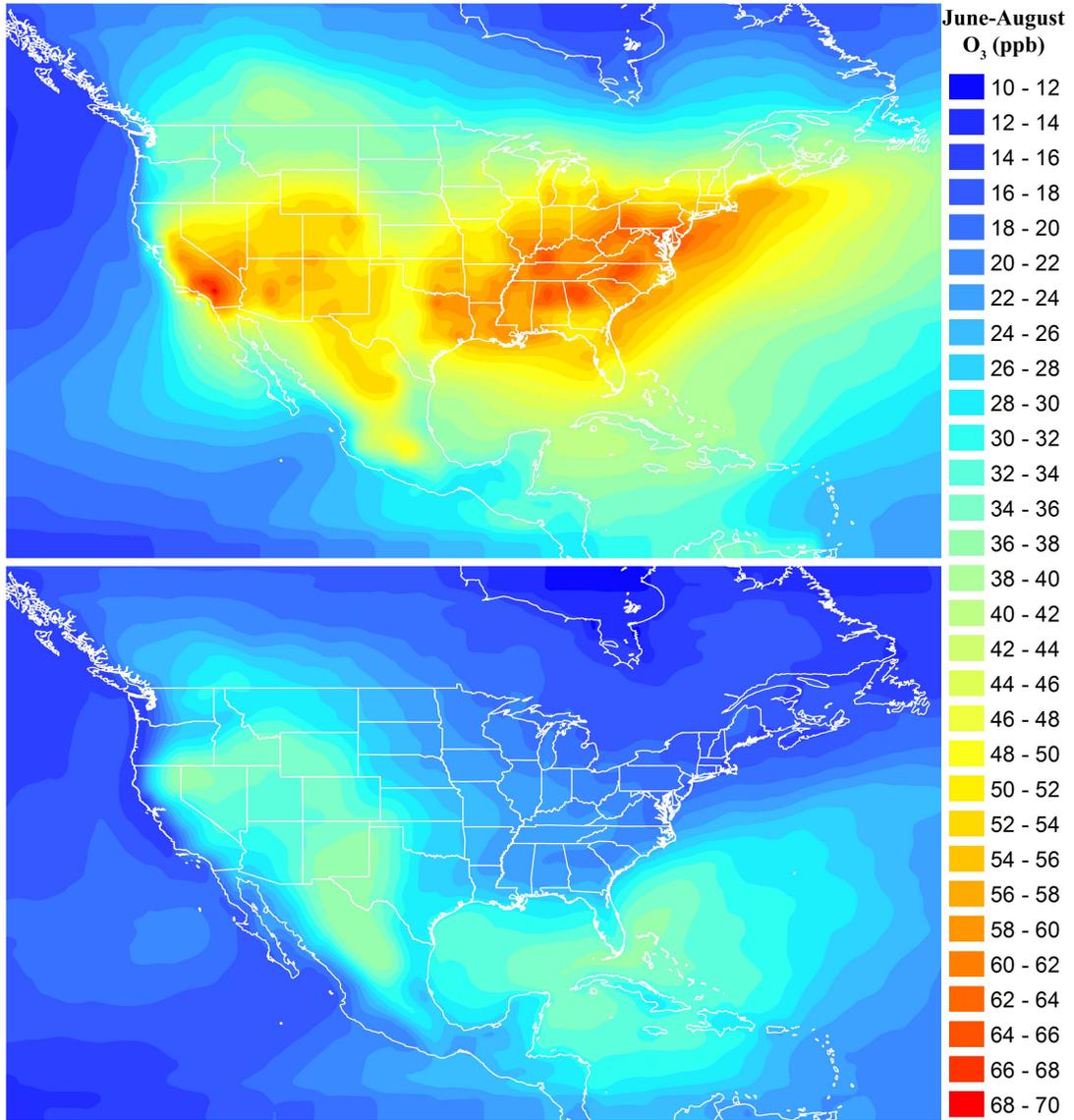
10 The base case O<sub>3</sub> concentrations show two broad maxima with highest concentrations  
11 extending throughout the Southwest, Mountainous West and the East in both spring and summer.  
12 These maxima extend over many thousands of kilometers demonstrating that O<sub>3</sub> is a regional  
13 pollutant. Low-level outflow from the Northeast, the Southwest and over the Gulf of Mexico is also  
14 apparent. The PRB O<sub>3</sub> concentrations are higher in spring than in summer over the entire U.S.  
15 However, highest concentrations are found over the Mountainous West during spring. The resulting  
16 PRB concentrations,  $26.3 \pm 8.3$  ppb for summer, are consistent with those reported by Fiore et al.  
17 (2003, [051226](#)) of  $26 \pm 7$  ppb, suggesting horizontal resolution was not a significant factor limiting  
18 the accuracy of the earlier results. In addition to computing North American PRB contributions,  
19 Wang et al. (2009, [622281](#)) also computed U.S. background concentrations (i.e., including  
20 anthropogenic contributions from Canada and Mexico) of  $29.6 \pm 8.3$  ppb with higher contributions  
21 near the Canadian and Mexican borders.

22 Panels a-d of Figure 3-11 show a comparison of O<sub>3</sub> calculated by the base and PRB model  
23 cases with measurements at low (<1500 m [1.5 km]) and high (>1500 m [1.5km]) elevation  
24 CASTNET sites. Note that all the elevated sites are located in the West. Results are then aggregated  
25 within these two sets of sites. In general, the model captures the behavior of O<sub>3</sub> observed across the  
26 concentration distribution, although there are some differences. In particular, the base model tends to  
27 under-predict O<sub>3</sub> at elevated sites. The reasons for this are not entirely clear and may be due to the  
28 under-predictions of intercontinental transport, downward transport of stratospheric O<sub>3</sub>, contributions  
29 from local and regional pollution, or some combination of these factors. Lower bounds to PRB  
30 concentrations tend to be higher by several ppb at high elevations than at low elevations, reflecting  
31 the altitude dependence of PRB sources such as stratospheric-tropospheric exchange and  
32 intercontinental transport. In addition, PRB concentrations tend to increase with increasing base  
33 model (and measured) concentrations at higher elevation sites, particularly during spring. At low  
34 elevation sites, there is some indication that PRB concentrations decrease with increasing base  
35 model concentrations at the upper end of the concentration range, i.e., during episode conditions.



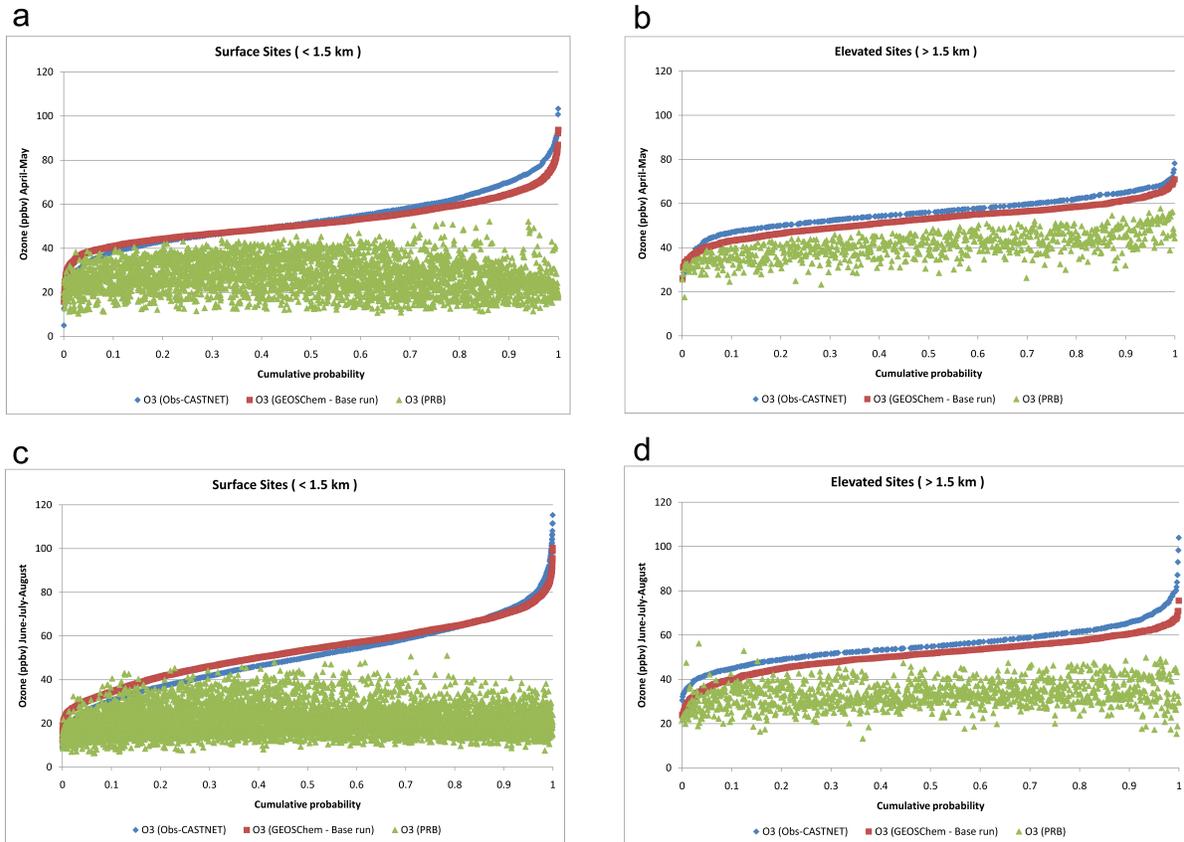
Source: Adapted with permission from Wang et al. (2009, [622281](#))

**Figure 3-9. Mean daily 8-h max ozone concentrations in surface air for the base case (top) and PRB case (bottom) in April-May, 2001.**



Source: Adapted with permission from Elsevier Ltd., Wang et al. (2009, [622281](#))

**Figure 3-10. Mean daily 8-h max ozone concentrations in surface air for base case (top) and PRB case (bottom) in June-August, 2001.**



**Figure 3-11. Distribution of ozone measured at CASTNET sites (blue diamonds), ozone calculated by the GEOS-Chem base model (red squares) and PRB ozone (green triangles) at (a) sites <1500 m elevation and (b) at sites >1500 m elevation for April – May; and (c) at sites <1500 m elevation and (d) at sites >1500 m elevation for June-July-August.**

1 Table 3-1 shows mean concentrations ( $\pm$  SD) of daily max 8-h avg O<sub>3</sub> concentrations at these  
 2 CASTNET sites and GEOS-Chem predictions for the base model and PRB for spring and summer.  
 3 At eastern sites, seasonal maxima occur during spring or summer. In the East (the first five entries in  
 4 Table 3-1), the base model mean is generally within a few ppb of measurements during the spring.  
 5 The largest difference at the sites shown in Table 3-1 occurs at the Everglades site, where mean  
 6 spring concentrations are over-predicted by 10 ppb. At most western sites, seasonal maxima are  
 7 observed to occur during spring as opposed to summer. The base model under-predicts mean  
 8 concentrations during spring at the high-elevation sites: Centennial by ~8 ppb and at Yellowstone by  
 9 ~5 ppb. However, maximum concentrations at these sites are too high by only 5 and 3 ppb. At the  
 10 other western sites examined, the model-predicted means do not differ significantly from the  
 11 measurements during spring, except at Pinnacles, NM.

12 Disagreements between model-predicted versus observed mean concentrations at eastern sites  
 13 tend to be larger during summer than during spring with over-predictions by the base model

1 generally higher and at more locations. In particular, summer mean O<sub>3</sub> concentrations at the  
2 Everglades site are over-predicted by 21 ppb and by 10 ppb at the Virgin Islands site. The Virgin  
3 Islands NP site appears to have not been affected by U.S. emissions, as can be seen from the close  
4 agreement between the base case and the PRB case and from wind roses calculated for these two  
5 sites indicating that flows affecting these sites are mainly easterly/southeasterly in summer. The  
6 over-predictions at the Virgin Islands site imply that air affecting this site, i.e., coming from the  
7 tropical Atlantic Ocean, is too high. As a result, inflow into the Gulf of Mexico may also be too high.  
8 Similar considerations apply to the excess at the Everglades site. However, the Everglades site is  
9 often subject to flow from the northeast and production of O<sub>3</sub> from emissions from Miami.

10 The base model under-predicts summer mean O<sub>3</sub> concentrations by 4 and 7 ppb at the  
11 Yellowstone and Centennial sites, with much larger under-predictions at the Lassen and Pinnacles  
12 sites. At the other western sites examined, the model either over-predicts or is essentially in  
13 agreement with observations. It is not clear why the under-predictions at the California sites are so  
14 large during summer. Under-estimation of local emissions may be part of the cause.

15 These model-predicted values can be compared to the baseline O<sub>3</sub> concentrations estimated by  
16 Chan and Vet (2010, [679710](#)) of 37 ± 9 ppb for the continental eastern U.S., 51 ± 6 ppb for the  
17 continental western U.S., 44 ± 10 ppb for the coastal western U.S. from March to May; and 32 ±  
18 2 ppb for the continental eastern U.S., 25 ± 10 ppb for the continental western U.S. and 39 ± 12 ppb  
19 for the coastal western U.S. from June to August.

20 Table 3-2 shows seasonal maximum concentrations measured at the same sites as in Table 3-1  
21 for spring (April-May, 61 days) and summer (June-July-August, 92 days) in 2001 and maximum O<sub>3</sub>  
22 concentrations calculated for the base case and the PRB case for the same time frame by GEOS-  
23 Chem at 1°×1° resolution. During the spring, maximum concentrations measured at the sites chosen  
24 ranged from 50 to 89 ppb at the CASTNET sites; GEOS-Chem predictions range from 52 to 72 ppb,  
25 and from 40 to 57 ppb for PRB. During summer, maximum concentrations measured at the  
26 CASTNET sites chosen ranged from 52 to 101 ppb; GEOS-Chem predictions range from 49 to  
27 90 ppb, and from 34 to 51 ppb for PRB.

28 The time series of the model predictions for the daily max 8-h avg O<sub>3</sub> concentrations, the  
29 corresponding PRB concentrations and measurements at the CASTNET sites shown in Table 3-1 and  
30 Table 3-2 are given in Chapter 3 Appendix, Figure 3A-1 through Figure 3A-15. In general, model  
31 predicted concentrations and observations tend to be slightly better correlated with observations at  
32 eastern sites (mean: 0.60, range 0.52-0.74) than at western sites (mean: 0.53, range 0.32-0.69). The  
33 lowest model-observed correlation (0.32) is found at Big Bend NP, TX, where rather large over-  
34 predictions are also found. Both results may be due in part to errors in Mexican emissions.  
35 Correlations between base model and PRB O<sub>3</sub> concentrations are very low and slightly negative at  
36 most eastern sites (mean: 0.01, range -0.27 to 0.45) and become larger at western sites (mean: 0.56,  
37 range (0.33-0.69). The Voyageurs NP site in Minnesota is the only 'eastern' site showing a positive  
38 correlation (r = 0.45) between base and PRB model O<sub>3</sub> concentrations. The low correlations at the  
39 eastern sites chosen arise because base model O<sub>3</sub> and PRB concentrations tend to be anti-correlated

- 1 at high O<sub>3</sub> concentrations, but are positively correlated at the lower end of the concentration range.
- 2 At high elevation western sites, on the other hand, base model and PRB O<sub>3</sub> concentrations tend to be
- 3 positively correlated throughout much of the concentration range.

**Table 3-1. Seasonal means of the daily max 8-h avg ozone concentrations in spring and summer at selected CASTNET and other National Park Service monitoring sites in the continental U.S. and in the U.S. Virgin Islands, in 2001. GEOS-Chem and PRB are included for comparison**

Sites	Spring (April-May)		Summer (June-August)	
	CASTNET ± SD	GEOS-Chem (PRB)	CASTNET ± SD	GEOS-Chem (PRB)
Acadia NP, ME	47.7 ± 9.9	48.2 ± 7.8 (29.8 ± 7.4)	50.6 ± 19.4	52.8 ± 15.4 (16.8 ± 5.6)
Everglades NP, FL	41.3 ± 12.4	51.2 ± 8.9 (32.9 ± 6.5)	24.3 ± 8.5	45.7 ± 6.8 (36.4 ± 4.2)
Crockett, KY	57.9 ± 9.9	56.8 ± 6.3 (27.1 ± 6.6)	54.5 ± 10.8	57.2 ± 7.1 (22.7 ± 5.6)
Coffeeville, MS	52.9 ± 10.9	53.8 ± 5.9 (27.5 ± 5.1)	50.8 ± 12.8	57.4 ± 9.4 (22.6 ± 5.0)
Voyageurs NP, MN	36.9 ± 10.7	42.9 ± 5.5 (26.3 ± 6.4)	40.2 ± 9.3	35.3 ± 9.6 (19.6 ± 4.8)
Big Bend NP, TX	39.1 ± 5.4	49.9 ± 6.0 (37.0 ± 7.0)	43.3 ± 9.1	50.9 ± 5.6 (36.1 ± 4.8)
Rocky Mtn. NP, CO	49.7 ± 11.9	51.9 ± 8.2 (39.3 ± 7.5)	47.7 ± 10.1	57.7 ± 6.4 (33.2 ± 5.6)
Mesa Verde NP, CO	56.0 ± 4.9	55.9 ± 6.1 (40.6 ± 6.3)	54.4 ± 6.4	58.2 ± 4.8 (33.6 ± 5.8)
Yellowstone NP, WY	56.1 ± 7.4	51.0 ± 7.1 (42.3 ± 5.6)	50.6 ± 5.4	46.5 ± 5.8 (34.7 ± 5.3)
Centennial, WY	59.9 ± 5.7	52.1 ± 7.1 (40.7 ± 6.1)	59.5 ± 5.5	52.2 ± 4.5 (34.2 ± 5.1)
Canyonlands NP, UT	54.3 ± 4.2	53.9 ± 6.4 (41.0 ± 5.5)	56.0 ± 6.4	53.2 ± 5.1 (33.8 ± 5.9)
Glacier NP, MT	41.3 ± 4.6	44.9 ± 5.0 (36.3 ± 5.2)	35.4 ± 7.1	36.3 ± 5.3 (29.6 ± 7.4)
Mt. Rainier NP, WA	39.7 ± 6.9	41.1 ± 6.4 (32.0 ± 7.1)	32.8 ± 12.7	34.6 ± 10.0 (19.6 ± 5.6)
Lassen Volcanic NP, CA	51.4 ± 7.9	48.9 ± 6.6 (39.6 ± 6.5)	54.7 ± 10.0	43.6 ± 7.5 (34.2 ± 7.5)
Pinnacles NM, CA	57.1 ± 10.6	47.6 ± 7.7 (26.8 ± 9.1)	55.3 ± 12.9	42.6 ± 11.9 (15.4 ± 5.2)
Virgin Islands NP	21.6 ± 6.4	31.7 ± 7.0 (27.0 ± 5.3)	18.3 ± 3.7	28.2 ± 5.3 (25.8 ± 5.5)

**Table 3-2. Seasonal maximums of the daily max 8-h avg ozone concentrations in spring and summer at selected CASTNET and other National Park Service monitoring sites in the continental U.S. and in the U.S. Virgin Islands, in 2001. GEOS-Chem and PRB are included for comparison**

Sites	Spring (April-May)		Summer (June-August)	
	CASTNET	GEOS-Chem (PRB)	CASTNET	GEOS-Chem (PRB)
Acadia NP, ME	85.1	68.1 (42.7)	101.0	90.3 (33.7)
Everglades NP, FL	65.4	71.7 (45.7)	61.3	72.5 (51.1)
Crockett, KY	81.5	71.4 (41.2)	78.0	72.4 (37.8)
Coffeeville, MS	77.9	66.6 (36.6)	81.0	85.1 (37.9)
Voyageurs NP, MN	61.0	61.1 (40.1)	70.4	58.7 (32.5)
Big Bend NP, TX	50.5	62.5 (52.2)	67.5	64.5 (48.0)
Rocky Mountain NP, CO	68.3	68.4 (56.6)	80.3	72.8 (46.1)
Mesa Verde NP, CO	65.3	70.9 (53.8)	72.9	68.5 (47.1)
Yellowstone NP, WY	68.9	65.7 (55.3)	63.9	59.5 (47.8)
Centennial, WY	70.9	66.0 (52.1)	74.4	61.7 (45.5)
Canyonlands NP, UT	64.0	65.3 (53.2)	76.0	64.2 (48.4)
Glacier NP, MT	54.4	52.8 (45.8)	52.2	48.9 (46.9)
Mt. Rainier NP, WA	61.6	52.3 (44.6)	67.9	59.6 (40.1)
Lassen Volcanic NP, CA	71.5	60.3 (54.0)	79.0	61.6 (51.5)
Pinnacles NM, CA	88.8	68.4 (50.8)	86.5	73.4 (29.6)
Virgin Islands NP	35	47.1 (38.1)	27	45.9 (45.1)

## 3.5. Monitoring

### 3.5.1. Routine Monitoring Techniques

1 The Federal Reference Method (FRM) for O<sub>3</sub> measurement is called the Chemiluminescence  
2 Method (CLM) and is based on the detection of chemiluminescence resulting from the reaction of O<sub>3</sub>  
3 with ethylene gas. The first ultraviolet (UV) absorption photometric analyzers were approved as  
4 Federal Equivalent Methods (FEMs) in 1977 and gained rapid acceptance for NAAQS compliance  
5 purposes due to ease of operation, relatively low cost, and reliability. The UV absorption method is  
6 based on the principle that O<sub>3</sub> molecules absorb UV radiation at a wavelength of 254 nm from a  
7 mercury lamp. The concentration of O<sub>3</sub> is computed from Beers law using the radiation absorbed  
8 across a fixed path length, the absorption coefficient, and the measured pressure and temperature in  
9 the detection cell. UV absorption photometry is the predominant method for assessing compliance  
10 with the NAAQS for O<sub>3</sub>. Almost all of the state or local air monitoring stations (SLAMS) that  
11 reported data to EPA Air Quality System (AQS) from 2005 to 2009 used UV absorption photometer  
12 FEMs. No CLM monitors, approved as FRMs or FEMs, reported O<sub>3</sub> data to AQS from 2005 to 2009  
13 and only one monitor reported data using a long-path or open path Differential Optical Absorption  
14 Spectrometer (DOAS) FEM during this period.

15 The rationale, history, and calibration of O<sub>3</sub> measurements were summarized in the 1996 O<sub>3</sub>  
16 AQCD (U.S. EPA, 1996, [017831](#)) and the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) and focused on  
17 the state of ambient O<sub>3</sub> measurements at that time as well as evaluation of interferences and new  
18 developments. This discussion will continue with the current state of O<sub>3</sub> measurements,  
19 interferences, and new developments for the period 2005 to 2009.

20 UV O<sub>3</sub> monitors use mercury lamps as the source of UV radiation and employ an O<sub>3</sub> scrubber  
21 (typically manganese dioxide) to generate an O<sub>3</sub>-free air flow to serve as a reference channel for O<sub>3</sub>  
22 measurements. There are known interferences with UV O<sub>3</sub> monitors. The 2006 O<sub>3</sub> AQCD (U.S. EPA,  
23 2006, [088089](#)) reported on the investigation of the effects of water vapor, aromatic compounds,  
24 ambient particles, mercury vapor and alternative materials in the instrument's O<sub>3</sub> scrubber. The  
25 overall conclusions from the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) review of the scientific  
26 literature are briefly summarized below.

27 Kleindienst et al., (1993, [043956](#)) found water vapor to have no significant impact and  
28 aromatic compounds to have a minor impact (as much as 3% higher than the FRM extrapolated to  
29 ambient conditions) on UV absorption measurements. UV O<sub>3</sub> monitor response evaluated by  
30 chamber testing using cigarette smoke, reported an elimination of the O<sub>3</sub> monitor response to the  
31 smoke when a particle filter was used that filtered out particles less than 0.2 μm in diameter  
32 (Arshinov et al., 2002, [080718](#)). One study (Leston et al., 2005, [080717](#)) in Mexico City compared a  
33 UV O<sub>3</sub> FEM to a CLM FRM. The UV FEM commonly reported consistently higher O<sub>3</sub> than the  
34 CLM FRM. The typical difference was 20 ppb with a range up to 50 ppb. Leston et al., (2005,  
35 [080717](#)) also presented smog chamber data which demonstrated that heated metal and heated silver

1 wool scrubbers perform better in the presence of aromatic hydrocarbon irradiations than manganese  
2 dioxide scrubbers when compared to the FRM. They also suggested the use of humidified calibration  
3 gas and alternative scrubber materials to improve UV O<sub>3</sub> measurements. Some O<sub>3</sub> monitor  
4 manufacturers now offer heated silver wool scrubbers as an alternative to manganese dioxide.  
5 Another possible solution to the O<sub>3</sub> scrubber problem may be the use of a gas phase scrubber such as  
6 NO. A commercial version of this has recently been introduced by 2B Technologies as an option on  
7 their model 202 FEM; however, it has not been field tested or approved for use as an FEM.

8 Subsequent study of UV monitors by Williams et al. (2006, [595152](#)) concluded that well  
9 maintained monitors showed no significant interferences when operated in locations with significant  
10 concentrations of potentially interfering VOCs including Nashville, Houston, and the Gulf of Maine.  
11 Monitors were tested in urban and suburban environments, as well as on board a ship in both  
12 polluted and clean marine air. Comparisons of UV measurements to a non-FRM/FEM NO based  
13 CLM demonstrated agreement to within 1%. At the Houston location, they did observe a brief period  
14 on one day for about 30 minutes where the UV measurements exceeded the CLM by about 8 ppb  
15 (max). This was attributed to probable instrument malfunction.

16 Wilson and Birks (2006, [595155](#)) investigated water vapor interference in O<sub>3</sub> measurements by  
17 four different UV monitors. In extreme cases where a rapid step change in relative humidity between  
18 0 and 90% was presented, large transitory responses (tens to hundreds of ppb) were found for all  
19 monitors tested. Rapid changes in relative humidity such as this would not be expected during  
20 typical ambient O<sub>3</sub> measurements and could only be expected during measurement of vertical  
21 profiles from balloon or aircraft. The magnitude of the interference and the direction (positive or  
22 negative) was dependent on the manufacturer and model. Wilson and Birks (2006, [595155](#)) also  
23 hypothesized that water vapor interference is caused by physical interactions of water vapor on the  
24 detection cell. The O<sub>3</sub> scrubber was also thought to act as a reservoir for water vapor and either  
25 added or removed water vapor from the air stream, subsequently affecting the detector signal and  
26 producing either a positive or negative response. They demonstrated the use of a Nafion<sup>®</sup> permeation  
27 membrane just before the O<sub>3</sub> detection cell to remove water vapor and eliminate this interference.

28 Dunlea et al. (2006, [595108](#)) evaluated multiple UV O<sub>3</sub> monitors with two different O<sub>3</sub>  
29 scrubber types (manganese dioxide and heated metal wool) in Mexico City. Large spikes in O<sub>3</sub>  
30 concentrations were observed while measuring diesel exhaust where large increases in particle  
31 number density were observed. The interference due to small particles passing through the Teflon<sup>®</sup>  
32 filter and scattering/absorbing light in the detection cell were estimated to cause at most a 3%  
33 increase in measurements in typical ambient air environments. This estimate pertains to  
34 measurements in the immediate vicinity of fresh diesel emissions and most monitor siting guidelines  
35 would not place the monitor close to such sources, so actual interferences are expected to be much  
36 less than 3%. Dunlea et al. (2006, [595108](#)) also observed no evidence for either a positive or  
37 negative interference or dependence due to variations in aromatics during their field study.

38 Li et al. (2006, [633892](#)) verified early reports of gas phase mercury interference with the UV  
39 O<sub>3</sub> measurement. They found that 300 ng/m<sup>3</sup> of mercury produced an instrument response of about

1 35 ppb O<sub>3</sub>. Background concentrations of mercury are around 1-2 ng/m<sup>3</sup> and expected to produce an  
2 O<sub>3</sub> response that would be <1 ppb.

3 Spicer et al. (2010, [670424](#)) examined potential UV O<sub>3</sub> monitor interferences by water vapor,  
4 mercury, aromatic compounds, and reaction products from smog chamber simulations. Laboratory  
5 tests showed little effect of changing humidity on conventional FEM UV O<sub>3</sub> monitors with  
6 manganese dioxide or heated metal wool scrubbers in the absence of other interferences. Mercury  
7 vapor testing produced an O<sub>3</sub> response by the UV monitors that was <1 ppb O<sub>3</sub> per 1 ppt (about  
8 8 ng/m<sup>3</sup>) mercury vapor. Interference by aromatic compounds at low (3% RH) and high (80% RH)  
9 humidity showed some positive responses that varied by UV monitor and ranged from 0 to 2.2 ppb  
10 apparent O<sub>3</sub> response, per ppb of aromatic compound tested. The authors acknowledged that the  
11 aromatic compounds most likely to interfere are rarely measured in the atmosphere and therefore,  
12 make it difficult to assess the impact of these compounds during ambient air monitoring.  
13 Comparison of UV and CLM responses to photochemical reaction products in smog chamber  
14 simulations at 74 to 85% RH showed varied responses under low (0.125 ppmv/0.06 ppmv) to high  
15 (0.50 ppmv/0.19 ppmv) hydrocarbon/NO<sub>x</sub> conditions. The conventional UV monitors were as much  
16 as 2 ppb higher than the CLM under low hydrocarbon/NO<sub>x</sub> conditions and 6 ppb higher under the  
17 high hydrocarbon/NO<sub>x</sub> conditions. Two FEM UV monitors were co-located at six sites in Houston  
18 from May to October, 2007 with one UV monitor equipped with Nafion® permeation membrane.  
19 The average difference between 8-h daily max O<sub>3</sub> concentrations using the UV and the UV with  
20 Nafion® permeation membrane ranged from -4.0 to 4.1 ppb.

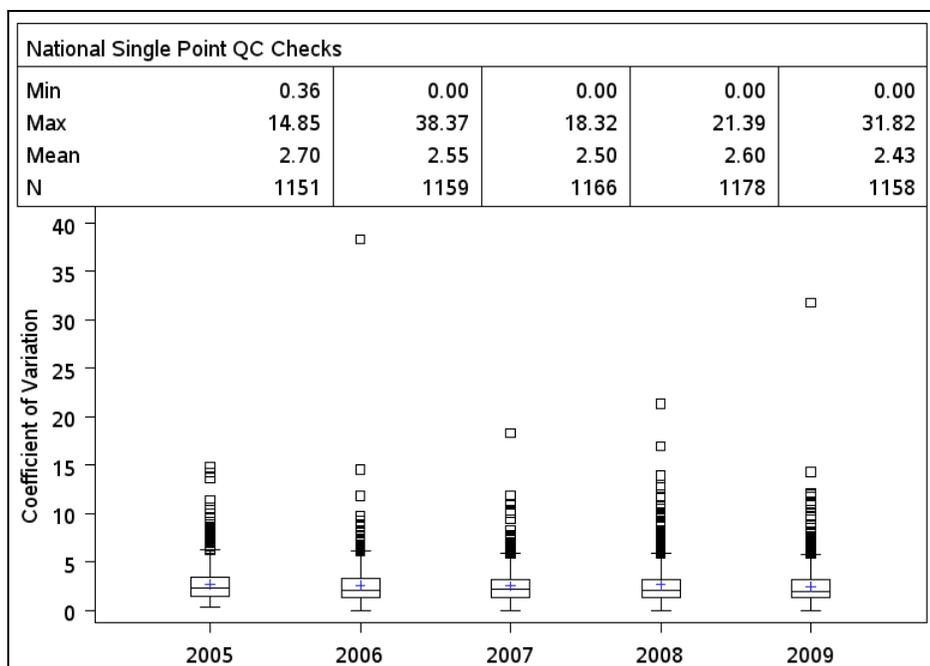
### 3.5.2. Precision and Bias

21 In order to provide decision makers with an assessment of data quality, EPA's Quality  
22 Assurance (QA) group derives estimates of both precision and bias for O<sub>3</sub> and the other gaseous  
23 criteria pollutants from the biweekly single point quality control (QC) checks using calibration gas,  
24 performed at each site by the monitoring agency. The single point QC checks are typically performed  
25 at concentrations around 90 ppb. Annual summary reports of precision and bias can be obtained for  
26 each monitoring site at <http://www.epa.gov/ttn/amtic/qareport.html> (U.S. EPA, 2011, [677486](#)). The  
27 assessment of precision and bias are based on the percent-difference values, calculated from single  
28 point QC checks. The percent difference is based on the difference between the pollutant  
29 concentration indicated by monitoring equipment and the known (actual) concentration of the  
30 sample used during the QC check. The monitor precision is estimated from the 90% upper  
31 confidence limit of the coefficient of variation (CV) of relative percent difference (RPD) values. The  
32 bias is estimated from the 95% upper confidence limit on the mean of the absolute values of percent  
33 differences. The data quality goal for O<sub>3</sub> precision and bias at the 90 and 95% upper confidence  
34 limits is 7% (40 CFR Part 58, Appendix A (1986, [035997](#))). Table 3-3 presents a summary of the  
35 number of monitors that meet the precision and bias goal of 7% for 2005 to 2009. Greater than 96%  
36 of O<sub>3</sub> monitors met the precision and bias goal between 2005 and 2009.

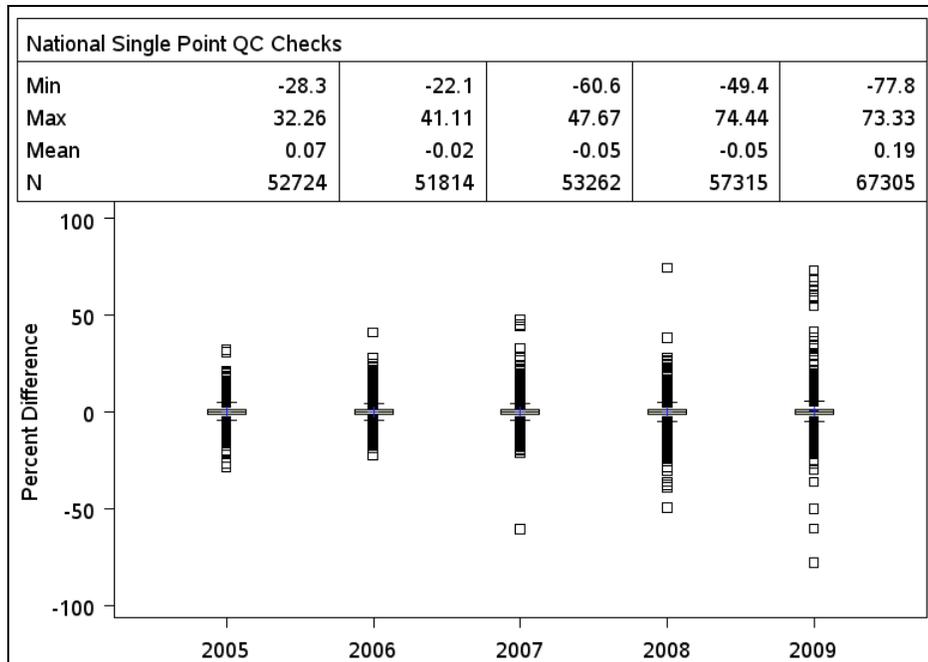
**Table 3-3. Summary of monitors meeting 40 CFR Part 58, Appendix A Precision and Bias Goals**

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

- 1 Another way to look at the precision and bias information from the monitoring network is to
- 2 present box plots of the monitors' individual precision and percent-difference data; Figure 3-12 and
- 3 Figure 3-13 included this information for O<sub>3</sub> monitors operating from 2005 to 2009.



**Figure 3-12. Box plots of precision data by year (2005-2009) for all ozone monitors reporting single-point QC check data to AQS.**



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

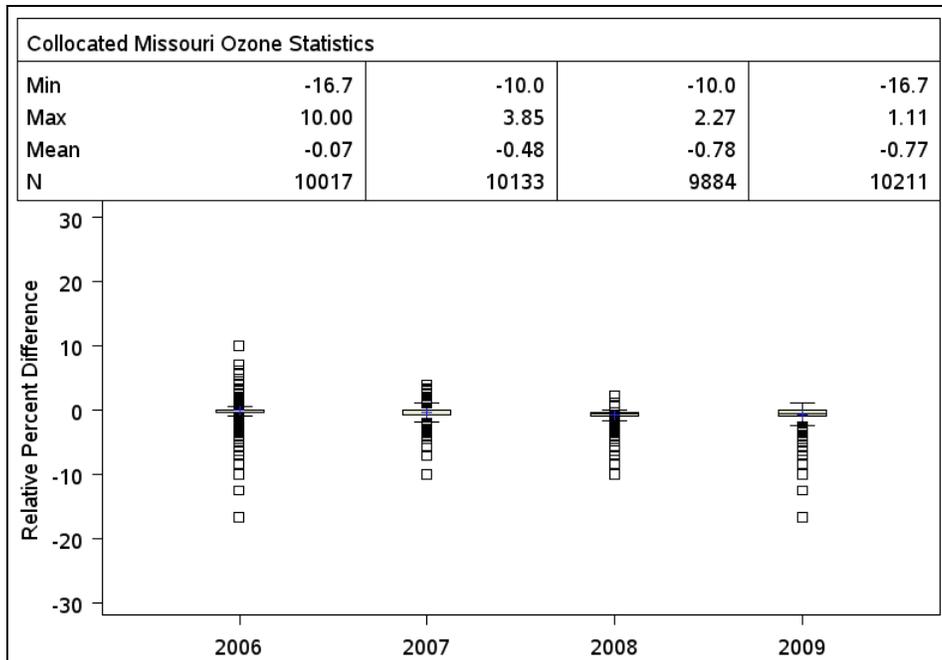


Figure 3-14. Box plots of RPD data by year for the two co-located sites in Missouri from 2006-2009.

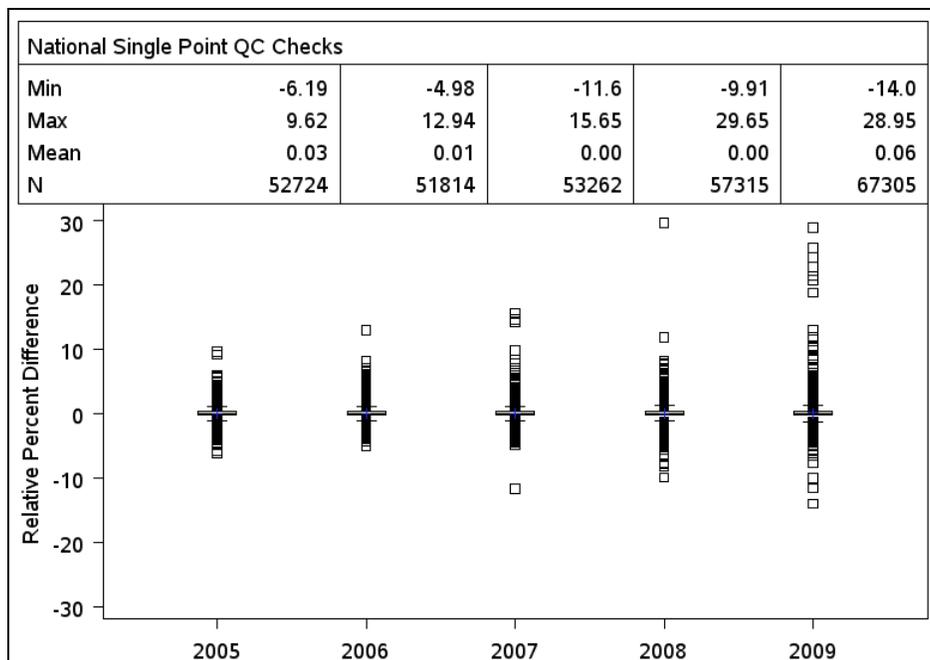


Figure 3-15. Box plots of RPD data by year for all U.S. ozone sites reporting single-point QC check data to AQS from 2005-2009.

### 3.5.3. Performance Specifications

1           The performance specifications for evaluating and approving new FEMs in accordance with  
2 40 CFR Part 53 (1976, [041090](#)) are provided in Table 3-4. These specifications were developed and  
3 originally published in the Federal Register in 1975 (1975, [043954](#)). Modern, commercially-  
4 available 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 typical  
6 vendor-stated performance for the LDL is less than 0.60 ppb. The amount of allowable interference  
7 equivalent for total interference substances is 60 ppb, and the current NAAQS for O<sub>3</sub> is 75 ppb, with  
8 an averaging time of 8 hours. Improvements in new measurement technology have occurred since  
9 these performance specifications were originally developed. These specifications should be revised  
10 to more accurately reflect the necessary performance requirements for O<sub>3</sub> monitors used to support  
11 the current NAAQS.

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

<b>Parameter</b>	<b>Specification</b>
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

12           The calibration of O<sub>3</sub> monitors was summarized in detail in the 1996 O<sub>3</sub> AQCD (U.S. EPA,  
13 1996, [017831](#)). The calibration of O<sub>3</sub> monitors is done using an O<sub>3</sub> generator and UV photometers.  
14 UV photometry is the prescribed procedure for the calibration of reference methods to measure O<sub>3</sub> in  
15 the atmosphere. Because O<sub>3</sub> is unstable and cannot be stored, the O<sub>3</sub> calibration procedure  
16 specifically allows the use of transfer standards for calibrating ambient O<sub>3</sub> monitors. A transfer  
17 standard is calibrated against a standard of high authority and traceability and then moved to another  
18 location for calibration of O<sub>3</sub> monitors. The EPA and the National Institute of Standards and

1 Technology (NIST) have established a network of standard reference photometers (SRPs) that are  
2 used to verify transfer standards. The International Bureau of Weights and Measures (BIPM)  
3 maintain one NIST SRP (SRP27) as the World's O<sub>3</sub> reference standard. NIST maintains two SRPs  
4 (SRP0 and SRP2) that are used for comparability to ten other SRPs maintained by the EPA's  
5 Regional QA staff.

6 SRPs have been compared to other reference standards. Tanimoto et al. (2006, [595131](#))  
7 compared NIST SRP35, owned by the National Institute for Environmental Studies in Japan, to gas  
8 phase titration (GPT). The SRP was found to be 2% lower than GPT. GPT is no longer used as a  
9 primary or transfer standard in the U.S. Viallon et al. (2006, [595145](#)) compared SRP27 built at BIPM  
10 to four other NIST SRPs maintained by BIPM (SRP28, SRP31, SRP32, and SRP33). A minimum  
11 bias of +0.5% was found for all SRP measurement results, due to use of the direct cell length  
12 measurement for the optical path length; this bias was accounted for by applying the appropriate  
13 correction factor. Study of the bias-corrected SRPs showed systematic biases and measurement  
14 uncertainties for the BIPM SRPs. A bias of -0.4% in the instrument O<sub>3</sub> mole fraction measurement  
15 was identified and attributed to non-uniformity of the gas temperature in the instrument gas cells,  
16 which was compensated by a bias of +0.5% due to an under-evaluation of the UV light path length in  
17 the gas cells. The relative uncertainty of the O<sub>3</sub> absorption cross section was 2.1% at 253.65 nm and  
18 this was proposed as an internationally accepted consensus value until sufficient experimental data is  
19 available to assign a new value.

20 In November, 2010, the EPA revised the Technical Assistance Document for *Transfer*  
21 *Standards for Calibration of Air Monitoring Analyzers for Ozone* (2010, [677553](#)) that was first  
22 finalized in 1979 (U.S. EPA, 1979, [039211](#)). The revision removed methods no longer in use and  
23 updated definitions and procedures where appropriate. In the revised document, the discussion of  
24 transfer standards for O<sub>3</sub> applies to the family of standards that are used beyond SRPs or Level 1  
25 standards. To reduce confusion, EPA reduced the number of common terms that were used in the  
26 past such as: primary standard, local primary standard, transfer standard, and working standard.  
27 Beyond the SRPs, all other standards are considered transfer standards. The revised Ozone Technical  
28 Assistance Document is available at  
29 <http://www.epa.gov/ttn/amtic/files/ambient/qaqc/OzoneTransferStandardGuidance.pdf> (U.S. EPA,  
30 2010, [677553](#)).

### 3.5.5. Other Monitoring Techniques

#### 3.5.5.1. Portable UV Ozone Monitors

31 Small, lightweight, and portable UV O<sub>3</sub> monitors with low power consumption are  
32 commercially available. These monitors are based on the same principle of UV absorption by O<sub>3</sub> at  
33 254 nm. Monitors of this type are typically used for vertical profiling using balloons, kites, or light  
34 aircraft where space and weight are limited. They have also been used for monitoring at remote

1 locations such as National Parks. Burley and Ray (2007, [149069](#)) compared portable O<sub>3</sub> monitor  
2 measurements to those from a conventional UV monitor in Yosemite National Park. Calibrations of  
3 the portable O<sub>3</sub> monitors against a transfer standard resulted in an overall precision of ± 4 ppb and  
4 accuracy of ± 6%. Field measurement comparisons between the portable and conventional monitor  
5 at Turtleback Dome showed the portable monitor to be 3.4 ppb lower on average, with daytime  
6 deviation typically on the order of 0-3 ppb. Agreement between the portable and conventional  
7 monitor during daylight hours (9:00 a.m. to 5:00 p.m. PST) resulted in an R<sup>2</sup> of 0.95, slope of 0.95,  
8 and intercept of 0.36 ppb. Significant deviations were observed in the predawn hours where the  
9 portable monitor was consistently low. These deviations were attributed to the difference in sampling  
10 inlet location. The portable monitor was located at 1.3 m above ground and the conventional monitor  
11 was located at 10 m above ground. Agreement between the portable and conventional monitors for  
12 all hours sampled resulted in an R<sup>2</sup> of 0.88, slope of 1.06, and intercept of -6.8 ppb. Greenberg et al.  
13 (2009, [595140](#)) also compared a portable UV O<sub>3</sub> monitor to a conventional UV monitor in  
14 Mexico City and obtained good agreement for a 14 day period with an R<sup>2</sup> of 0.97, slope of 0.97, and  
15 intercept of 6 ppb. One portable O<sub>3</sub> monitor was recently approved as an FEM (EQOA-0410-190) on  
16 April 27, 2010 (75 FR 22126) (2010, [687659](#)).

### **3.5.5.2. Teledyne Advanced Pollution Instrumentation Model 265E CLM**

17 The Teledyne Advanced Pollution Instrument (TAPI) NO-based chemiluminescence  
18 instrument is currently undergoing FEM testing. It may also be designated as a second or  
19 replacement FRM since the ethene based FRMs are no longer manufactured. Although the TAPI is a  
20 relatively new instrument, other NO-based CLM instruments have been custom built for various  
21 field studies since the early 1970s. A commercial version that measured both O<sub>3</sub> and NO<sub>x</sub> was  
22 offered by Aerochem Research Laboratories (Princeton, NJ) in the early 1970s but failed to gain  
23 commercial acceptance. Initial testing with SO<sub>2</sub>, NO<sub>2</sub>, Cl<sub>2</sub>, C<sub>2</sub>H<sub>2</sub>, C<sub>2</sub>H<sub>4</sub> and C<sub>3</sub>H<sub>6</sub> (Stedman et al.,  
24 1972, [033730](#)) failed to identify any interferences. In the intervening years, custom built versions  
25 have not been found to have any interferences; however, they do experience a slight decrease in  
26 response with increasing relative humidity (due to quenching of the excited species by the water  
27 molecules). The TAPI instrument solves this problem with the use of a Nafion<sup>®</sup> membrane dryer. A  
28 custom built instrument similar to the 265E was used by Williams et al. (2006, [595152](#)) in Houston,  
29 TX; Nashville, TN; and aboard ship along the New England coast. It was found to be in good  
30 agreement with a standard UV based FEM and with a custom built Differential Optical Absorption  
31 Spectrometer (DOAS).

### **3.5.5.3. Passive Air Sampling Devices and Sensors**

32 A passive O<sub>3</sub> sampling device depends on the diffusion of O<sub>3</sub> in air to a collecting or indicating  
33 medium. In general, passive samplers are not adequate for compliance monitoring because of the  
34 limitations in averaging time (typically one week or more), particularly for O<sub>3</sub>. However, these  
35 devices are valuable for personal human exposure estimates and for obtaining long-term data in rural

1 areas where conventional UV monitors are not practical or feasible to deploy. The 1996 O<sub>3</sub> AQCD  
2 (U.S. EPA, 1996, [017831](#)) provided a detailed discussion of passive samplers, along with the  
3 limitations and uncertainties of the samplers evaluated and published in the literature from 1989 to  
4 1995. The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) provided a brief update on available passive  
5 samplers developed for use in direct measurements of personal exposure published through 2004.  
6 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) also noted the sensitivity of these samplers to wind  
7 velocity, badge placement, and interference by other co-pollutants that may result in measurement  
8 error.

9 Subsequent evaluations of passive diffusion samplers in Europe showed good correlation  
10 when compared to conventional UV O<sub>3</sub> monitors, but a tendency for the diffusion samplers to  
11 overestimate the O<sub>3</sub> concentration (Buzica et al., 2008, [595173](#); Gottardini et al., 2010, [562911](#);  
12 Vardoulakis et al., 2009, [595141](#)). The bias of O<sub>3</sub> diffusion tubes were also found to vary with  
13 concentration, season, and exposure duration (Vardoulakis et al., 2009, [595141](#)). Development of  
14 simple, inexpensive, passive O<sub>3</sub> measurement devices that rely on O<sub>3</sub> detection papers and a variety  
15 of sensors with increased time resolution (sampling for hours instead of weeks) and improved  
16 sensitivity have been reported (Ebeling et al., 2009, [595115](#); Maruo, 2007, [595102](#); Maruo et al.,  
17 2010, [595104](#); Miwa et al., 2009, [595110](#); O-Keeffe et al., 2007, [595114](#); Ohira et al., 2009, [595113](#);  
18 Utembe et al., 2006, [595137](#)). Limitations for some of these sensors and detection papers include air  
19 flow dependence and relative humidity interference.

#### 3.5.5.4. Differential Optical Absorption Spectrometry

20 Optical remote sensing methods can provide direct, sensitive, and specific measurements of O<sub>3</sub>  
21 over a broad area or open path in contrast with conventional single-point UV monitors. The 1996 O<sub>3</sub>  
22 AQCD (U.S. EPA, 1996, [017831](#)) provided a brief discussion of DOAS for O<sub>3</sub> measurements and  
23 cited references to document the sensitivity (1.5 ppb for a 1-minute averaging time), correlation ( $r =$   
24 0.89), and agreement (on the order of 10%) with UV O<sub>3</sub> monitors (Stevens et al., 1993, [046404](#)). The  
25 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) provided an update on DOAS where a positive  
26 interference due to an unidentified absorber was noted (Reisinger, 2000, [053936](#)).

27 More recent study of the accuracy of UV absorbance monitors by Williams et al. (2006,  
28 [595152](#)) compared UV and DOAS measurements at two urban locations. In order to compare the  
29 open path measurements and UV, the data sets were averaged to 30-minute periods and only data  
30 when the boundary layer was expected to be well mixed (between 10:00 a.m. and 6:00 p.m. CST)  
31 were evaluated. The comparisons showed variations of no more than  $\pm 7\%$  (based on the slope of the  
32 LLS regression over a concentration range from about 20 to 200 ppb) and good correlation ( $R^2 =$   
33 0.96 and 0.98). Lee et al. (2008, [595175](#)) evaluated DOAS and UV O<sub>3</sub> measurements in Korea and  
34 found the average DOAS concentration to be 8.6% lower than the UV point measurements with a  
35 good correlation ( $R^2 = 0.94$ ).

36 DOAS has also been used for the measurement of HNO<sub>2</sub> (or HONO). DOAS was compared to  
37 chemical point-measurement methods for HONO. Acker et al. (2006, [595095](#)) obtained good results

1 when comparing wet chemical and DOAS during well mixed atmospheric conditions (wet chemical  
2 = 0.009 + 0.92 x DOAS; r = 0.7). Kleffmann and Wiesen (2008, [488342](#)) noted that interferences  
3 with the HONO wet chemical methods can affect results from inter-comparison studies if not  
4 addressed. In an earlier study, Kleffman et al. (2006, [130481](#)) demonstrated that when the  
5 interferences were addressed, excellent agreement with DOAS can be obtained. Stutz et al. (2009,  
6 [595124](#)) found good agreement (15% or better) between DOAS and a wet chemical method (Mist  
7 Chamber/IC) in Houston, TX except generally during mid-day when the chemical method showed a  
8 positive bias that may have been related to concentrations of O<sub>3</sub>. DOAS remains attractive due to its  
9 sensitivity, speed of response, and ability to simultaneously measure multiple pollutants; however,  
10 further inter-comparisons and interference testing are recommended.

### 3.5.5.5. Satellite Remote Sensing

11 Satellite observations for O<sub>3</sub> are growing as a resource for many purposes, including model  
12 evaluation, assessing emissions reductions, pollutant transport, and air quality management. Satellite  
13 remote sensing instruments do not directly measure the composition of the atmosphere. Satellite  
14 retrievals are conducted using the solar backscatter or thermal infrared emission spectra and a variety  
15 of algorithms. Most satellite measurement systems have been developed for stratospheric  
16 measurement of the total O<sub>3</sub> column. Mathematical techniques have been developed and must be  
17 applied to derive information from these systems about tropospheric O<sub>3</sub> (Tarasick and Slater, 2008,  
18 [596431](#); Ziemke JR: Chandra et al., 2006, [595159](#)). Direct retrieval of global tropospheric O<sub>3</sub>  
19 distributions from solar backscattered UV spectra have been reported from the Ozone Monitoring  
20 Instrument (OMI) and Global Ozone Monitoring Experiment (GOME)(Liu et al., 2006, [093013](#)).  
21 Another satellite measurement system, Tropospheric Emission Spectrometer (TES), produces global-  
22 scale vertical concentration profiles of tropospheric O<sub>3</sub> from measurements of thermal infrared  
23 emissions. TES has been designed specifically to focus on mapping the global distribution of  
24 tropospheric O<sub>3</sub> extending from the surface to about 10-15 km altitude (Beer, 2006, [633893](#)). In  
25 order to improve the understanding of the quality and reliability of the data, satellite-based  
26 observations of total column and tropospheric O<sub>3</sub> have been validated in several studies using a  
27 variety of techniques, such as aircraft observations, ozonesondes, CTMs, and ground-based  
28 spectroradiometers (Antón et al., 2009, [595098](#); Richards et al., 2008, [617597](#); Worden et al., 2007,  
29 [623018](#); Zhang et al., 2010, [633894](#)). Satellite observations have also been combined (e.g., OMI and  
30 TES) to improve estimates of tropospheric O<sub>3</sub> (Worden et al., 2007, [623020](#)).

### 3.5.6. Ambient Ozone Network Design

#### 3.5.6.1. Monitor Siting Requirements

31 To monitor compliance with the NAAQS, state and local monitoring agencies operate O<sub>3</sub>  
32 monitoring sites at various locations depending on the area size (population and geographic

1 characteristics<sup>1</sup>) and typical peak concentrations (expressed in percentages below, or near the O<sub>3</sub>  
2 NAAQS). SLAMS make up the ambient air quality monitoring sites that are primarily needed for  
3 NAAQS comparisons, but may also serve some other basic monitoring objectives that include:  
4 providing air pollution data to the general public in a timely manner; support for compliance with the  
5 NAAQS and emissions strategy development; and support for air pollution research. SLAMS  
6 include National Core (NCore), Photochemical Assessment Monitoring Stations (PAMS), and all  
7 other State or locally-operated stations except for the monitors designated as SPMs.

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

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

28 Since O<sub>3</sub> concentrations decrease significantly in the colder parts of the year in many areas, O<sub>3</sub>  
29 is required to be monitored at SLAMS monitoring sites only during the “ozone season.” Table D-3 of  
30 40 CFR Part 58, Appendix D lists the beginning and ending month of the "ozone season" for each  
31 U.S. state or territory. Most operate O<sub>3</sub> monitors only during the O<sub>3</sub> season. Those that operate some

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<sup>1</sup> Geographic characteristics such as complexity of terrain, topography, land use, etc.

<sup>2</sup> 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, 2010, 677582) for guidance on how these values are defined.

1 or all of their O<sub>3</sub> monitors on a year-round basis include Arizona, California, Hawaii, Louisiana,  
2 Nevada, New Mexico, Puerto Rico, Texas, American Samoa, Guam and the Virgin Islands.

3 The total number of SLAMS O<sub>3</sub> sites needed to support the basic monitoring objectives  
4 includes more sites than the minimum numbers required in 40 CFR Part 58, Appendix D. In 2009,  
5 there were 1208 SLAMS O<sub>3</sub> monitors reporting values to the EPA AQS database (Figure 3-16).  
6 Monitoring site information for EPA's air quality monitoring networks is available in spreadsheet  
7 format (CSV) and keyhole markup language format (KML or KMZ) that is compatible with Google  
8 Earth™ and other software applications on the AirExplorer website (U.S. EPA, 2011, [677547](#)).  
9 States may operate O<sub>3</sub> monitors in non-urban or rural areas to meet other objectives (e.g., support for  
10 research studies of atmospheric chemistry or ecosystem impacts). These monitors are often identified  
11 as special purpose monitors (SPMs) and can be operated up to 24 months without being considered  
12 in NAAQS compliance determinations. The current monitor and probe siting requirements have an  
13 urban focus and do not address the siting for SPMs or monitors in non-urban, rural areas to support  
14 ecosystem impacts and the secondary standards.

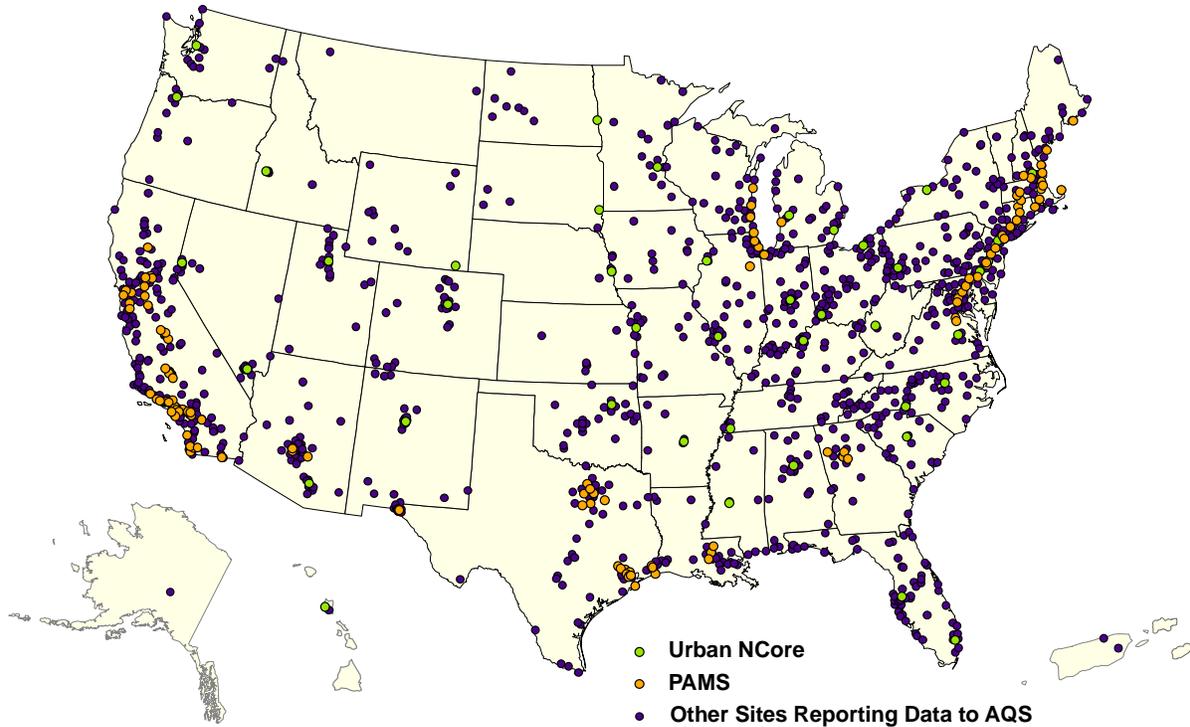
15 NCore is a new multi-pollutant monitoring network implemented to meet multiple monitoring  
16 objectives. Those objectives include: timely reporting of data to the public through AirNow  
17 (U.S. EPA, 2011, [677548](#)); support for the development of emission reduction strategies; tracking  
18 long-term trends of criteria pollutants and precursors; support to ongoing reviews of the NAAQS and  
19 NAAQS compliance; model evaluation; support for scientific research studies; and support for  
20 ecosystem assessments. Each state is required to operate at least one NCore site and the entire  
21 network consists of about 60 urban and 20 rural sites as of January 1, 2011. NCore has leveraged  
22 sites in existing networks; for example, some CASTNET and IMPROVE sites serve as rural NCore  
23 sites. In addition to O<sub>3</sub>, other components including CO, NO, NO<sub>Y</sub>, NH<sub>3</sub>, and HNO<sub>3</sub> are also  
24 measured at NCore sites. The spatial scale for urban NCore stations is urban or neighborhood;  
25 however, a middle-scale<sup>1</sup> site may be acceptable in cases where the site can represent many such  
26 locations throughout a metropolitan area. Rural NCore sites are located at a regional or larger scale,  
27 away from any large local emission sources so that they represent ambient concentrations over an  
28 extensive area. Ozone monitors at NCore sites are operated year round.

29 PAMS provides more comprehensive data on O<sub>3</sub> in areas classified as serious, severe, or  
30 extreme nonattainment for O<sub>3</sub>. In addition to O<sub>3</sub>, PAMS provides data for NO<sub>x</sub>, VOCs, and  
31 meteorology. The PAMS network design criteria are based on locations relative to O<sub>3</sub> precursor  
32 source areas and predominant wind directions associated with high O<sub>3</sub> concentrations. The overall  
33 network design is location specific and geared toward enabling characterization of precursor  
34 emission sources in the area, O<sub>3</sub> transport, and photochemical processes related to O<sub>3</sub> nonattainment.  
35 Minimum monitoring for O<sub>3</sub> and its precursors is required annually during the months of June, July,  
36 and August when peak O<sub>3</sub> concentrations are expected. In 2006, the EPA reduced the minimum

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

1 PAMS monitoring requirements. There were a total of 119 PAMS reporting values to the AQS data  
2 base in 2009.



**Figure 3-16. U.S. ozone sites reporting data to AQS as of 2009.**

3 The Clean Air Status and Trends Network (CASTNET) is a regional monitoring network  
4 established to assess trends in acidic deposition due to emission reduction regulations. CASTNET  
5 also provides concentration measurements of air pollutants involved in acidic deposition, such as  
6 sulfate and nitrate, in addition to the measurement of O<sub>3</sub>. CASTNET O<sub>3</sub> monitors operate year round  
7 and are primarily located in rural areas. At the beginning of 2010, there were 80 CASTNET sites  
8 located in, or near, rural areas. As part of CASTNET, the National Park Service (NPS) operates 23  
9 sites located in national parks and other Class-I areas. Ozone measurements at the CASTNET sites  
10 were not collected with the QA requirements for SLAMS outlined in 40 CFR Part 58, Appendix A,  
11 and therefore, the O<sub>3</sub> cannot be used for NAAQS compliance purposes. The network is currently  
12 implementing the SLAMS QA requirements and procedures. Ozone data collected at the 23 NPS  
13 sites is compliant with the SLAMS QA requirements in 40 CFR Part 58.

14 The NPS also operates a Portable Ozone Monitoring Systems (POMS) network. The POMS  
15 couples the small, low-power O<sub>3</sub> monitor with a data logger, meteorological measurements, and solar  
16 power in a self contained system for monitoring in remote locations. Typical uses for the POMS data  
17 include research projects, survey monitoring, and assessments of spatial O<sub>3</sub> distribution. The portable

1 O<sub>3</sub> monitor in use by the NPS was recently designated as an equivalent method for O<sub>3</sub> (75 FR 22126)  
2 (2010, [687659](#)). Twenty NPS POMS reported O<sub>3</sub> data to AQS in 2010.

3 A map of the current and proposed rural NCore sites, along with the CASTNET, and the NPS  
4 POMS sites are shown in Figure 3-17.

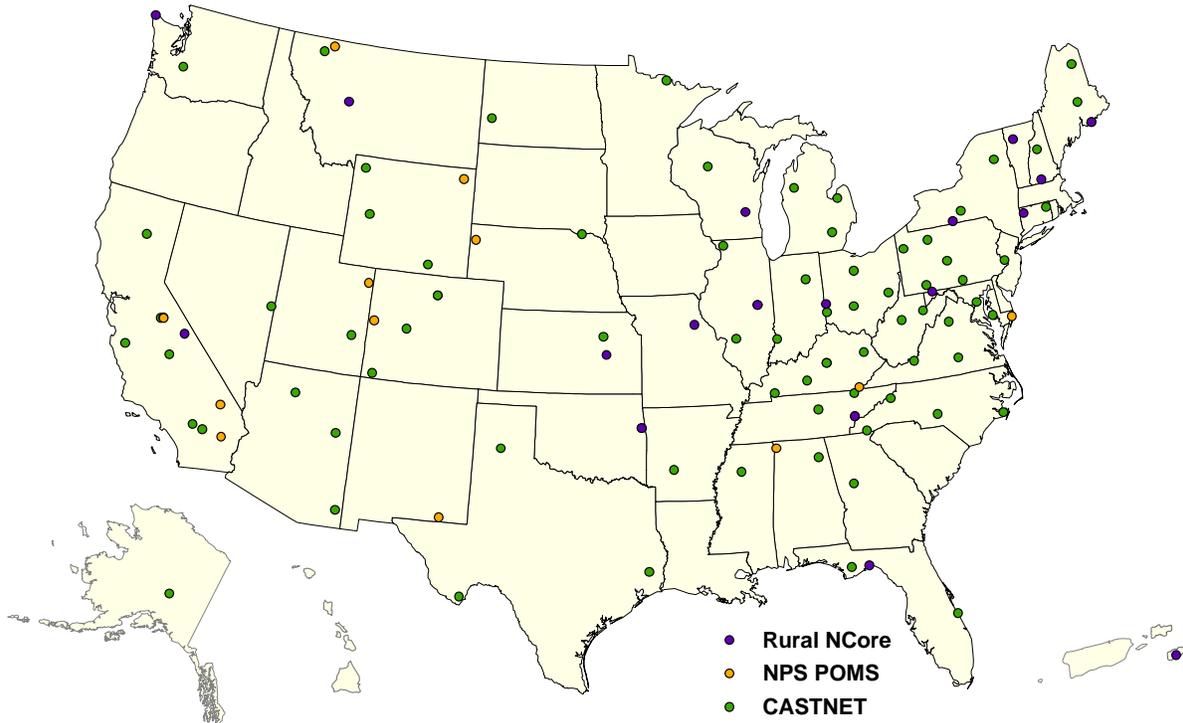


Figure 3-17. U.S. Rural NCore, CASTNET and NPS POMS current and proposed sites as of October, 2010.

### 3.5.6.2. Probe/Inlet Siting Requirements

5 Probe and monitoring path siting criteria for ambient air quality monitoring are contained in  
6 40 CFR Part 58, Appendix E. For O<sub>3</sub>, the probe must be located between 2 and 15 m above ground  
7 level and be at least 1 m away (both in the horizontal and vertical directions) from any supporting  
8 structure, walls, etc. If it is located on the side of a building, it must be located on the windward side,  
9 relative to prevailing wind direction during the season of highest potential O<sub>3</sub> concentration. Ozone  
10 monitors are placed to determine air quality in larger areas (neighborhood, urban, or regional scales)  
11 and therefore, placement of the monitor probe should not be near local, minor sources of NO,  
12 O<sub>3</sub>-scavenging hydrocarbons, or O<sub>3</sub> precursors. The probe or inlet must have unrestricted air flow in  
13 an arc of at least 180 degrees and be located away from any building or obstacle at a distance of at  
14 least twice the height of the obstacle. The arc of unrestricted air flow must include the predominant  
15 wind direction for the season of greatest O<sub>3</sub> concentrations. Some exceptions can be made for

1 measurements taken in street canyons or sites where obstruction by buildings or other structures is  
2 unavoidable. The scavenging effect of trees on O<sub>3</sub> is greater than other pollutants and the probe/inlet  
3 must be located at least 10 m from the tree drip line to minimize interference with normal air flow.  
4 When siting O<sub>3</sub> monitors near roadways, it is important to minimize the destructive interferences  
5 from sources of NO, since NO reacts readily with O<sub>3</sub>. For siting neighborhood and urban scale O<sub>3</sub>  
6 monitors, guidance on the minimum distance from the edge of the nearest traffic lane is based on  
7 roadway average daily traffic count (40 CFR Part 58, Appendix E, Table E-1). The minimum  
8 distance from roadways is 10 m (average daily traffic count  $\leq 10,000$ ) and increases to a maximum  
9 distance of 250 m (average daily traffic count  $\geq 110,000$ ).

## 3.6. Ambient Concentrations

10 This section investigates spatiotemporal variability in ambient O<sub>3</sub> concentrations and  
11 associations between O<sub>3</sub> and co-pollutants. To set the stage for the rest of the section, common O<sub>3</sub>  
12 measurement units, metrics, and averaging times are described and compared in Section 3.6.1.  
13 Spatial variability is covered in Section 3.6.2 and is divided into urban-focused variability and rural-  
14 focused variability. Urban-focused variability is organized by scale, extending from national-scale  
15 down to neighborhood-scale and the near-road environment. Rural-focused variability is organized  
16 by region and includes observations of ground-level vertical O<sub>3</sub> gradients where available. Temporal  
17 variability is covered in Section 3.6.3 and is organized by time, extending from multiyear trends  
18 down to hourly (diel) variability. In many instances, spatial and temporal variability are inseparable  
19 (e.g., seasonal dependence to spatial variability), resulting in some overlap between Sections 3.6.2  
20 and 3.6.3. Finally, Section 3.6.4 covers associations between O<sub>3</sub> and co-pollutants including CO,  
21 SO<sub>2</sub>, NO<sub>2</sub>, PM<sub>2.5</sub> and PM<sub>10</sub>.

22 As noted in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), O<sub>3</sub> is the only photochemical  
23 oxidant other than nitrogen dioxide (NO<sub>2</sub>) that is routinely monitored and for which a comprehensive  
24 database exists. Data for other photochemical oxidants (e.g., PAN, H<sub>2</sub>O<sub>2</sub>, etc.) typically have been  
25 obtained only as part of special field studies. Consequently, no data on nationwide patterns of  
26 occurrence are available for these other oxidants; nor are extensive data available on the  
27 relationships of concentrations and patterns of these oxidants to those of O<sub>3</sub>. As a result, this section  
28 focuses solely on O<sub>3</sub>, the NAAQS indicator for photochemical oxidants. The majority of ambient O<sub>3</sub>  
29 data reported in this section were obtained from AQS, EPA's repository for detailed, hourly data that  
30 has been subject to EPA quality control and assurance procedures (see Section 3.5 for a description  
31 of the AQS network).

### 3.6.1. Measurement Units, Metrics, and Averaging Times

32 Several approaches are commonly used for reporting O<sub>3</sub> data. In atmospheric sciences and  
33 epidemiology, O<sub>3</sub> is frequently reported as a concentration, expressed as a volume-to-volume mixing  
34 ratio, commonly measured in ppm or ppb. In human exposure, O<sub>3</sub> is frequently reported as a

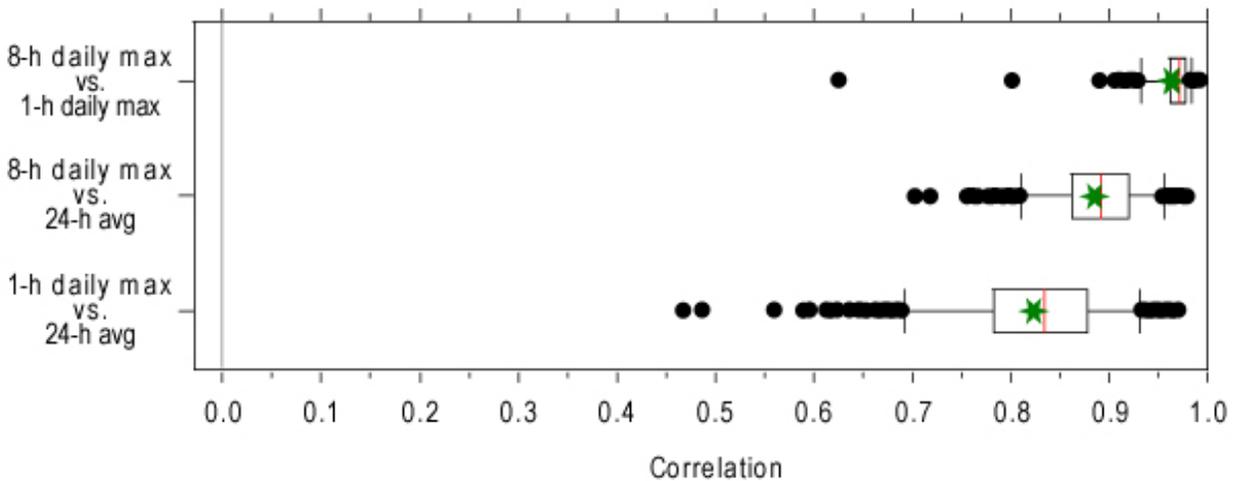
1 cumulative exposure, expressed as a mixing ratio times time (e.g., ppm-h). In ecology, cumulative  
2 exposure indicators are frequently used that extend over longer time periods, such as growing season  
3 or year. This section focuses on ambient concentrations derived primarily from hourly average O<sub>3</sub>  
4 measurements and concentrations are reported in ppb wherever possible. Further details on human  
5 and ecological exposure metrics can be found in Chapter 4 and Chapter 9, respectively.

6 As discussed in Section 3.5, most continuous O<sub>3</sub> monitors report hourly average  
7 concentrations. This data can be used as reported (1-h avg), or further summarized in one of several  
8 ways to focus on important aspects of the data while simultaneously reducing the volume of  
9 information. Three common daily reporting metrics include: (1) the average of the hourly  
10 observations over a 24-h period (24-h avg); (2) the maximum hourly observation occurring in a 24-h  
11 period (1-h daily max); and (3) the maximum 8-h running average of the hourly observations  
12 occurring in a 24-h period (8-h daily max)<sup>1</sup>. Throughout this ISA and the literature, O<sub>3</sub>  
13 concentrations are reported using different averaging times as appropriate, making it important to  
14 recognize the differences between these metrics.

15 Nation-wide, year-round 1-h avg O<sub>3</sub> data reported to AQS from 2007-2009 was used to  
16 compare these different daily metrics. Correlations between the 24-h avg, 1-h daily max and 8-h  
17 daily max metrics were generated on a site-by-site basis. Figure 3-18 contains box plots of the  
18 distribution in correlations from all sites. The top comparison in Figure 3-18 is between 8-h daily  
19 max and 1-h daily max O<sub>3</sub>. Not surprisingly, these two metrics are very highly correlated (median r =  
20 0.97, IQR = 0.96-0.98). There are a couple outlying sites, with correlations between these two  
21 metrics as low as 0.63, but 95% of sites have correlations above 0.93. The middle comparison in  
22 Figure 3-18 is between 8-h daily max and 24-h avg O<sub>3</sub>. For these metrics, the distribution in  
23 correlations is shifted down and broadened out (median r = 0.89, IQR = 0.86-0.92). Finally, the  
24 bottom comparison in Figure 3-18 is between 1-h daily max and 24-h avg O<sub>3</sub>. Again, for these  
25 metrics the distribution in correlations is shifted down and broadened out relative to the other two  
26 comparisons (median r = 0.83, IQR = 0.78-0.88). The correlation between the two daily maximum  
27 metrics (1-h daily max and 8-h daily max) are quite high for most sites, but correlations between the  
28 daily maximum metrics and the daily average metric (24-h avg) are lower. This illustrates the  
29 influence of the overnight period on the 24-h avg O<sub>3</sub> concentration. In contrast, the 1-h daily max  
30 and 8-h daily max are more indicative of the daytime, high O<sub>3</sub> periods. The correlation between these  
31 metrics, however, can be very site-specific, as is evident from the broad range in correlations in  
32 Figure 3-18 for all three comparisons.

---

<sup>1</sup> For O<sub>3</sub> 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.



**Figure 3-18. 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. (Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers), and extremes (black dots).**

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

### 3.6.2. Spatial Variability

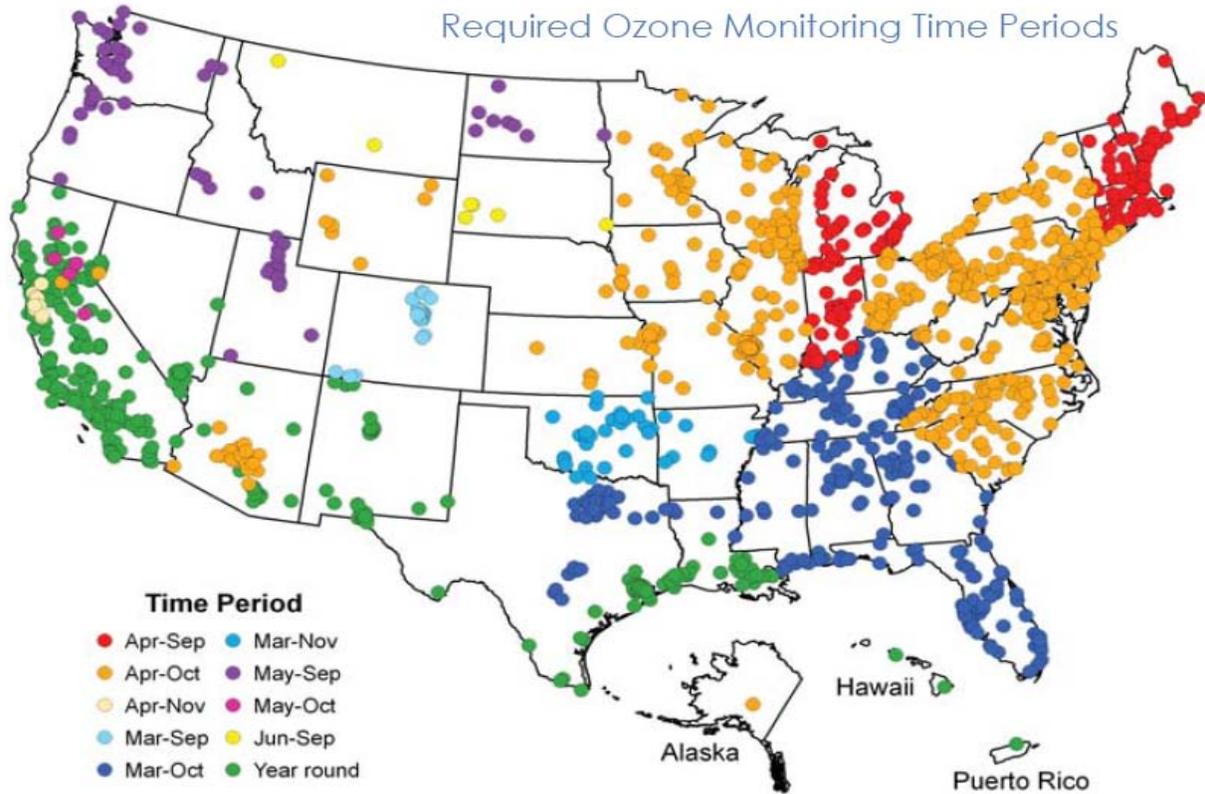
#### 3.6.2.1. Urban-Focused Variability

##### National-Scale Variability

9 AQS contains a large depository of national O<sub>3</sub> data collected to meet the monitoring  
 10 objectives described in Section 3.5.6.1. In many areas, O<sub>3</sub> concentrations decrease significantly  
 11 during months with lower temperatures and decreased sunlight. As a result, year-round O<sub>3</sub>  
 12 monitoring is only required in certain areas. Table D-3 of 40 CFR Part 58, Appendix D lists the  
 13 beginning and ending month of the O<sub>3</sub> season by geographic area and Figure 3-19 illustrates these

<sup>1</sup> 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 O<sub>3</sub> concentrations are at their highest, resulting in an 8-h daily max somewhere between the 1-h daily max and the 24-h avg.

1 time periods on a monitor-by-monitor basis. Monitoring is optional outside the "ozone season" and  
2 many states elect to operate their monitors year-round or for time periods outside what is strictly  
3 mandated.



Source: U.S. EPA (2008, [191190](#))

**Figure 3-19. Required ozone monitoring time periods (ozone season) identified by monitoring site.**

4 Hourly FRM and FEM O<sub>3</sub> data reported to AQS for the period 2007 - 2009 were used to  
5 investigate national-scale spatial variability in O<sub>3</sub> concentrations. Given the variability in O<sub>3</sub>  
6 monitoring time periods available in AQS as a result of the regionally-varying "ozone seasons", the  
7 analyses in this section were based on two distinct data sets:

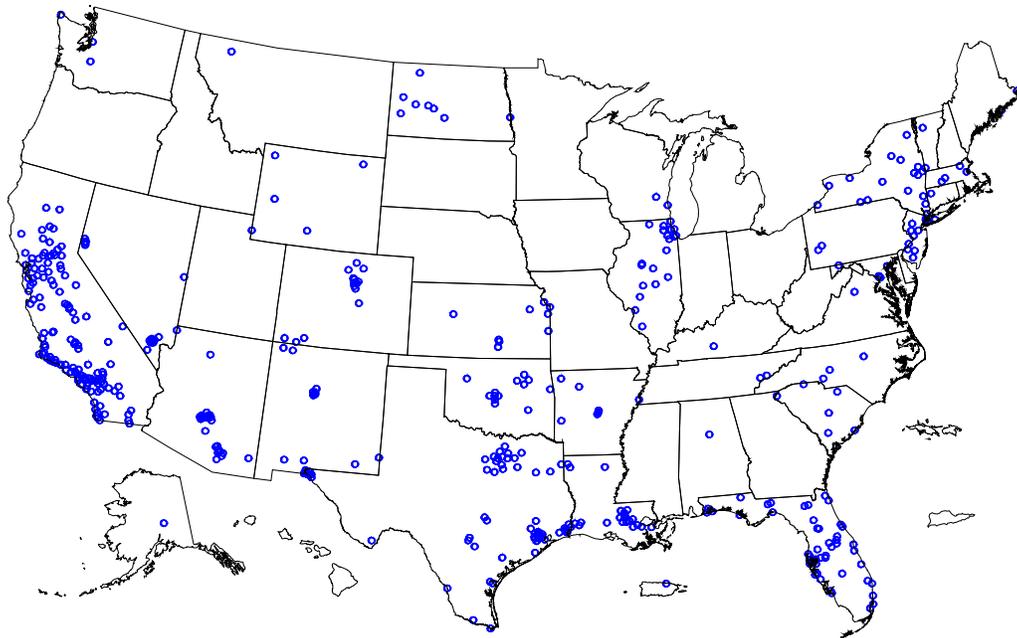
- 8       ▪ **year-round** data set: data only from monitors reporting year-round;
- 9       ▪ **warm-season** data set: data from all monitors reporting May through September.

10 The warm-season data set was used to capture the majority of O<sub>3</sub> season data while providing a  
11 consistent time-frame for comparison across states. All available monitoring data including data  
12 from year-round monitors was included in the warm-season data set after removing observations  
13 outside the 5-month window. Data were retrieved from AQS for these two data sets regardless of

1 flags or regional concurrence<sup>1</sup>. A summary of the two O<sub>3</sub> data sets including the applied  
 2 completeness criteria is provided in Table 3-5. Figure 3-20 and Figure 3-21 show the location of the  
 3 458 year-round and 1,064 warm-season monitors meeting the completeness criteria for all  
 4 three years (2007-2009).

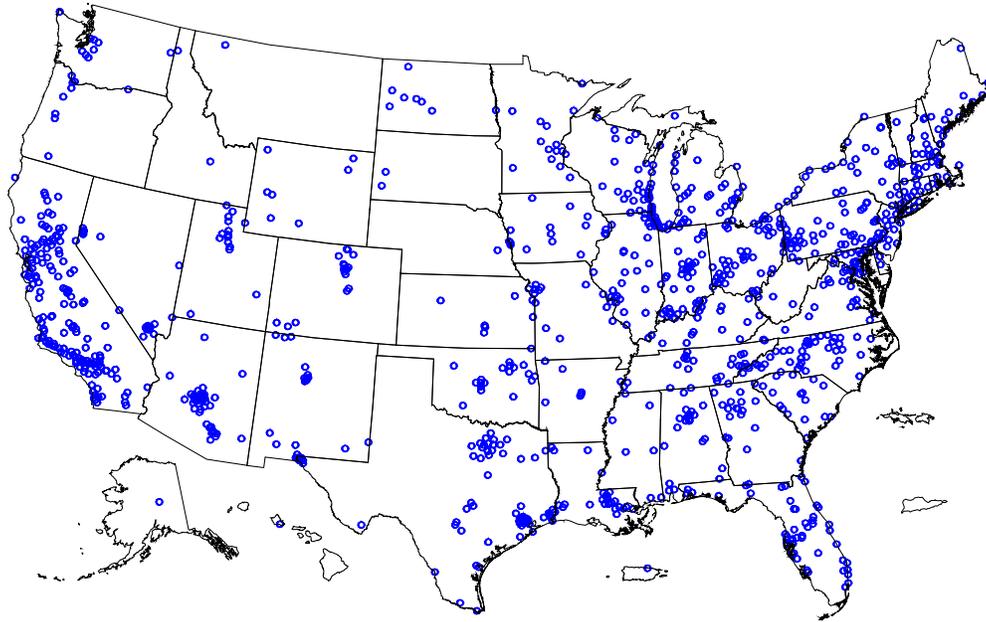
**Table 3-5. Summary of ozone data sets originating from AQS**

	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 all 4 quarters per year	75% of days between May - September
Number of monitors meeting completeness criteria	618 containing at least one valid year in 2007-2009	1,265 containing at least one valid year in 2007-2009
	549 containing at least two valid years in 2007-2009	1,168 containing at least two valid years in 2007-2009
	458 containing all three valid years in 2007-2009	1,064 containing all three valid years in 2007-2009



**Figure 3-20. Location of the 458 ozone monitors meeting the year-round completeness criterion for all 3 years between 2007 and 2009.**

<sup>1</sup> 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 3-21. Location of the 1,064 ozone monitors meeting the warm-season completeness criteria for all 3 years between 2007 and 2009.**

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

**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	96	97	98	99
1-h avg																	
2005	499	4,284,219	29	18	2	2	2	2	15	28	41	53	61	64	67	71	78
2006	532	4,543,205	30	18	2	2	2	5	16	29	42	54	61	64	67	71	78
2007	522	4,547,280	29	18	2	2	2	5	16	29	41	52	60	62	65	68	75
2008	520	4,470,065	30	17	2	2	2	6	17	29	41	52	59	61	64	67	74
2009	551	4,716,821	29	16	2	2	2	6	17	29	40	50	56	58	61	64	70
2007-2009	599	13,734,166	29	17	2	2	2	6	17	29	40	51	58	60	63	67	73
24-h avg																	
2005	504	183,815	29	13	2	4	9	13	20	28	37	46	51	52	54	57	61
2006	536	194,884	30	13	2	5	10	14	21	29	38	47	52	54	55	58	62
2007	531	194,873	29	12	2	5	11	14	20	29	37	45	50	52	53	56	60
2008	528	191,875	30	12	2	5	11	14	21	29	38	46	50	52	54	56	61
2009	556	202,147	29	11	2	6	11	14	21	28	37	44	48	49	51	53	57
2007-2009	611	588,895	29	12	2	5	11	14	21	29	37	45	49	51	53	55	60
1-h daily max																	
2005	504	183,815	48	18	2	11	21	26	35	46	58	71	80	83	86	91	100
2006	536	194,884	48	18	2	13	23	28	36	46	58	71	80	82	86	91	100
2007	531	194,873	47	17	2	14	23	28	36	45	57	69	77	79	82	87	94
2008	528	191,875	47	17	2	14	23	27	35	45	56	67	76	78	82	87	96
2009	556	202,147	45	16	2	14	22	27	35	44	54	64	72	75	78	83	91
2007-2009	611	588,895	46	16	2	14	23	27	35	44	55	67	75	78	81	86	94
8-h daily max																	
2005	504	183,279	42	16	2	7	16	21	30	40	52	63	70	72	75	78	84
2006	536	194,285	42	16	2	9	18	23	31	41	52	63	70	72	75	79	85
2007	528	194,266	41	15	2	10	19	23	31	40	51	61	68	69	72	75	81
2008	528	191,283	41	15	2	11	19	23	31	40	51	60	66	69	71	75	82
2009	556	201,535	40	14	2	11	18	23	30	39	49	57	63	65	68	71	77
2007-2009	608	587,084	41	15	2	10	19	23	31	40	50	60	66	68	70	74	80
8-h daily max (pooled by site)																	
2005	508	508	42	6	23	27	32	34	38	42	45	48	51	51	52	53	55
2006	538	538	42	6	12	28	31	34	38	43	46	50	52	53	53	54	55
2007	538	538	41	6	17	27	31	34	38	41	45	49	51	52	53	54	55
2008	529	529	41	6	20	28	31	34	37	40	45	50	52	52	54	55	57
2009	558	558	40	6	20	26	30	33	36	39	44	48	50	51	52	53	54
2007-2009	458	458	41	6	19	29	32	34	38	40	45	49	51	52	52	54	55

<sup>a</sup>AQS 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	96	97	98	99
1-h avg																	
2005	1,023	7,455,018	30	19	2	2	2	5	16	29	43	55	64	66	69	73	79
2006	1,036	7,590,796	31	18	2	2	2	6	17	30	43	55	62	65	67	71	77
2007	1,021	7,711,463	31	18	2	2	2	6	18	30	43	55	63	65	68	71	77
2008	1,034	7,701,597	31	17	2	2	2	7	18	30	42	53	60	62	65	68	74
2009	1,027	7,825,513	29	16	2	2	2	7	17	29	40	50	56	58	60	63	69
2007-2009	1,102	23,238,573	30	17	2	2	2	7	18	30	42	53	60	62	64	68	74
24-h avg																	
2005	1,103	319,410	30	12	2	5	10	14	22	30	39	46	51	53	55	57	61
2006	1,110	324,993	31	12	2	6	12	15	22	30	39	47	52	53	55	58	61
2007	1,100	330,197	31	12	2	6	12	16	23	31	39	47	51	53	55	57	61
2008	1,120	329,918	31	12	2	6	12	16	22	30	38	46	50	52	53	56	60
2009	1,139	334,951	29	11	2	6	12	15	21	29	37	44	48	49	50	53	56
2007-2009	1,196	995,066	30	12	2	6	12	16	22	30	38	45	50	51	53	55	59
1-h daily max																	
2005	1,103	319,410	50	18	2	12	23	28	38	49	61	74	81	84	87	91	99
2006	1,110	324,993	50	17	2	15	25	29	38	48	60	72	80	82	85	90	98
2007	1,100	330,197	50	17	2	16	25	30	38	48	60	72	80	82	85	88	95
2008	1,120	329,918	48	16	2	16	25	29	37	47	58	69	76	78	81	86	93
2009	1,139	334,951	46	15	2	15	23	28	36	45	54	64	71	73	76	80	87
2007-2009	1,196	995,066	48	16	2	16	24	29	37	47	58	68	76	78	81	85	93
8-h daily max																	
2005	1,104	318,771	44	16	2	9	18	23	32	43	55	66	72	74	76	79	85
2006	1,112	324,327	44	16	2	11	20	25	33	43	54	64	70	72	75	78	84
2007	1,097	329,482	44	15	2	12	20	25	33	43	54	65	71	72	75	78	82
2008	1,120	329,223	43	15	2	12	20	25	33	42	52	61	67	69	71	74	80
2009	1,139	334,250	40	13	2	12	19	24	31	40	49	57	63	64	66	69	75
2007-2009	1,193	992,955	42	15	2	12	20	24	32	42	52	61	67	69	71	75	80
8-h daily max (pooled by site)																	
2005	1,141	1,141	45	6	14	28	34	36	41	46	49	52	54	54	55	56	57
2006	1,152	1,152	44	6	12	29	34	37	41	45	48	51	54	54	55	58	59
2007	1,164	1,164	45	7	17	28	34	36	40	45	50	54	56	56	57	58	59
2008	1,163	1,163	43	6	20	29	33	36	39	44	48	50	53	53	55	56	58
2009	1,170	1,170	41	5	20	28	32	35	38	41	44	47	50	51	52	53	55
2007-2009	1,064	1,064	43	6	19	29	34	36	39	43	47	50	52	53	54	55	57

1           The year-round data set includes data from less than half the number of monitors as the warm-  
2 season data set and a larger fraction of the year-round monitors are located in the southern half of the  
3 U.S. due to extended monitoring requirements in these areas. Despite these differences, the mean,  
4 SD and percentiles of the nation-wide O<sub>3</sub> concentrations were quite similar for the year-round data  
5 presented in Table 3-6 and the warm-season data presented in Table 3-7. In both data sets, there was  
6 very little variability across years in the central statistics; for example, the median 1-h avg  
7 concentrations between 2005 and 2009 ranged from 28 to 29 ppb for the year-round data and from

1 29 to 30 ppb for the warm-season data. The 8-h daily max showed similar uniformity in median  
2 across the five years, with concentrations ranging from 39 to 41 ppb for the year-round data and  
3 from 40 to 43 for the warm-season data. The upper percentiles (95th and above) showed a downward  
4 trend from 2005 to 2009 in both nation-wide data sets. For example, the 99th percentile of the 8-h  
5 daily max observed in the warm-season data dropped from 85 ppb in 2005 to 75 ppb in 2009. Trends  
6 in O<sub>3</sub> concentrations investigated over a longer time period are included in Section 3.6.3.1.

7 Given the strong diurnal pattern in O<sub>3</sub> concentrations, the selection of averaging time has a  
8 substantial effect on the magnitude of concentration reporting. The nation-wide median 1-h avg,  
9 24-h avg, 1-h daily max, and 8-h daily max concentrations for the year-round data set in 2009 were  
10 29, 28, 44 and 39 ppb, respectively. The median concentrations for the warm-season data set in 2009  
11 were: 29, 29, 45 and 40 ppb, respectively. The 1-h avg and 24-h avg both include the lowest  
12 concentrations typically observed in the overnight period which lowers their values relative to the  
13 daily maximum statistics.

14 A strong seasonal pattern in O<sub>3</sub> concentrations can also be seen in the year-round data.  
15 Table 3-8 shows the 8-h daily max stratified by season, with the seasons defined as:

- 16       ▪ winter: December-February;
- 17       ▪ spring: March-May;
- 18       ▪ summer: June-August; and
- 19       ▪ fall: September-November.

20 In addition, warm-season (May-Sept) and cold-season (Oct-Apr) stratifications of the year-round  
21 data set are included in the table for comparison with the four seasonal stratifications. Substantial  
22 seasonal variability in the 8-h daily max concentration for the period 2007-2009 was evident with  
23 lower concentrations present in fall (median = 36 ppb) and winter (median = 32 ppb) and higher  
24 concentrations in spring (median = 47 ppb) and summer (median = 46 ppb). The seasonal differences  
25 were even more pronounced in the upper percentiles. For example, the 99th percentile in the 8-h  
26 daily max over the 2007-09 time period ranged from 52 ppb in winter to 90 ppb in summer. The  
27 distribution in 8-h daily max O<sub>3</sub> during the warm-season (as defined above) and during summer were  
28 very similar, which is not surprising given their close overlap in months. The distribution during the  
29 cold-season (as defined above) is shifted toward higher 8-h daily max O<sub>3</sub> concentrations compared  
30 with the distribution during winter. This is a result of including the four transition months (Oct, Nov,  
31 Mar and Apr) in the cold-season when high O<sub>3</sub> concentrations can occur. Further investigation of  
32 temporal 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	96	97	98	99
8-h daily max (2007-2009)																	
Year-round	608	587,084	41	15	2	10	19	23	31	40	50	60	66	68	70	74	80
8-h daily max by season (2007-2009)																	
Winter (Dec-Feb)	608	143,847	31	10	2	6	14	18	25	32	38	43	46	47	48	49	52
Spring (Mar-May)	612	148,399	47	12	2	20	28	33	40	47	55	62	67	68	70	72	77
Summer (Jun-Aug)	613	148,280	47	16	2	16	22	26	35	46	57	67	75	77	80	84	90
Fall (Sep-Nov)	608	146,558	37	13	2	10	17	21	28	36	45	54	61	63	65	68	75
Warm-season (May-Sep)	616	246,225	47	16	2	16	22	27	35	46	57	66	73	75	78	81	87
Cold-season (Oct-Apr)	608	340,859	36	12	2	8	16	21	28	36	44	52	57	59	61	63	67

1 A national picture of AQS O<sub>3</sub> concentrations was generated from the year-round and warm-  
2 season data sets by aggregating the 8-h daily max observations by U.S. county. For this purpose, the  
3 8-h daily max concentrations at each site were averaged over one or more calendar years and then  
4 the highest site in each county was selected for that county. Figure 3-22 contains the county-scale  
5 8-h daily max O<sub>3</sub> concentrations from the year-round data set for 2007-2009 (top map) with seasonal  
6 stratification (bottom four maps). Figure 3-23 contains the county-scale 8-h daily max O<sub>3</sub>  
7 concentrations from the warm-season data set for 2007-2009 (top map) along with individual maps  
8 for each calendar year between 2007 and 2009 (bottom three maps). These maps are meant to  
9 illustrate the general national-scale distribution in long-term average 8-h daily max O<sub>3</sub>  
10 concentrations and are not representative of O<sub>3</sub> concentrations at all locations or times within the  
11 counties shown; considerable spatial variability can exist within a county. This is particularly  
12 important in the West where counties are larger on average than in the East. These maps are limited  
13 by monitor availability, resulting in the majority of U.S. counties not having available data (the white  
14 regions in Figure 3-22 and Figure 3-23).

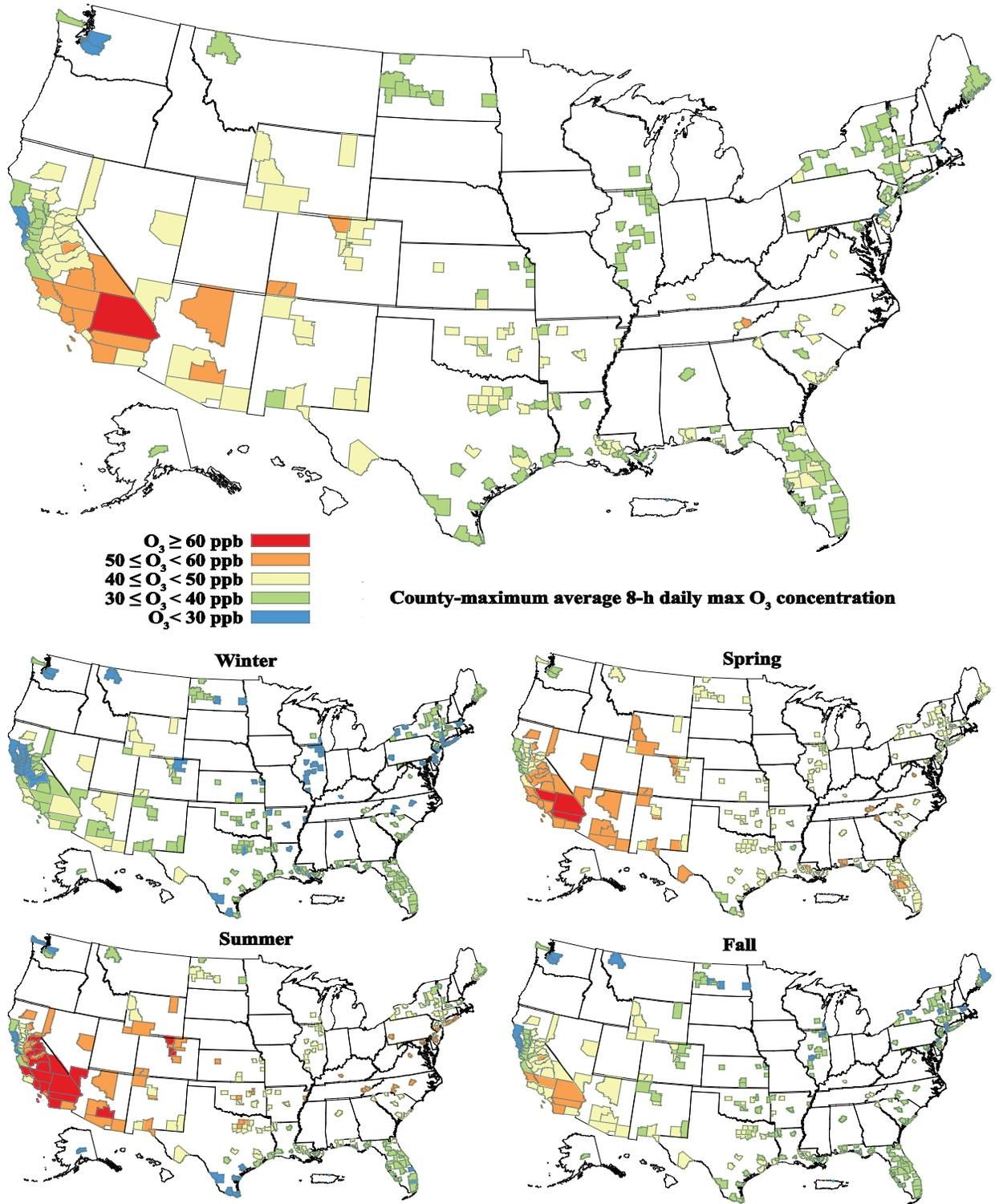


Figure 3-22. Highest monitor (by county) 3-year avg (2007-2009) of the 8-h daily max ozone concentration based on the year-round data set (top map) with seasonal stratification (bottom 4 maps).

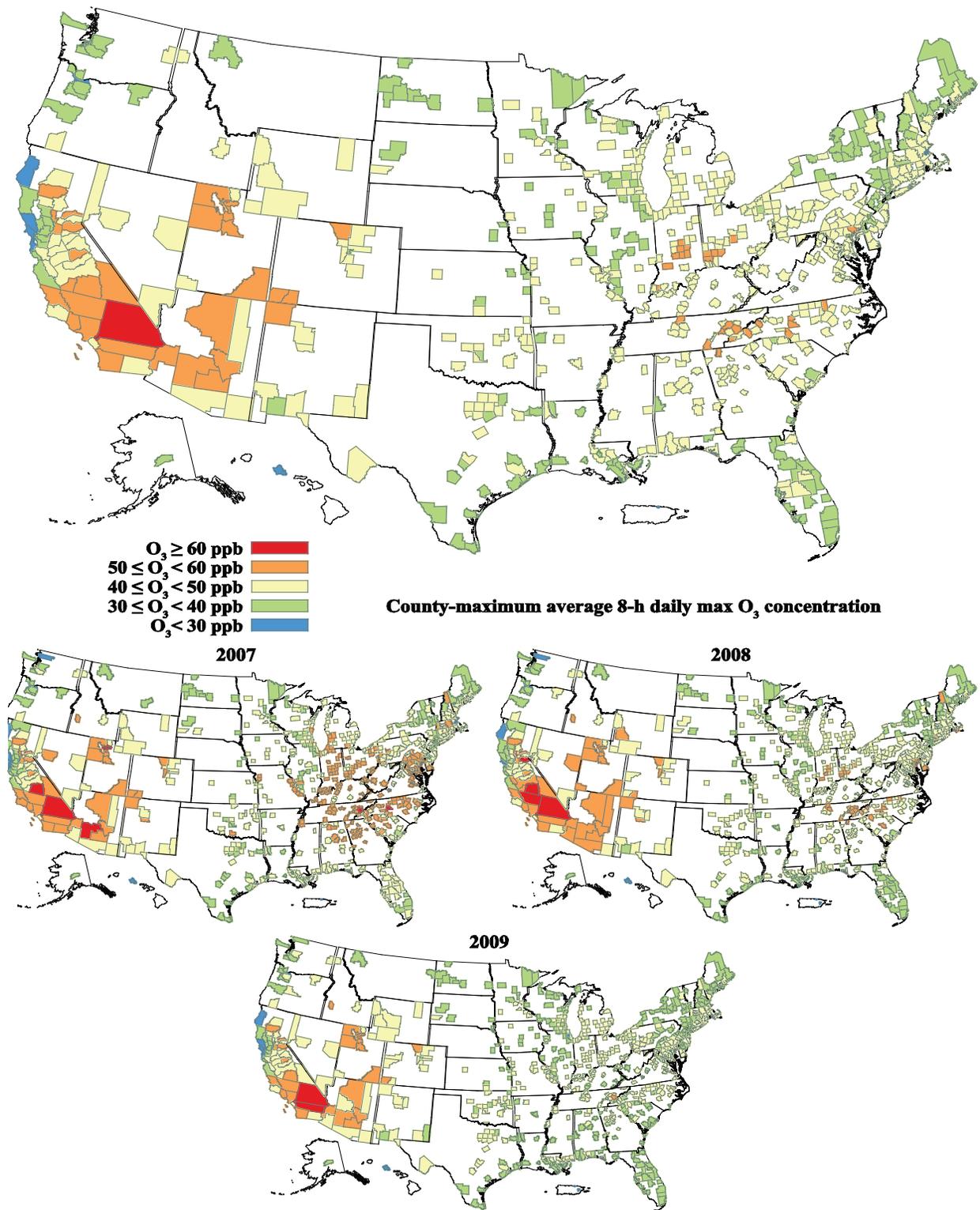


Figure 3-23. Highest monitor (by county) 3-year avg (2007-2009) of the 8-h daily max ozone concentration based on the warm-season data set (top map) with annual stratification (bottom 3 maps).

1 As shown in the top county-scale map in Figure 3-22, the highest 3-year avg (2007-2009) 8-h  
2 daily max O<sub>3</sub> concentrations (≥ 50 ppb) occur in counties in southern California, Arizona, Colorado  
3 and high elevation counties in Tennessee. Site #060710005 in San Bernardino County, CA had the  
4 highest average of 61 ppb over this period. The lowest 3-year avg 8-h daily max O<sub>3</sub> concentrations  
5 (<30 ppb) occur in Pacific Coast counties in northern California and Washington as well as in two  
6 northeastern counties in Pennsylvania and Massachusetts. The seasonally-stratified county-scale  
7 maps in Figure 3-23 reinforce the strong seasonality in 8-h daily max O<sub>3</sub> concentrations shown in  
8 Table 3-8. The highest wintertime concentrations (≥ 40 ppb) occur in the West with the highest  
9 3-year wintertime avg of 46 ppb calculated for site #080690007 in Larimer County, CO. In spring  
10 and summer, the concentrations increase considerably across all counties, with the highest  
11 concentrations (≥ 60 ppb) occurring during the summer in 15 counties in southern California, 3  
12 counties in Colorado and 1 county each in Nevada and Arizona. Many counties in rural Wyoming,  
13 Montana, North Dakota, Maine, and along the Gulf Coast peak in the spring instead of the summer.  
14 In the fall, 8-h daily max O<sub>3</sub> concentrations drop back down below their spring and summer  
15 concentrations.

16 The top county-scale map in Figure 3-23 based on the 2007-2009 warm-season data set looks  
17 similar to the corresponding map in Figure 3-22 based on the year-round data set. The warm-season  
18 map, however, incorporates approximately twice as many monitors across the U.S., providing more  
19 spatial coverage. Several counties in Utah, New Mexico, Indiana, Ohio, Maryland, North Carolina,  
20 and Georgia in addition to California, Arizona, Colorado and Tennessee identified above have 3-year  
21 avg (2007-2009) 8-h daily max O<sub>3</sub> concentrations ≥ 50 ppb based on the warm-season data set. The  
22 individual yearly average county-maximum 8-h daily max O<sub>3</sub> concentrations in the lower half of  
23 Figure 3-22 show a general decrease in most counties from 2007 to 2009. The number of counties  
24 containing a monitor reporting an annual average 8-h daily max O<sub>3</sub> concentration above 50 ppb  
25 dropped from 231 counties in 2007 to 29 counties in 2009. This is consistent with the general  
26 decrease across these years shown in Table 3-6 and Table 3-7 for the upper percentiles of the 8-h  
27 daily max O<sub>3</sub> concentration.

### **Urban-Scale Variability**

28 Statistical analysis of the human health effects of airborne pollutants based on aggregate  
29 population time-series data have often relied on ambient concentrations of pollutants measured at  
30 one or more central monitoring sites in a given metropolitan area. The validity of relying on central  
31 monitoring sites is strongly dependent on the spatial variability in concentrations within a given  
32 metropolitan area. To investigate urban-scale variability, 20 focus cities were selected for closer  
33 analysis of O<sub>3</sub> concentration variability; these cities are listed in Table 3-9 and were selected based  
34 on their importance in O<sub>3</sub> epidemiology studies and on their geographic distribution across the U.S.  
35 In order to provide a well-defined boundary around each city, the combined statistical area (CSA)  
36 encompassing each city was used. If the city was not within a CSA, the smaller core-based statistical  
37 area (CBSA) was selected. The CSAs/CBSAs are defined by the U.S. Census Bureau

1 (U.S. Census Bureau, 2011, [677549](#))<sup>1</sup> and have been used to establish analysis regions around cities  
 2 in previous ISAs for particulate matter (U.S. EPA, 2009, [179916](#)) and carbon monoxide (U.S. EPA,  
 3 2010, [626035](#)).

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

Focus City	Short Name	CSA/CBSA Name <sup>a</sup>	Year-Round O <sub>3</sub> Monitoring Sites <sup>b</sup>	Warm-Season O <sub>3</sub> Monitoring Sites <sup>c</sup>	Included in Prior ISAs <sup>d</sup>
Atlanta, GA	Atlanta CSA	Atlanta-Sandy Springs-Gainesville	0	11	CO, PM, SO <sub>x</sub> , NO <sub>x</sub>
Baltimore, MD	Baltimore CSA	Washington-Baltimore-northern Virginia	9	19	NO <sub>x</sub>
Birmingham, AL	Birmingham CSA	Birmingham-Hoover-Cullman	1	9	PM
Boston, MA	Boston CSA	Boston-Worcester-Manchester	3	18	CO, PM, NO <sub>x</sub>
Chicago, IL	Chicago CSA	Chicago-Naperville-Michigan City	11	15	PM, NO <sub>x</sub>
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 <sub>x</sub>
Los Angeles, CA	Los Angeles CSA	Los Angeles-Long Beach-Riverside	47	3	CO, PM, SO <sub>x</sub> , NO <sub>x</sub>
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 <sub>x</sub> , NO <sub>x</sub>
Philadelphia, PA	Philadelphia CSA	Philadelphia-Camden-Vineland	9	8	PM, NO <sub>x</sub>
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 <sub>x</sub>

<sup>a</sup>Defined based on 2000 Census data from the U.S. Census Bureau (U.S. Census Bureau, 2011, [677549](#)).

<sup>b</sup>The number of sites with AQS monitors meeting the year-round data set inclusion criteria; the year-round data set is limited to these monitors.

<sup>c</sup>The number of sites 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.

<sup>d</sup>Boundaries for CO ISA (U.S. EPA, 2010, [626035](#)) and PM ISA (U.S. EPA, 2009, [179916](#)) focus cities were based on CSA/CBSA definitions; boundaries for SO<sub>x</sub> ISA (U.S. EPA, 2008, [157075](#)) and NO<sub>x</sub> ISA (U.S. EPA, 2008, [157073](#)) focus cities were based on similar metropolitan statistical area (MSA) definitions from the 1990 U.S. Census.

4 The distribution of the 8-h daily max O<sub>3</sub> concentrations from 2007-2009 for each of the 20  
 5 focus cities is included in Table 3-10. These city-specific distributions were extracted from the  
 6 warm-season data set and can be compared to the nationwide warm-season 8-h daily max  
 7 distribution for 2007-2009 in Table 3-7 (and repeated in the first line of Table 3-10). The median 8-h  
 8 daily max concentration in these focus cities was 41 ppb, similar to the nationwide median of  
 9 42 ppb. Seattle had the lowest median and Salt Lake City had the highest median of the 20 cities  
 10 with median 8-h daily max concentrations of 31 and 53 ppb, respectively. The 99th percentile of the  
 11 8-h daily max concentration in the focus cities was 84 ppb; similar once again to the nationwide 99th

<sup>1</sup>A 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.

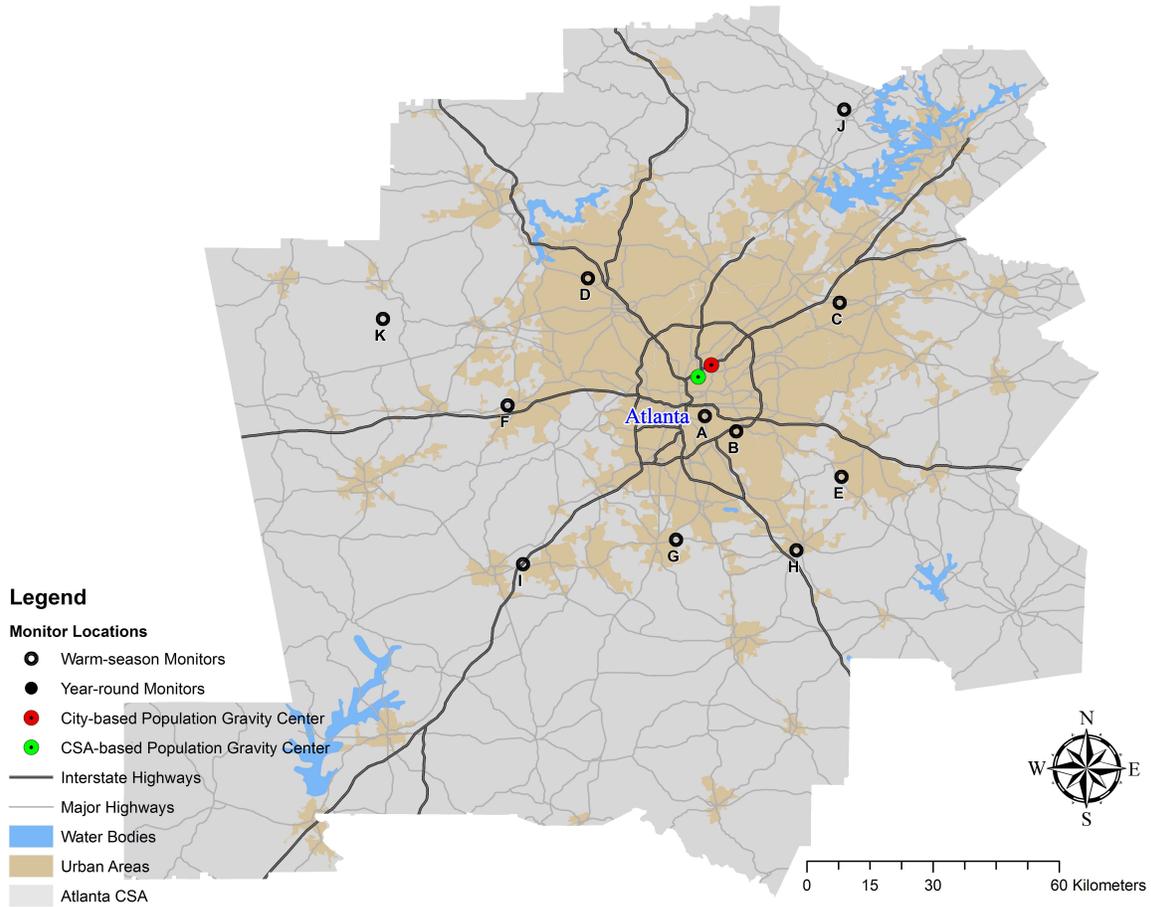
1 percentile of 80 ppb. Seattle had the lowest 99th percentile and Los Angeles had the highest 99th  
 2 percentile of the 20 cities with values of 64 and 98 ppb, respectively. In aggregate, the 20 focus cities  
 3 selected are similar in distribution to the nationwide data set, but there is substantial city-to-city  
 4 variability in the individual distributions of the 8-h daily max concentrations based on the warm-  
 5 season data set.

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

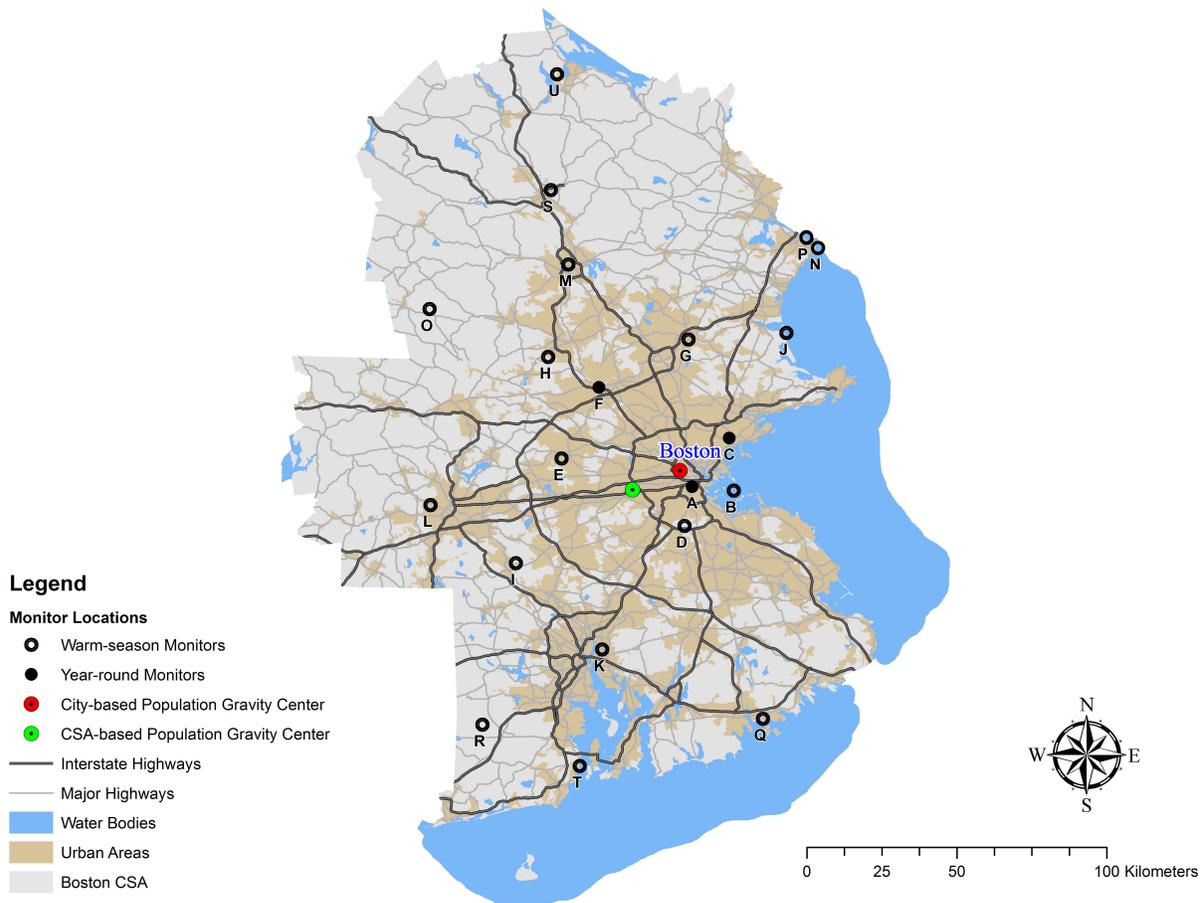
Time Period	N Monitors	N Obs	Mean	SD	Min	1	5	10	25	50	75	90	95	96	97	98	99
8-h daily max (2007-2009)																	
Nationwide	1,193	992,955	42	15	2	12	20	24	32	42	52	61	67	69	71	75	80
8-h daily max by CSA/CBSA (2007-2009)																	
Atlanta CSA	11	7,844	47	16	2	15	22	27	36	47	58	67	72	75	77	81	87
Baltimore CSA	28	20,999	43	16	2	9	18	23	31	43	54	64	70	72	74	78	83
Birmingham CSA	10	7,676	44	15	2	14	21	25	34	44	54	63	68	70	73	76	83
Boston CSA	21	12,603	41	14	2	13	21	25	31	40	49	59	67	69	71	75	81
Chicago CSA	27	20,764	37	14	2	9	15	19	27	37	47	57	62	64	66	69	74
Dallas CSA	19	19,858	41	15	2	11	20	24	31	39	50	61	67	69	71	74	79
Denver CSA	15	12,217	44	15	2	8	18	24	34	44	55	63	68	69	70	72	76
Detroit CSA	9	5,016	45	14	2	15	23	28	35	44	52	62	69	72	74	77	83
Houston CSA	21	22,305	36	15	2	8	15	19	25	34	46	57	64	66	68	72	78
Los Angeles CSA	49	49,291	47	18	2	10	20	26	35	45	58	72	81	83	86	91	98
Minneapolis CSA	8	5,285	40	12	2	14	21	25	31	40	48	54	58	59	61	63	67
New York CSA	21	26,304	39	16	2	6	15	20	28	37	47	59	68	70	73	77	83
Philadelphia CSA	14	12,673	41	17	2	8	17	21	29	39	52	64	70	73	75	78	83
Phoenix CBSA	22	26,129	49	12	2	18	27	32	41	50	58	65	68	69	70	72	75
Pittsburgh CSA	13	9,814	43	15	2	12	19	24	32	43	53	62	68	70	72	74	78
Salt Lake City CSA	12	5,146	51	14	2	8	23	32	44	53	61	67	71	73	75	77	80
San Antonio CSA	5	4,701	39	13	2	13	20	23	29	37	46	56	62	63	65	67	72
San Francisco CSA	31	27,961	34	12	2	8	16	20	27	33	41	48	55	57	59	63	68
Seattle CSA	5	6,148	31	12	2	4	12	17	23	31	39	46	51	53	55	59	64
St Louis CSA	19	11,569	43	15	2	12	19	23	32	43	53	61	68	69	72	76	81
All CSAs/CBSAs listed	360	314,303	42	16	2	9	18	22	31	41	52	63	69	71	74	78	84

6 Maps showing the location of central monitoring sites with O<sub>3</sub> monitors reporting to AQS for  
 7 each of the 20 focus cities are included in Chapter 3Appendix, Figure 3A-16 through Figure 3A-35;  
 8 examples for Atlanta, Boston and Los Angeles are shown in Figure 3-24 through Figure 3-26. The  
 9 sites are delineated in the maps as year-round or warm-season based on their inclusion in the year-  
 10 round data set and the warm-season data set (the warm-season data set includes May-September data  
 11 from both the warm-season monitors and the year-round monitors). The maps also include the  
 12 CSA/CBSA boundary selected for monitor inclusion, the location of urban areas and water bodies,  
 13 the major roadway network, as well as the population gravity center based on the entire CSA/CBSA  
 14 and the individual focus city boundaries. Population gravity center is calculated from the average

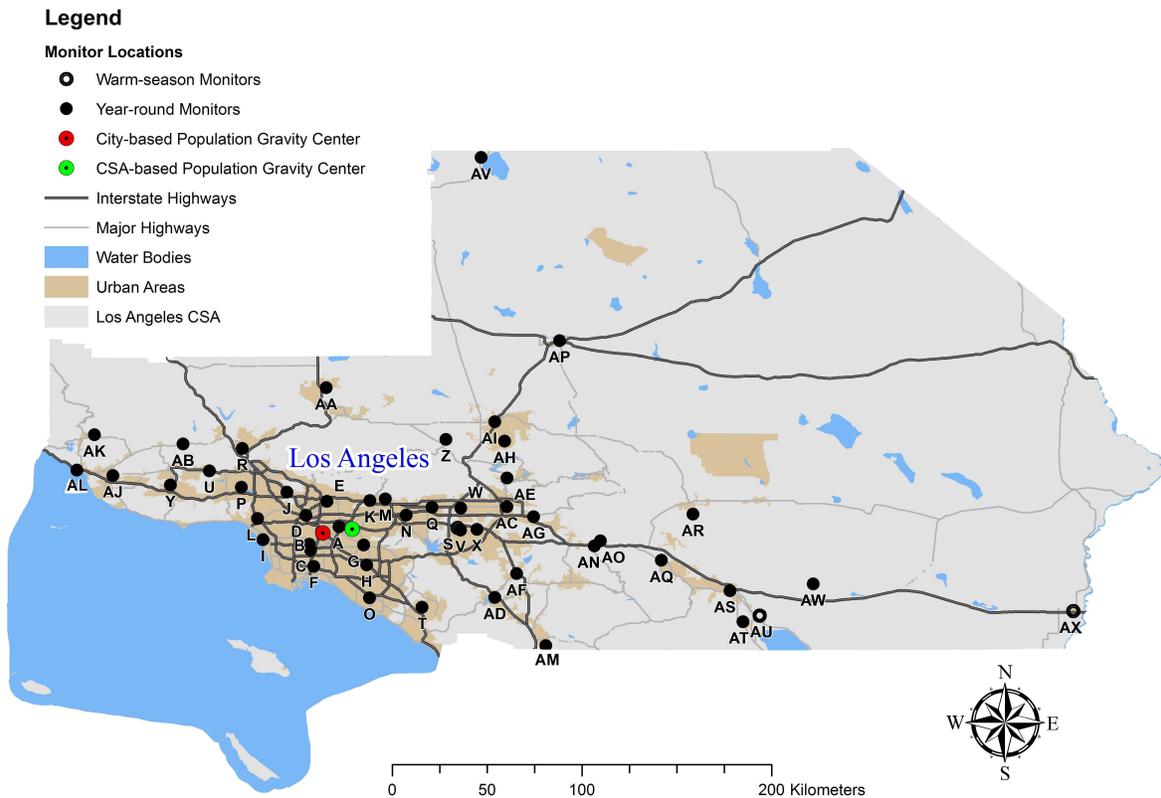
- 1 longitude and latitude values for the input census tract centroids and represents the mean center of
- 2 the population in a given area. Census tract centroids are weighted by their population during this
- 3 calculation.



**Figure 3-24. Map of the Atlanta CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



**Figure 3-25. Map of the Boston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



**Figure 3-26. 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 around the  
2 city center (Figure 3-24). The population gravity center for the city and the larger CSA are only  
3 separated by 4 km, indicating that the majority of the population lives within or evenly distributed  
4 around the city limits. Atlanta is landlocked with a radial network of interstate highways leading to  
5 the city center. The Boston CSA contains 3 year-round and 18 warm-season monitors spread evenly  
6 throughout the CSA. Boston is a harbor city with the Atlantic Ocean to the east, resulting in the city-  
7 based population gravity center being located 17 km east of the CSA-based population gravity  
8 center. The Los Angeles CSA contains the largest number of monitors of the 20 CSA/CBSAs  
9 investigated with 47 year-round and 3 warm-season monitors. These monitors are primarily  
10 concentrated in the Los Angeles urban area with relatively few monitors extending out to the  
11 northern and eastern reaches of the CSA. These unmonitored areas are very sparsely populated,  
12 resulting in only 15 km separating the city-based and the CSA-based population gravity centers  
13 despite the vast area of the Los Angeles CSA.

1 Other CSAs/CBSAs (see Chapter 3 Appendix) with monitors concentrated within the focus  
2 city limits include Birmingham, Chicago, Denver, Houston, Phoenix, San Antonio, and Salt Lake  
3 City. The remaining CSAs/CBSAs have monitors distributed more evenly throughout the  
4 CSA/CBSA area. Baltimore is contained within the same CSA as Washington DC and suburbs,  
5 resulting in a 50-km separation (the largest of the focus cities investigated) between the city-based  
6 population gravity center for Baltimore and the CSA-based population gravity center for the  
7 Washington-Baltimore-Northern Virginia CSA.

8 Box plots depicting the distribution of 2007-2009 warm-season 8-h daily max O<sub>3</sub> data from  
9 each individual monitor in the 20 focus cities are included in Chapter 3 Appendix, Figure 3A-36  
10 through Figure 3A-55; examples for Atlanta, Boston and Los Angeles are shown in Figure 3-27  
11 through Figure 3-29. The Atlanta CSA has very little spatial variability in 8-h daily max O<sub>3</sub>  
12 concentrations with median concentrations ranging from 47 ppb at Sites I and J located far from the  
13 city center to 54 ppb at Site A located closest to the city center. The variation in warm-season 8-h  
14 daily max concentrations are also relatively uniform across monitors with an IQR ranging from  
15 17 ppb at Site J to 23 ppb at Site B. The Boston CSA has more spatial variability in 8-h daily max O<sub>3</sub>  
16 concentrations than the Atlanta CSA with median concentrations ranging from 33 ppb at Site A  
17 nearest to the city center to 46 ppb at Site L located 84 km west of the city center. Like the Atlanta  
18 CSA, the variation in warm-season 8-h daily max concentrations are relatively uniform across  
19 monitors within the Boston CSA with an IQR ranging from 15 ppb at Site U to 21 ppb at Site K. The  
20 Los Angeles CSA exhibits the most variability in O<sub>3</sub> concentrations between monitors of all the  
21 CSAs/CBSAs investigated. The median 8-h daily max O<sub>3</sub> concentration in the Los Angeles CSA  
22 ranged from 20 ppb at Site AM in the south-central extreme of the CSA to 80 ppb at Site AE near  
23 Crestline, CA in the San Bernardino National Forest just north of San Bernardino, CA. These two  
24 sites are at approximately the same longitude and are separated by only 85 km, but the Crestline site  
25 is downwind of the Los Angeles basin, resulting in substantially higher O<sub>3</sub> concentrations. Site AM  
26 also contains data for only 2009, which could explain some of the deviation when comparing this  
27 site with others in the Los Angeles CSA. Sites AM and AE also had the lowest (8 ppb) and highest  
28 (28 ppb) IQR, respectively. The remaining focus cities included in Chapter 3 Appendix exhibited  
29 spatial variability ranging from uniform as in the Atlanta CSA to non-uniform as observed in the  
30 Los Angeles CSA.

### Atlanta CSA

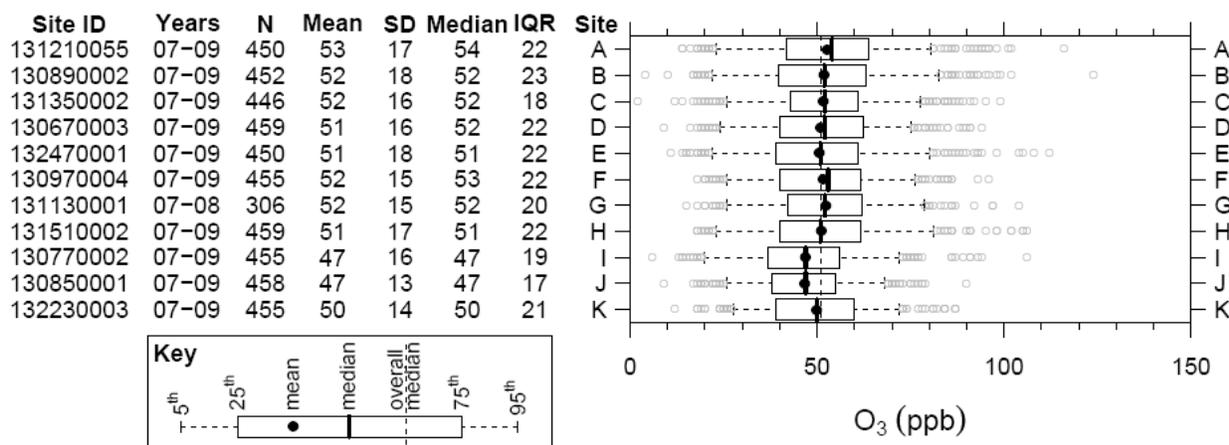


Figure 3-27. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Atlanta CSA.

### Boston CSA

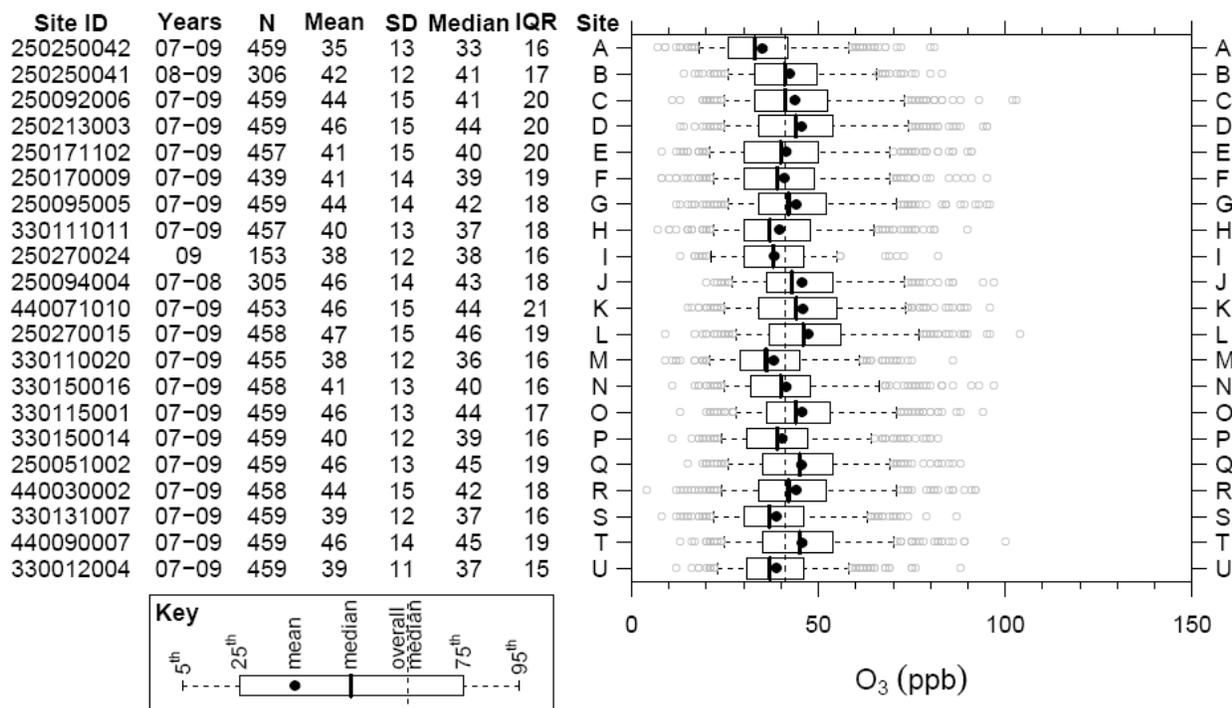
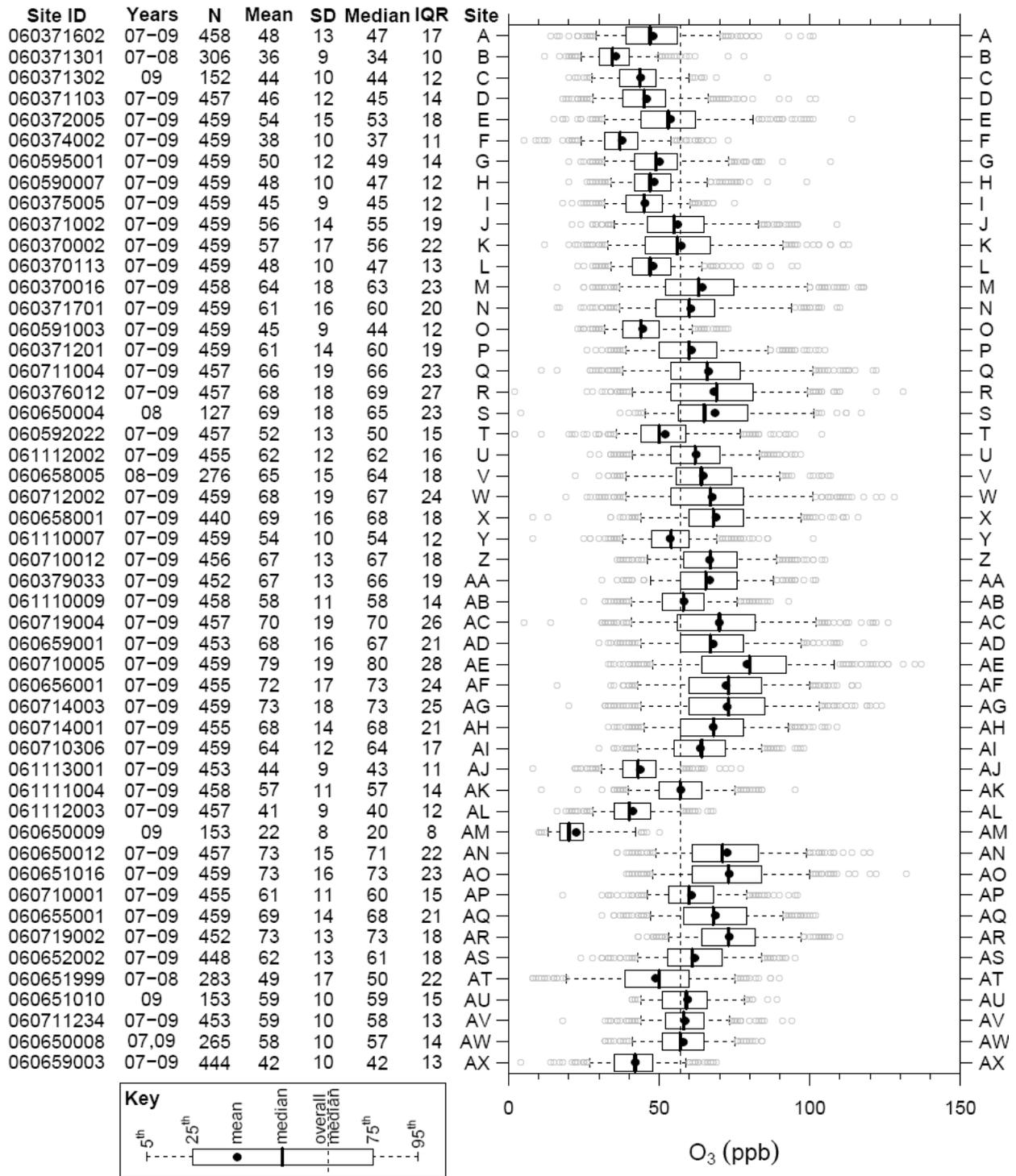


Figure 3-28. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Boston CSA.

## Los Angeles CSA



**Figure 3-29. 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.**

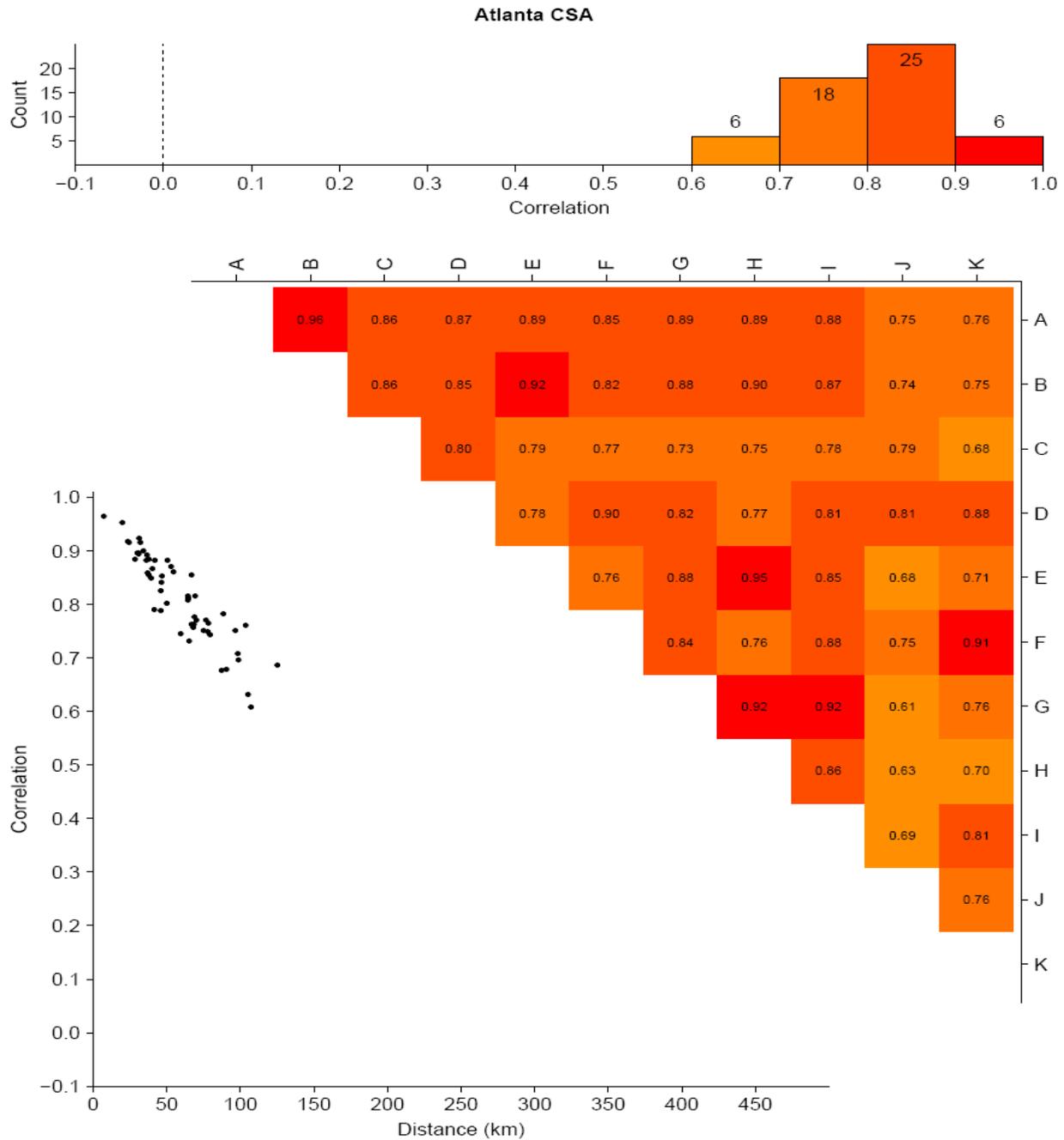
1 Pair-wise monitor comparisons were used to further evaluate spatial variability between  
2 monitors within the 20 focus cities. In the particular case of ground-level O<sub>3</sub>, central-site monitoring  
3 has been justified as a regional measure of exposure mainly on the grounds that correlations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

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

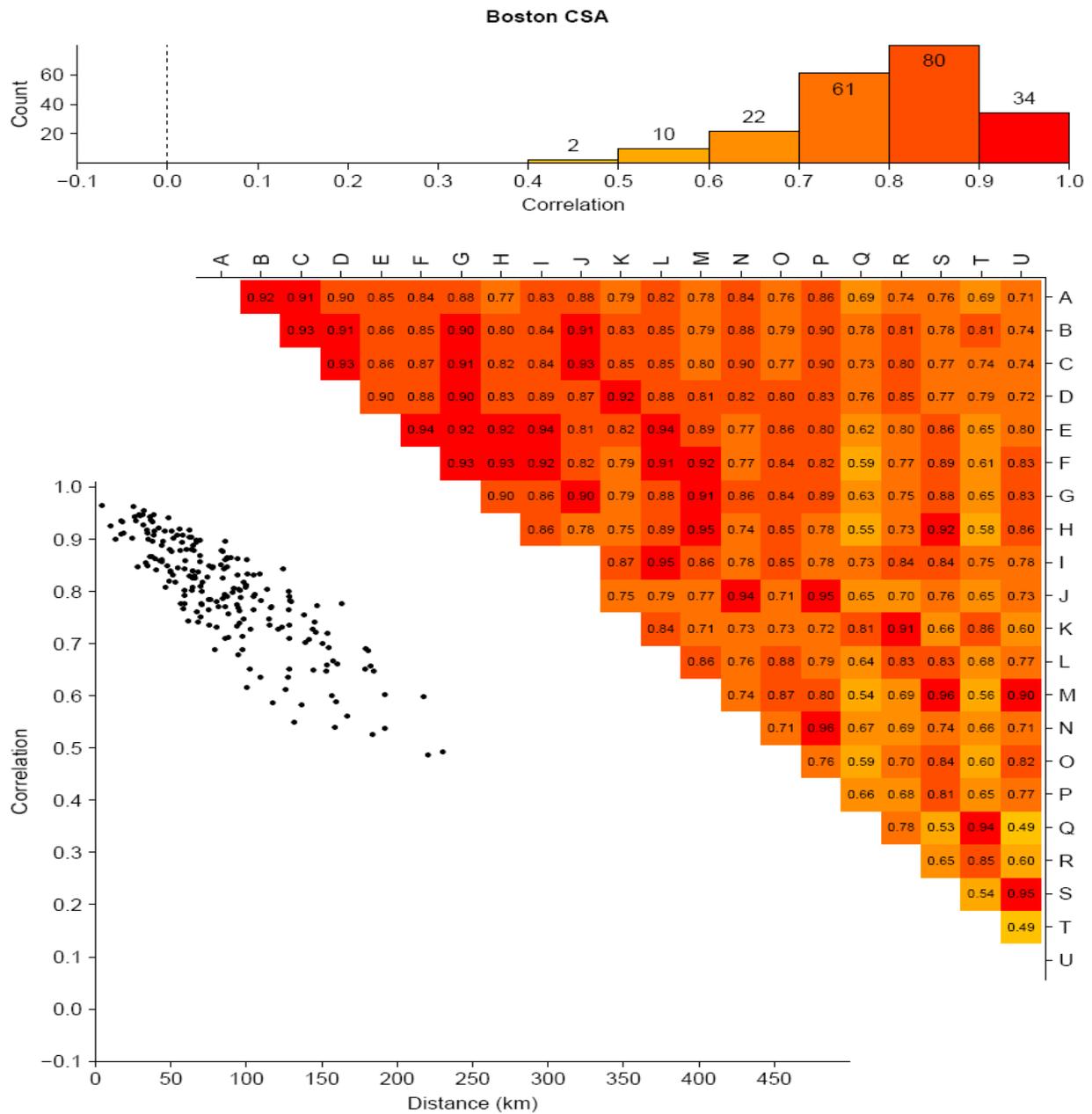
Equation 3-1

13 where X<sub>ij</sub> and X<sub>ik</sub> represent observed concentrations averaged over some measurement averaging  
14 period i (hourly, daily, etc.) at sites j and k, and p is the number of paired observations. A COD of 0  
15 indicates there are no differences between concentrations at paired sites (spatial homogeneity), while  
16 a COD approaching 1 indicates extreme spatial heterogeneity. These methods for analysis of spatial  
17 variability follow those used in previous ISAs for CO, PM, SO<sub>x</sub> and NO<sub>x</sub> as well as those used in  
18 Pinto et al. (2004, [025033](#)) for PM<sub>2.5</sub>.

19 Histograms and contour matrices of the Pearson correlation coefficient between 8-h daily max  
20 O<sub>3</sub> concentrations from each monitor pair are shown in Chapter 3 Appendix, Figure 3A-56 through  
21 Figure 3A-75; examples for Atlanta, Boston and Los Angeles are shown in Figure 3-30 through  
22 Figure 3-32. Histograms, contour matrices, and scatter plots of the COD between 8-h daily max O<sub>3</sub>  
23 concentrations from each monitor pair are shown in Figure 3A-76 through Figure 3A-95; examples  
24 for Atlanta, Boston and Los Angeles are shown in Figure 3-33 through Figure 3-35. These figures  
25 also contain scatter plots of correlation and COD as a function of straight-line distance between  
26 monitor pairs.



**Figure 3-30. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA. 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 3-31. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA. 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.**

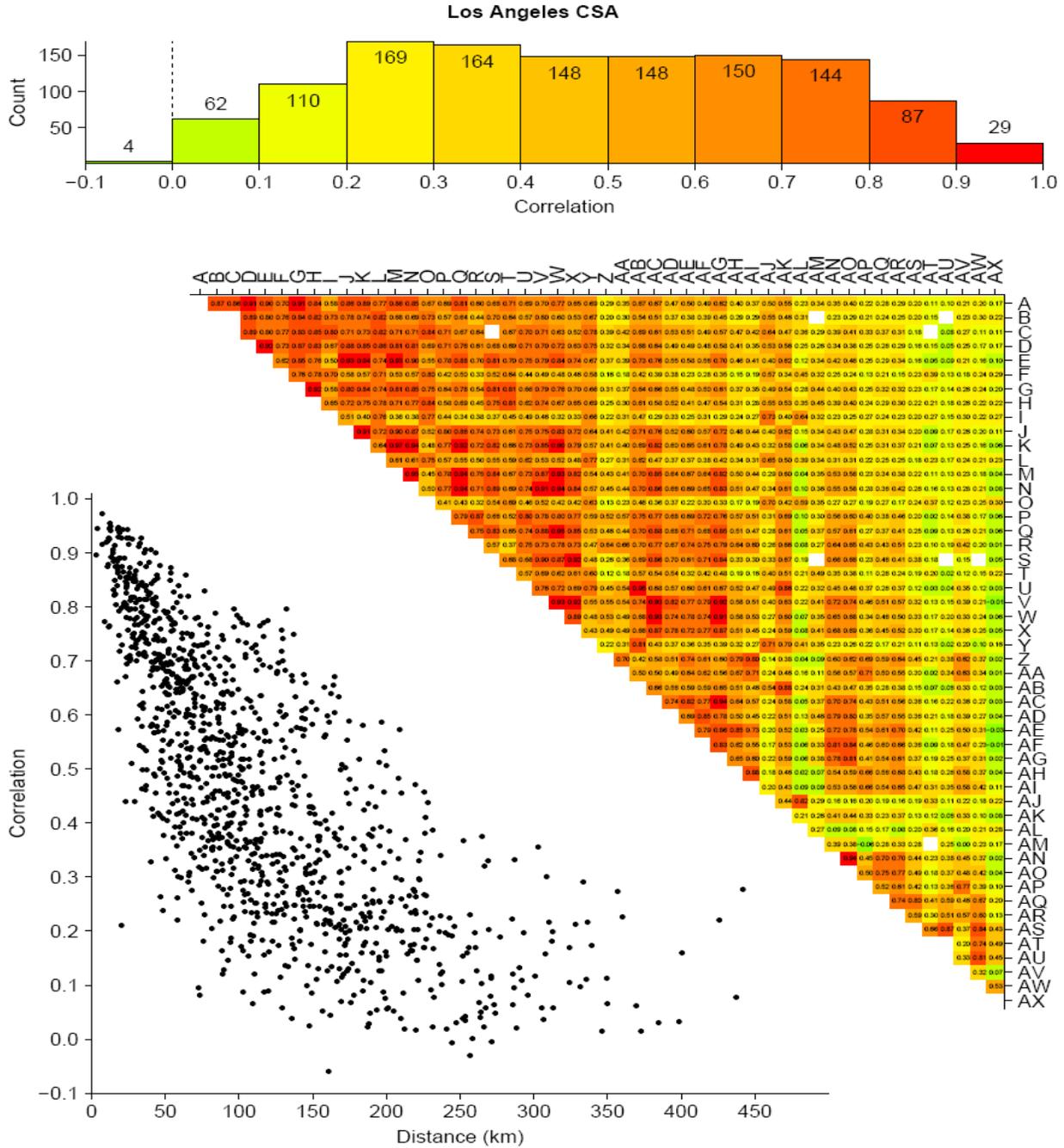
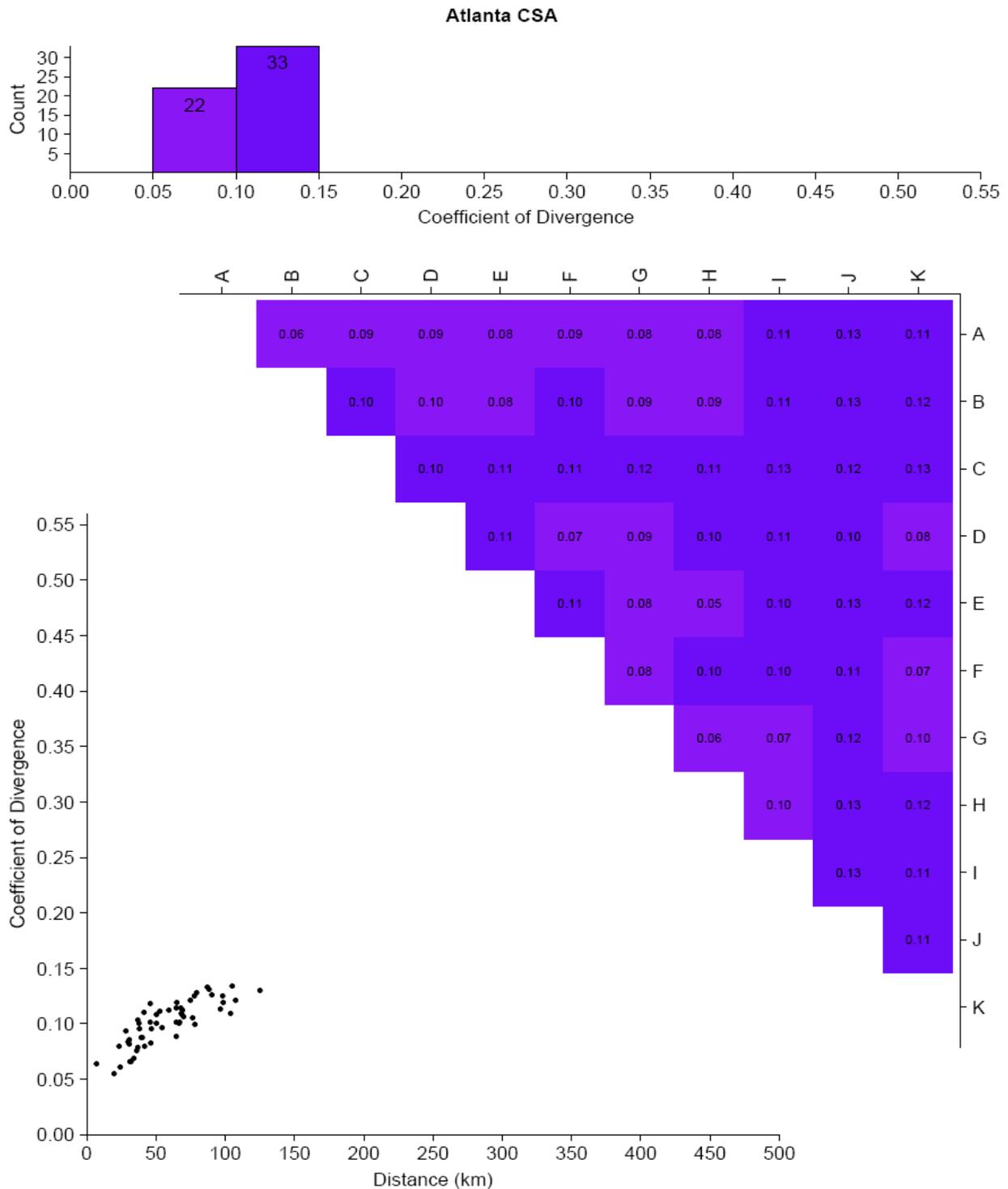
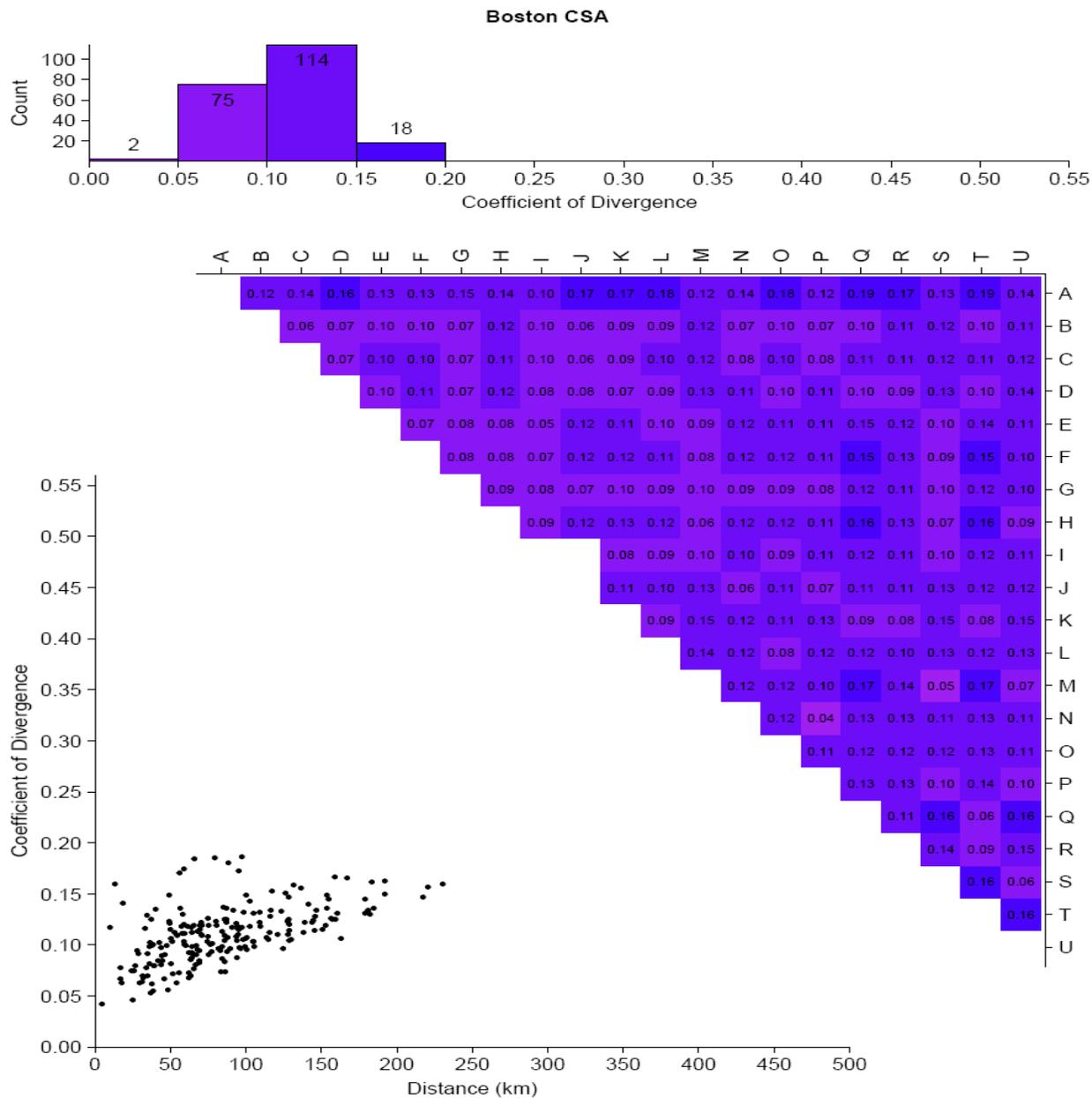


Figure 3-32. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.



**Figure 3-33. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA. 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 3-34. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA. 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.**

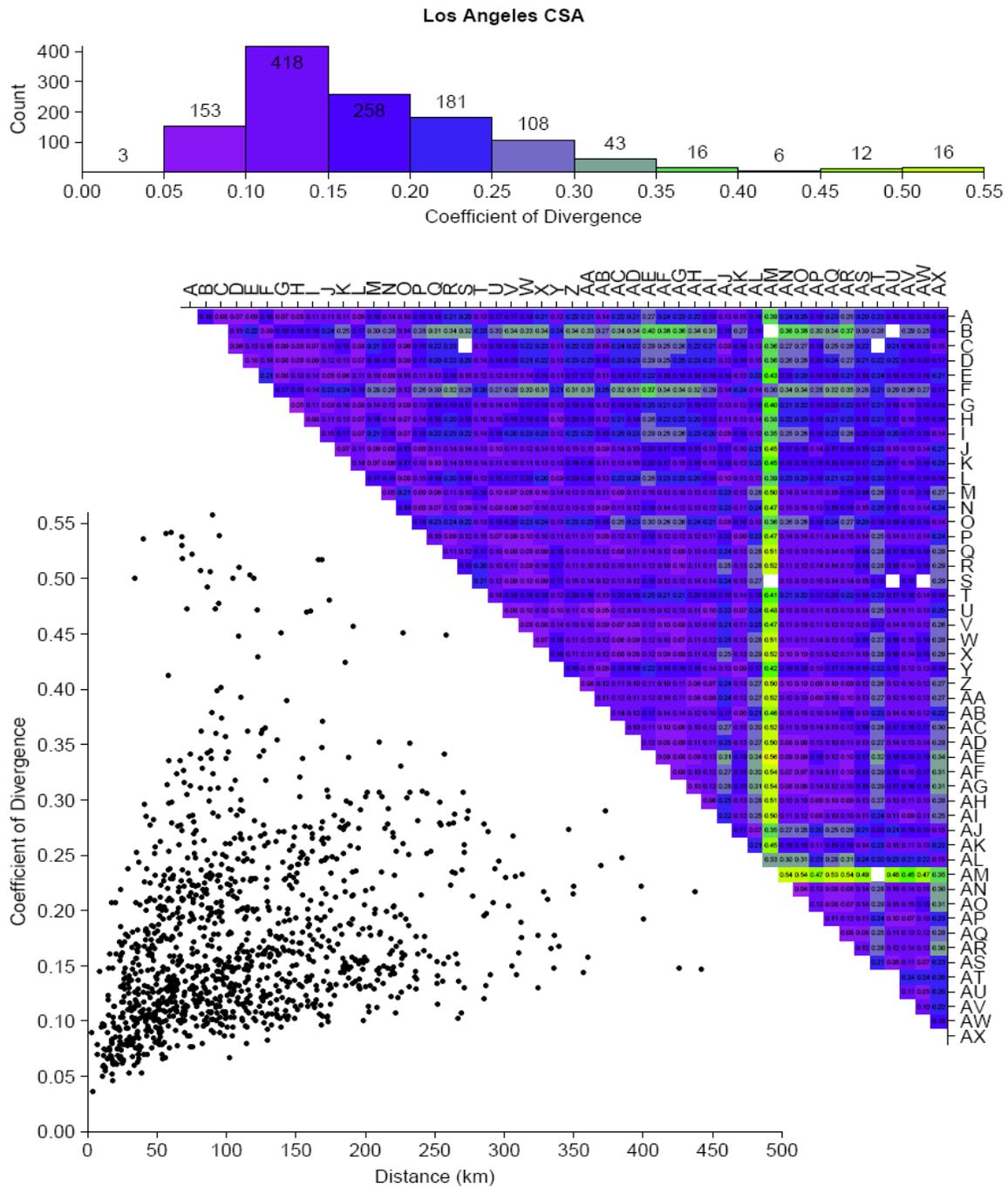
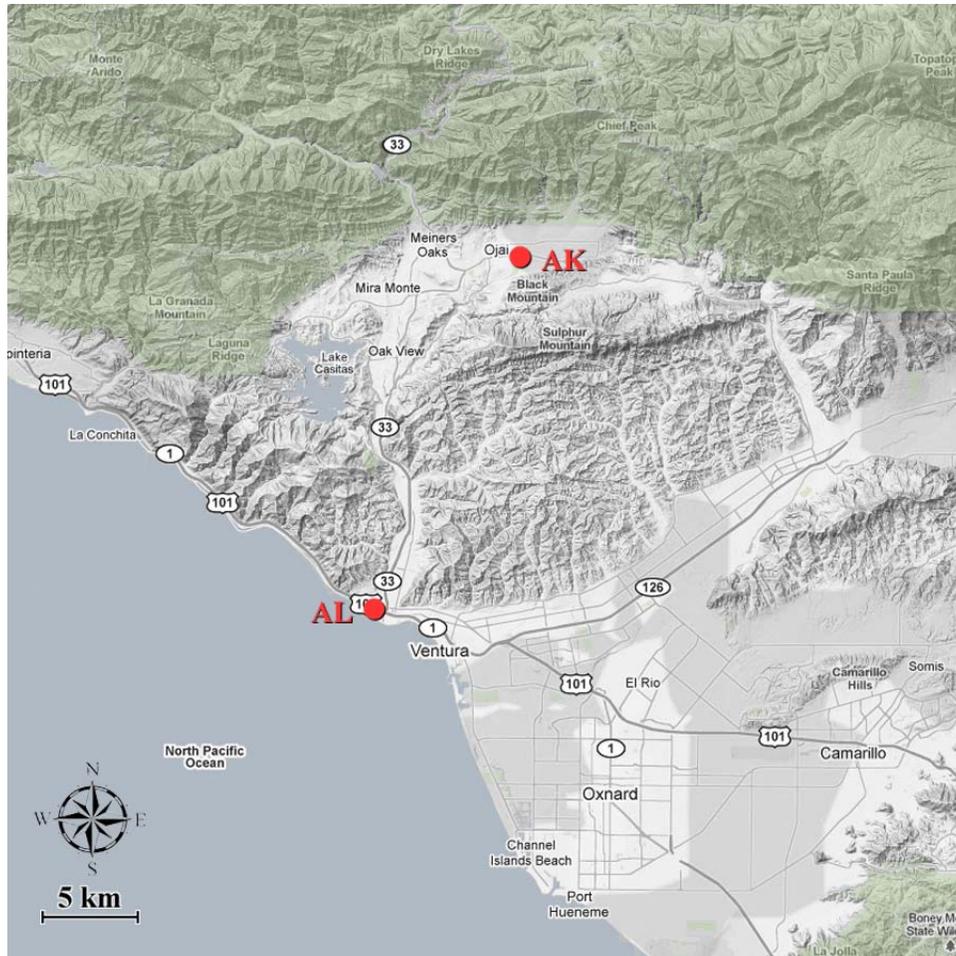


Figure 3-35. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.

1           The monitor pairs within the Atlanta CSA (Figure 3-30) were generally well correlated with  
2 correlations between 8-h daily max O<sub>3</sub> concentrations ranging from 0.61 to 0.96. The correlations  
3 shown in the scatter plot were highest for close monitor pairs and dropped off with distance in a  
4 near-linear form. At a monitor separation distance of 50 km or less, the correlations ranged from 0.79  
5 to 0.96. The monitor pairs within the Boston CSA (Figure 3-31) were also generally well correlated  
6 with correlations ranging from 0.56 to 0.97. Again, the correlations shown in the scatter plot were  
7 highest for close monitor pairs, but there was slightly more scatter in correlation as a function of  
8 distance in the Boston CSA compared with the Atlanta CSA. At a monitor separation distance of 50  
9 km or less, the correlations ranged from 0.74 to 0.97. The monitor pairs within the Los Angeles CSA  
10 (Figure 3-32) showed a much broader range in correlations, extending from -0.06 to 0.97. At a  
11 monitor separation distance of 50 km or less, the correlations shown in the scatter plot ranged from  
12 0.21 to 0.97. The negative and near-zero correlations were between monitors with a relatively large  
13 separation distance (>150 km), but even some of the closer monitor pairs were not very highly  
14 correlated. For example, Site AL located at Emma Wood State Beach in Ventura and Site AK situated  
15 in an agricultural valley surrounded by mountains 20 km inland (see map in Figure 3-36) had a  
16 correlation coefficient of only 0.21 over the 2007-2009 warm-season time period. This was slightly  
17 lower than the correlation between Site AL and Site AX on the Arizona border, 441 km away (R =  
18 0.28). San Francisco (Figure 3A-73) and Seattle (Figure 3A-74) also showed a broad range in pair-  
19 wise correlations, likely resulting from their similar geography where background air coming in  
20 from the Pacific Ocean rapidly mixes with urban pollutants such as NO<sub>x</sub> and VOCs from coastal  
21 cities and is transported downwind into diversified terrain to create highly spatially varying O<sub>3</sub>  
22 concentrations.



**Figure 3-36. 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 m above sea level.**

**Site AK is in an agricultural valley surrounded by mountains, 262 m above sea level.**

1           The COD between 8-h daily max O<sub>3</sub> measured at paired monitors in all CSAs/CBSAs  
 2 (Figure 3A-76 through Figure 3A-95) were generally low, with values similar to those shown in  
 3 Figure 3-33 and Figure 3-34 for Atlanta and Boston. This suggests a generally uniform distribution  
 4 in the 8-h daily max O<sub>3</sub> concentration across monitors within these cities and is consistent with the  
 5 uniformity observed in the box plots (e.g., Figure 3-27, Figure 3-28, Figure 3A-36 through Figure  
 6 3A-55). Los Angeles (Figure 3-29) and San Francisco (Figure 3A-93), however, had several monitor  
 7 pairs with COD >0.30 indicating greater spatial heterogeneity. This is consistent with the variability  
 8 observed in the box plots for these two CSAs (Figure 3-29 and Figure 3A-53). In particular, Site AM  
 9 in the Los Angeles CSA had consistently lower concentrations (median = 20 ppb, IQR = 17-25 ppb)  
 10 relative to other sites in the CSA (Figure 3-26), resulting in high CODs across the board in Figure 3-  
 11 35. The O<sub>3</sub> monitor at Site AM is a tribal monitor located on the Pechanga Tribal Government  
 12 Building in Temecula, CA, and began collecting data on June 9, 2008. It is located in a suburban

1 setting and is classified as a general background monitor. Another close by tribal monitoring site  
2 (site ID = 060731201) located in the Pala Reservation, 9.5 km south of this one (just outside the  
3 boundary of the Los Angeles CSA) reported similarly low 2009 8-h daily max O<sub>3</sub> concentrations  
4 (median = 28 ppb, IQR = 23-32 ppb) between May-June, 2009 (the only warm-season months with  
5 available data from this site between 2007 and 2009).

6 Comparison of monitoring data within the selected focus cities has demonstrated considerable  
7 variability in the concentration fields. Median O<sub>3</sub> concentrations vary considerably within some  
8 urban areas and less so in others. Likewise, pair-wise monitor statistics (R and COD) are very  
9 dependent on the urban area under investigation. There are instances where sites in an urban area  
10 may be moderately correlated, but show substantial differences in absolute concentrations (e.g., Sites  
11 A and D in Boston with R = 0.90, COD = 0.16, and an 11 ppb difference in median 8-h daily max O<sub>3</sub>  
12 concentration). These conclusions are consistent with those drawn in the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
13 2006, [088089](#)) where a subset of these focus cities were investigated using similar statistics. As a  
14 result, caution should be observed in using data from a sparse network of ambient O<sub>3</sub> monitors to  
15 approximate community-scale exposures.

### **Neighborhood-Scale Variability and the Near-Road Environment**

16 O<sub>3</sub> is a secondary pollutant formed in the atmosphere from precursor emissions and therefore  
17 is generally more regionally homogeneous than primary pollutants emitted from stationary or mobile  
18 point sources. However, O<sub>3</sub> titration from primary NO emissions does result in substantial localized  
19 O<sub>3</sub> gradients. This is evident in the near-road environment where fresh NO emissions from motor  
20 vehicles titrate O<sub>3</sub> present in the urban background air, resulting in an O<sub>3</sub> gradient down-wind from  
21 the roadway. Ozone titration occurring in street canyons where NO emissions are continuously being  
22 generated is more efficient because of inhibited transport away from the source of NO.

23 Several studies have reported O<sub>3</sub> concentrations that increase with increasing distance from the  
24 roadway, both upwind and downwind of the road. Beckerman et al. (2008, [096484](#)) measured O<sub>3</sub>  
25 profiles in the vicinity of heavily traveled roadways with Annual Average Daily Traffic (AADT)  
26 >340,000 vehicles in Toronto, Canada. Ozone was observed to increase with increasing distance  
27 from the roadway, both upwind and downwind of the road. This is consistent with scavenging of O<sub>3</sub>  
28 in the near-road environment by reaction with NO to form NO<sub>2</sub>. Upwind of the road, concentrations  
29 were >75% of the maximum observed value at >100 m from the road; downwind, concentrations  
30 were approximately 60% of the maximum within 200-400 m of the road. The O<sub>3</sub> concentration  
31 adjacent to the road on the upwind side was approximately 40% of the maximum value observed at  
32 the site. Concentrations measured with Ogawa passive samplers over a 1-week period ranged from  
33 7.3-19.4 ppb with the mean at the two sites ranging from 13.0-14.7 ppb. In a study of patrol cars  
34 during trooper work shifts, Riediker et al. (2003, [043761](#)) made simultaneous 9-h O<sub>3</sub> measurements  
35 inside patrol cars, at the roadside, and at a centrally-located ambient monitoring site. The roadside  
36 concentrations were approximately 81% of the ambient values (mean of 22.8 ppb versus 28.3 ppb).  
37 Wind direction relative to the roadway was not reported.

1 Johnson (1995, [079215](#)) measured O<sub>3</sub>, NO, and CO concentrations at upwind and downwind  
2 locations near a variety of roadways in Cincinnati, OH. The effects of O<sub>3</sub> scavenging by NO were  
3 apparent in the O<sub>3</sub> reduction in the interval between 9 m upwind and 82 m downwind of the road. A  
4 similar effect was observed by Rodes and Holland (1981, [041110](#)) during an earlier study in which  
5 outdoor O<sub>3</sub> concentrations were monitored downwind of a freeway in Los Angeles, CA. In this study,  
6 O<sub>3</sub> concentrations measured near the roadway were approximately 20% of the concentrations  
7 measured simultaneously at more distant locations judged to be unaffected by the roadway. Minimal  
8 separation distances of the samplers from the roadway to eliminate measurable influence were  
9 estimated to be approximately 400-500 m for NO, NO<sub>2</sub>, and O<sub>3</sub>. Similar results have been observed  
10 outside the U.S., e.g., in the city of Daegu, Korea, where the yearly roadside concentrations of CO  
11 and SO<sub>2</sub> showed a well-defined decreasing trend with distance from the roadway, whereas  
12 concentrations of NO<sub>2</sub> and O<sub>3</sub> exhibited the reverse trend, suggesting that attention should be given  
13 to the NO<sub>2</sub> and O<sub>3</sub> exposures of residents living near roadways (Jo and Park, 2005, [674762](#)). During  
14 the peak O<sub>3</sub> month of May, O<sub>3</sub> concentrations in a residential neighborhood were approximately 40%  
15 higher than concentrations at roadside monitors located 1 m from the edge of multiple-lane freeways.

### 3.6.2.2. Rural-Focused Variability and Ground-Level Vertical Gradients

16 AQS O<sub>3</sub> data for monitors located at several rural monitoring sites (e.g., national parks,  
17 national forests, state parks, etc.) were used to investigate rural-focused O<sub>3</sub> concentration variability  
18 in contrast with the urban-focused variability discussed in Section 3.6.2.1. These rural monitoring  
19 sites tend to be less directly affected by obvious anthropogenic pollution sources than urban sites.  
20 However, they can be regularly affected by transport of O<sub>3</sub> or O<sub>3</sub> precursors from upwind urban  
21 areas, or by local anthropogenic emissions within the rural areas such as emissions from motor  
22 vehicles, power generation, biomass combustion, or oil and gas operations. As a result, monitoring  
23 data from these rural locations are not unaffected by anthropogenic emissions.

24 Six rural focus areas were selected for their geographic distribution across the U.S. as well as  
25 their unique topography and relevance to the ecological assessment in Chapter 9. Table 3-11 lists the  
26 rural focus areas and provides some cursory site information along with the number of available  
27 AQS monitors reporting year-round and only during the warm-season. Accompanying box plots  
28 depicting the distribution of 2007-2009 warm-season 8-h daily max O<sub>3</sub> data from each individual  
29 monitor in the six rural focus areas are included in Figure 3-37. This analysis was restricted to AQS  
30 monitors meeting the same data completeness criteria outlined in Table 3-5 for a direct comparison  
31 with the 20 urban focus areas investigated in Section 3.6.2.1. Given the population-center emphasis  
32 of the AQS network, limited monitoring sites (between one and five) were available for each rural  
33 focus area. Expanded analyses of O<sub>3</sub> concentrations measured using the more rural-focused  
34 CASTNET monitoring network are included in Chapter 9.

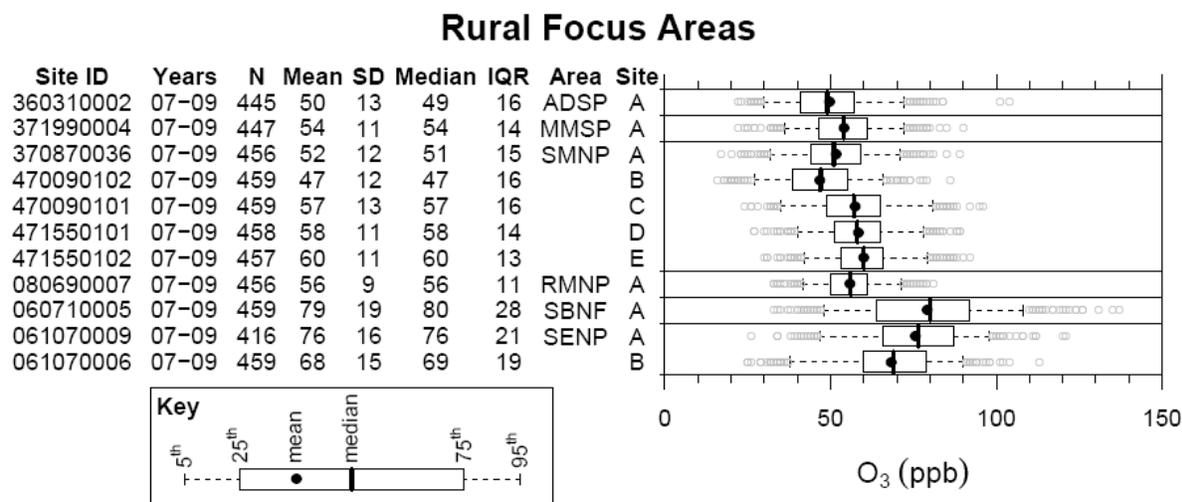
**Table 3-11. Rural focus areas**

Focus Area	Short Name	Year-Round O <sub>3</sub> Monitoring Sites <sup>a</sup>	Warm-Season O <sub>3</sub> Monitoring Sites <sup>b</sup>	Monitor Elevation (m)	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 <sup>c</sup>	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

<sup>a</sup>Number of AQS monitors meeting the year-round data set inclusion criteria; the year-round data set is limited to these monitors.

<sup>b</sup>Number 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.

<sup>c</sup>Same AQS site as Site AE in the Los Angeles CSA shown in Figure 3-26.



**Figure 3-37. 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 including: 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).**

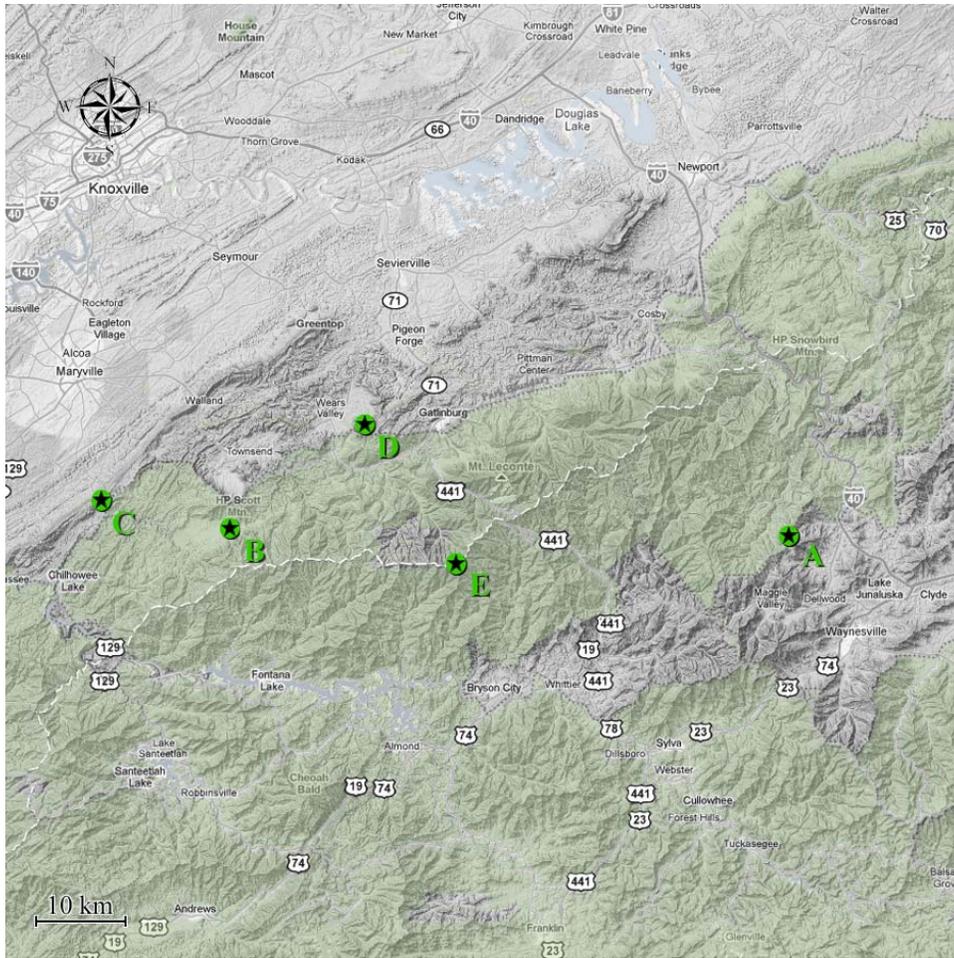
**Eastern Rural Focus Areas**

- 1 In the East, the distribution in warm-season 8-h daily max O<sub>3</sub> concentrations from the
- 2 Adirondack State Park (ADSP) site on Whiteface Mountain in Upstate NY (median = 49 ppb)
- 3 (Figure 3-37) was among the lowest of the rural focus monitors investigated, but was still higher

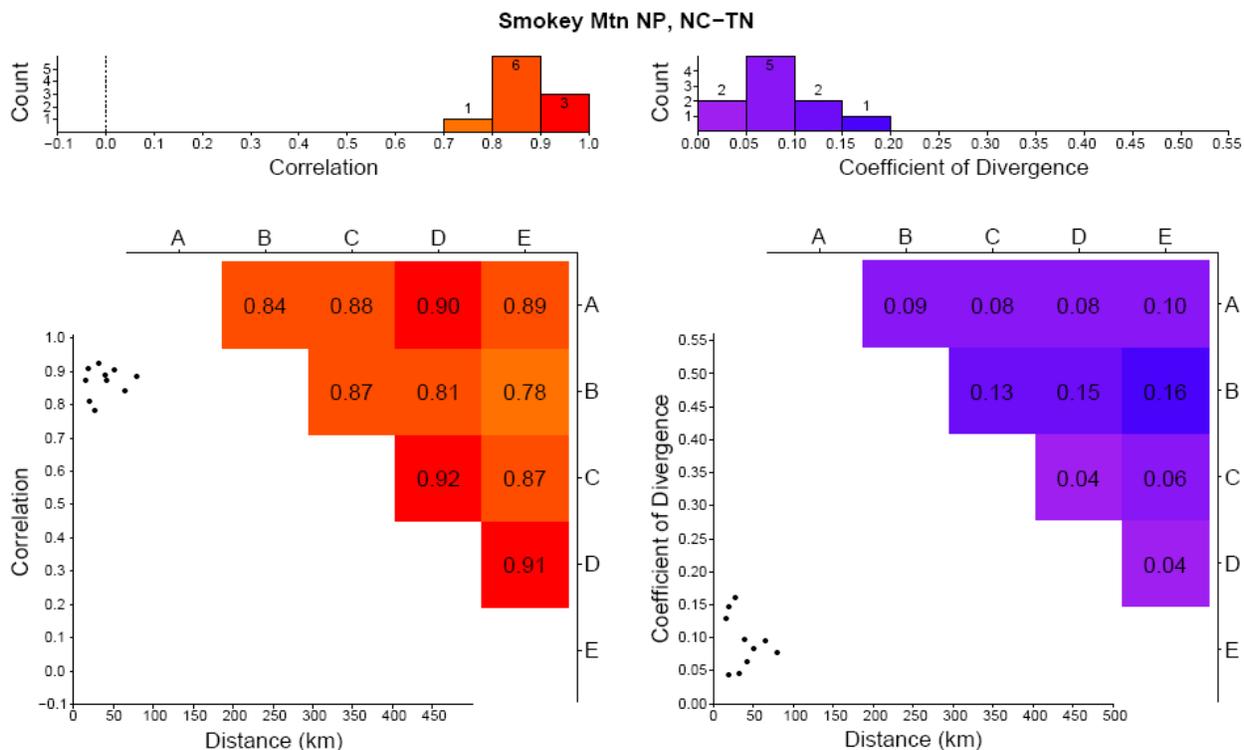
1 than concentration distributions measured in the Boston CSA (medians ranging from 33 to 46 ppb)  
2 (Figure 3-28) located 320 km to the southeast. The ADSP AQS site was included in an analysis for  
3 the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) and had the lowest year-round median hourly O<sub>3</sub>  
4 concentration of the rural forested sites investigated (including Yellowstone NP, the Great Smoky  
5 Mountains NP, and Shenandoah NP). For the Appalachian Mountain monitors in Mount Mitchell  
6 State Park, NC (MMSP) and Great Smoky Mountain National Park, NC-TN (SMNP), there was a  
7 fair amount of variability in concentration distribution. Within SMNP, the median warm-season 8-h  
8 daily max O<sub>3</sub> concentration ranged from 47 ppb at the lowest elevation site (elevation = 564 m; site  
9 ID = 470090102) to 60 ppb at the highest elevation site (elevation = 2021 m; site ID = 471550102);  
10 these sites are shown on the terrain map in Figure 3-38. The warm-season median 8-h daily max O<sub>3</sub>  
11 concentration gradient between these two sites located 26.2 km apart in SMNP was 0.9 ppb per  
12 100 m elevation gain.

13 Data from the five sites within SMNP allowed for further investigation of spatial variability  
14 within the park; Figure 3-39 contains histograms, contour plots and scatter plots as a function of  
15 distance for the pair-wise correlation and COD (defined in Equation 3-1) for SMNP. The correlations  
16 between the five sites ranged from 0.78 to 0.92 and the CODs ranged from 0.04 to 0.16. The plots of  
17 correlation and COD as a function of distance between SMNP monitor pairs in Figure 3-39 show a  
18 large degree of spatial variability between monitors over relatively short distances. A host of factors  
19 may contribute to these variations, including proximity to local O<sub>3</sub> precursor emissions, variations in  
20 boundary-layer influences, meteorology and stratospheric intrusion as a function of elevation, and  
21 differences in wind patterns and transport behavior due to local topography.

22



**Figure 3-38. Terrain map showing the location of five AQS ozone monitoring sites (green/black stars) in Great Smoky Mountain National Park, NC-TN (SMNP). □The lowest elevation site (site ID = 470090102) is 564 m above sea level and the highest elevation site (site ID = 471550102) is 2021 m above sea level.**

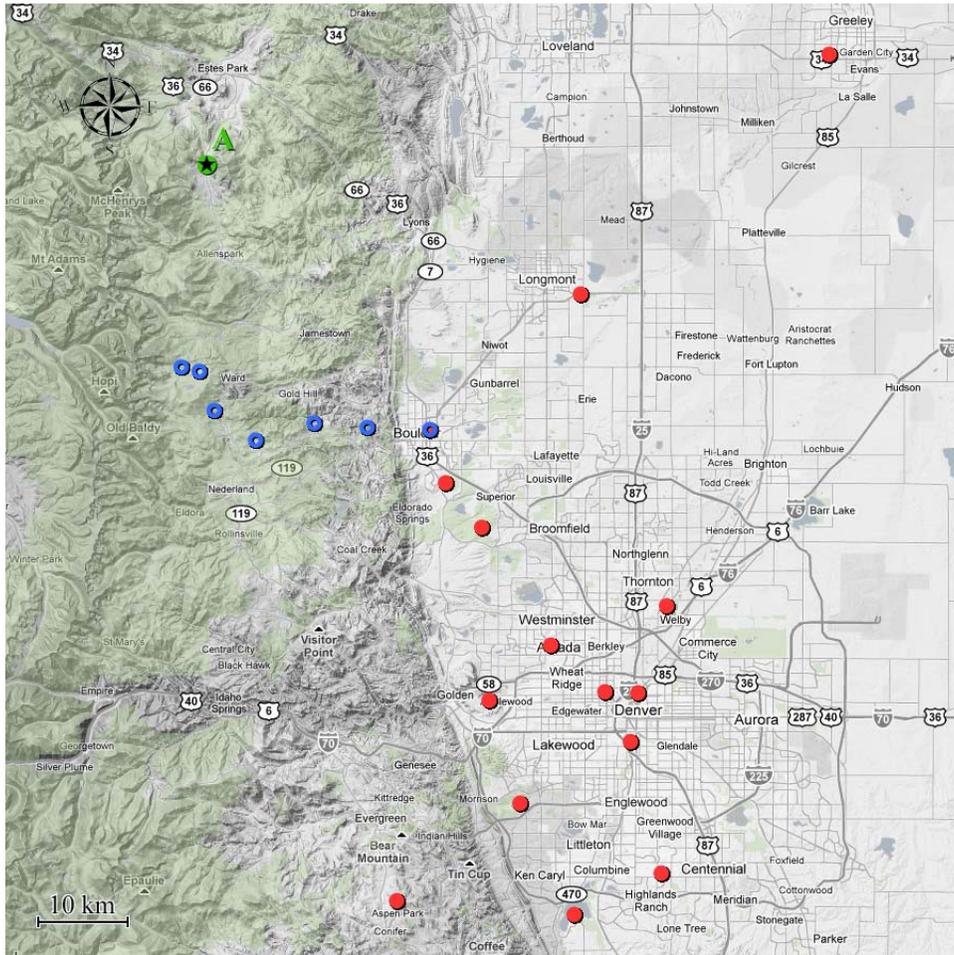


**Figure 3-39. Pair-wise monitor correlations (left) and coefficients of divergence (COD, right) expressed as a histogram (top), contour matrix (middle) and scatter plot vs distance between monitors (bottom) for Great Smoky Mountain National Park, NC-TN (SMNP). The colors in the histogram bins correspond 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.**

### Western Rural Focus Areas

1 The Rocky Mountain National Park (RMNP) site in Colorado at 2743 m in elevation had a  
 2 warm-season 8-h daily max O<sub>3</sub> concentration distribution (median = 56 ppb, IQR = 11 ppb) (Figure  
 3 3-37) that is comparable to the distributions at sites in the Denver CSA located 75 km southeast at  
 4 elevations around 1,600 m (medians ranging from 41 to 59 ppb, IQRs ranging from 10 to 16 ppb; see  
 5 Figure 3A-27). In nearby Boulder County, CO, a 1-year time-series (Sep 2007 - Aug 2008) of  
 6 ambient surface-level O<sub>3</sub> measurements was collected by Brodin et al. (2010, [663706](#)) along an  
 7 elevation gradient ranging from 1608 m to 3528 m. The 7 sites used in this study are shown in  
 8 Figure 3-40 along with the RMNP site and the 15 Denver CSA sites. In fall, winter, and spring, they  
 9 observed a clear monotonic increase in O<sub>3</sub> concentration with elevation, with a rate of increase in the  
 10 mean O<sub>3</sub> concentration of 1.5 ppb per 100 m elevation gain during winter. In summer, the O<sub>3</sub>  
 11 gradient was similar in magnitude over the seven-site transect (1.3 ppb per 100 m), but much less  
 12 monotonic; the majority of the vertical gradient occurred between the lowest two sites (4.5 ppb per  
 13 100 m) and between the highest two sites (5.5 ppb per 100 m), with the middle five sites all having  
 14 approximately equal median O<sub>3</sub> concentrations. Ozone concentrations at the lowest site in Boulder

1 were influenced by NO titration as evidenced by traffic-related diel cycles in O<sub>3</sub> concentrations, but  
2 the remaining six sites were located at elevation in more rural/remote settings and illustrate a  
3 positive surface-level O<sub>3</sub> elevation gradient similar to that seen in SMNP and typical of areas under  
4 less direct influence of boundary layer pollution.



**Figure 3-40. 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, 663706) (blue circles) study. Elevations range from approximately 1600 m above sea level in Denver and Boulder to 3528 m above sea level at the highest mountainous site.**

5 The three sites in California—one in San Bernardino National Forest (SBNF) and two in  
6 Sequoia National Park (SENP)—had the highest distribution of 8-h daily max O<sub>3</sub> concentrations of  
7 the selected rural focus area monitors included in Figure 3-37. The SBNF site had a warm-season 8-  
8 h daily max O<sub>3</sub> concentration mean of 80 ppb and a maximum of 137 ppb measured on July 1, 2007.  
9 This site is located in Crestline, CA, 90 km down-wind of Los Angeles in the San Bernardino

1 Mountains. This site was included in the Los Angeles CSA shown in Figure 3-26 (Site AE) and had  
2 the highest median 8-h daily max O<sub>3</sub> concentration of any AQS site in the Los Angeles CSA during  
3 this time period (Figure 3-29). This site was also included in an analysis performed for the 2006 O<sub>3</sub>  
4 AQCD (U.S. EPA, 2006, [088089](#)) where similarly high O<sub>3</sub> concentrations were observed using  
5 2004 year-round hourly observations.

6 The two sites in SENP are located 9.7 km apart at contrasting elevations as is illustrated in the  
7 terrain map in Figure 3-41. The correlation in 8-h daily max O<sub>3</sub> between these two sites was 0.86 and  
8 the COD was 0.09, which are within the range in correlations and CODs for SMNP (Figure 3-39).  
9 The distribution of 8-h daily max O<sub>3</sub> concentrations at the lower elevation site (elevation = 560 m;  
10 site ID = 061070009) is shifted slightly higher with a median of 76 ppb compared to the higher  
11 elevation site (elevation = 1890 m; site ID = 061070006) with a median of 69 ppb. The lower  
12 elevation site is located at the entrance to the park and is at a low enough elevation to be influenced  
13 by boundary layer pollution coming upwind from Fresno and the San Joaquin Valley. The higher  
14 elevation site is in the free troposphere above the planetary boundary layer and is less influenced by  
15 such pollution. This gives rise to a negative average surface-level elevation gradient of -0.5 ppb per  
16 100 m elevation gain in SENP, illustrating the location-specific complexities inherent to high-altitude  
17 surface-level O<sub>3</sub> concentrations.

18 Since O<sub>3</sub> produced from emissions in urban areas is transported to more rural downwind  
19 locations, elevated O<sub>3</sub> concentrations can occur at considerable distances from urban centers. In  
20 addition, major sources of O<sub>3</sub> precursors such as highways, power plants, biomass combustion, and  
21 oil and gas operations are commonly found in rural areas, adding to the O<sub>3</sub> in these areas. Due to  
22 lower chemical scavenging in nonurban areas, O<sub>3</sub> tends to persist longer in rural than in urban areas  
23 which tends to lead to higher cumulative exposures in rural areas influenced by anthropogenic  
24 precursor emissions. The persistently high O<sub>3</sub> concentrations observed at many of these rural sites  
25 investigated here indicate that cumulative exposures for humans and vegetation in rural areas can be  
26 substantial and often higher than cumulative exposures in urban areas.

27

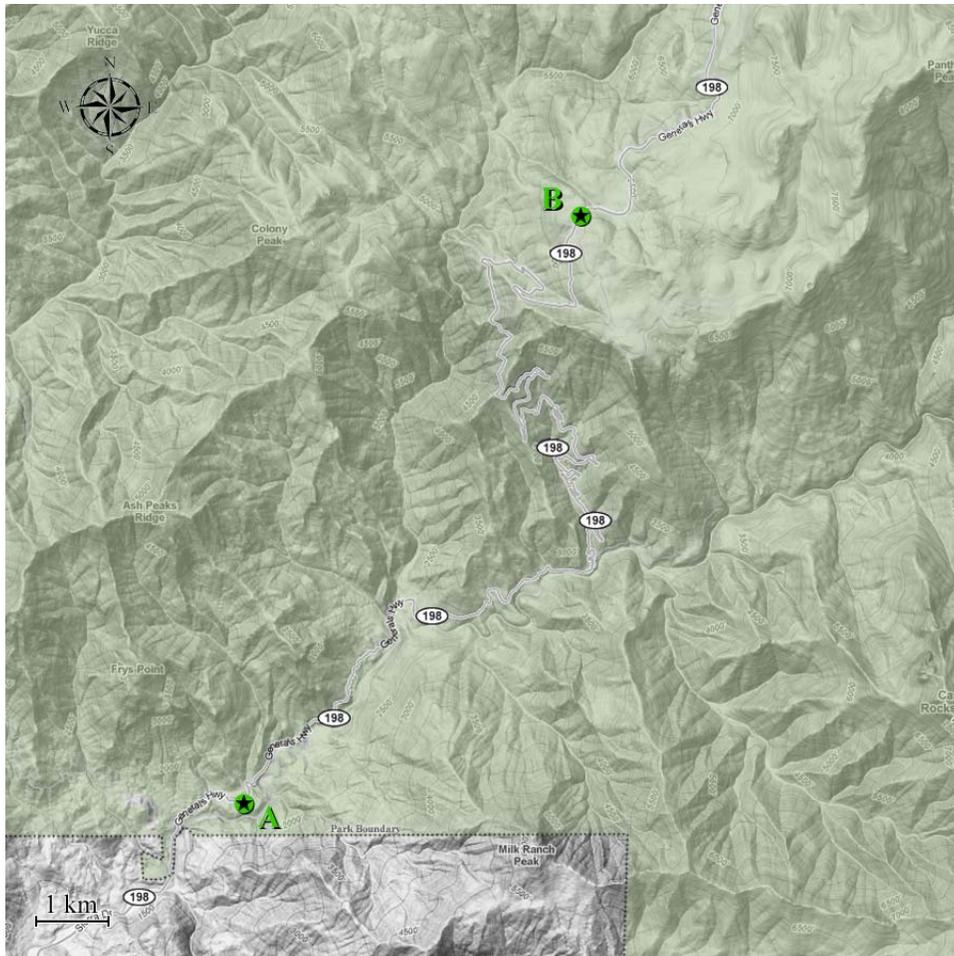
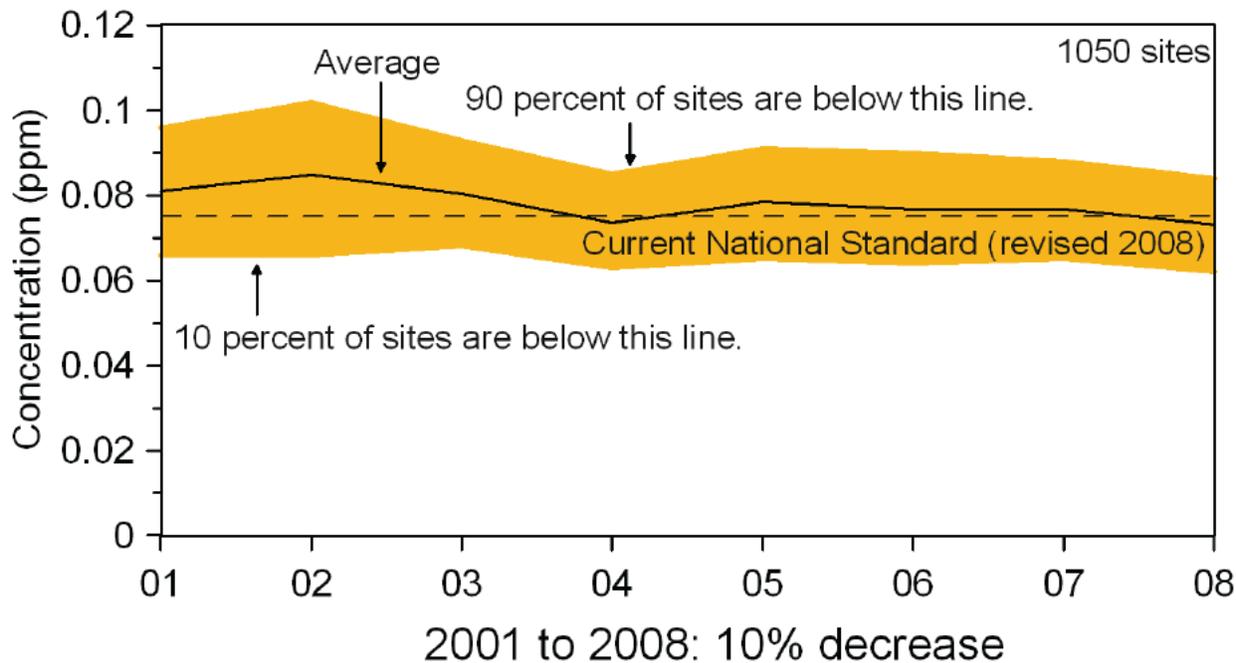


Figure 3-41. Terrain map showing the location of two AQS ozone monitoring sites (black/green stars) in Sequoia National Park, CA. The lower site (site ID = 061070009) is 560 m above sea level and the higher site (site ID = 061070006) is 1890 m above sea level.

### 3.6.3. Temporal Variability

#### 3.6.3.1. Multiyear Trends

1           Nationally, O<sub>3</sub> concentrations have declined over the last decade, as shown in Figure 3-42  
 2 from the 2010 National Air Quality Status and Trends report (U.S. EPA, 2010, [647278](#)). The  
 3 majority of this decline occurred before 2004 with national average concentrations remaining  
 4 relatively flat between 2004 and 2008. The large decreases in 2003 and 2004 coincides with NO<sub>x</sub>  
 5 emissions reductions resulting from implementation of the NO<sub>x</sub> State Implementation Plan (SIP)  
 6 Call rule, which began in 2003 and was fully implemented in 2004. This rule was designed to reduce  
 7 NO<sub>x</sub> emissions from power plants and other large combustion sources in the eastern U.S. The  
 8 reduction in NO<sub>x</sub> and O<sub>3</sub> during the 2003-2004 timeframe is particularly evident in the eastern U.S.  
 9 where the NO<sub>x</sub> SIP Call was focused (U.S. EPA, 2010, [647278](#)).



Source: U.S. EPA (2010, [647278](#))

**Figure 3-42. National 8-h ozone trends, 2001-2008 (average of the annual fourth highest 8-h daily max concentrations in ppm).**

1 Weather can have a strong influence on O<sub>3</sub> and O<sub>3</sub> trends as well. The number of hot, dry days  
 2 can significantly alter the number of high-O<sub>3</sub> days in any given year, even if O<sub>3</sub>-forming emissions  
 3 do not change. To better evaluate the progress and effectiveness of emissions reduction programs,  
 4 EPA uses a statistical model to estimate the influence of atypical weather on O<sub>3</sub> formation  
 5 (U.S. EPA, 2010, [647278](#)). After adjusting for the influence of weather, the trend in national 8 h O<sub>3</sub>  
 6 concentrations between 2001 and 2008 increases slightly from an 8% reduction to an 11% reduction.  
 7 These trends are region-specific, with lower reductions (3%) in California and higher reductions  
 8 (15%) in eastern states over this same time period (U.S. EPA, 2010, [647278](#)).

9 Sites that showed the greatest reduction in O<sub>3</sub> over this period were in or near the following  
 10 metropolitan areas: Anderson, IN; Chambersburg, PA; Chicago, IL; Cleveland, OH; Houston, TX;  
 11 Michigan City, IN; Milwaukee, WI; New York, NY; Racine, WI; Watertown, NY; and parts of  
 12 Los Angeles, CA. Sites that showed an increase in O<sub>3</sub> over this time period and had measured  
 13 concentrations above the 2008 O<sub>3</sub> standard<sup>1</sup> during the 2006-2008 time period were located in or  
 14 near the following metropolitan areas: Atlanta, GA; Baton Rouge, LA; Birmingham, AL; Denver,  
 15 CO; El Centro, CA; San Diego, CA; Seattle, WA; and parts of Los Angeles, CA.

16 As noted in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), trends in national parks and rural  
 17 areas are similar to nearby urban areas, reflecting the regional nature of O<sub>3</sub> pollution. However,  
 18 caution should be exercised in using trends calculated at national parks to infer contributions from

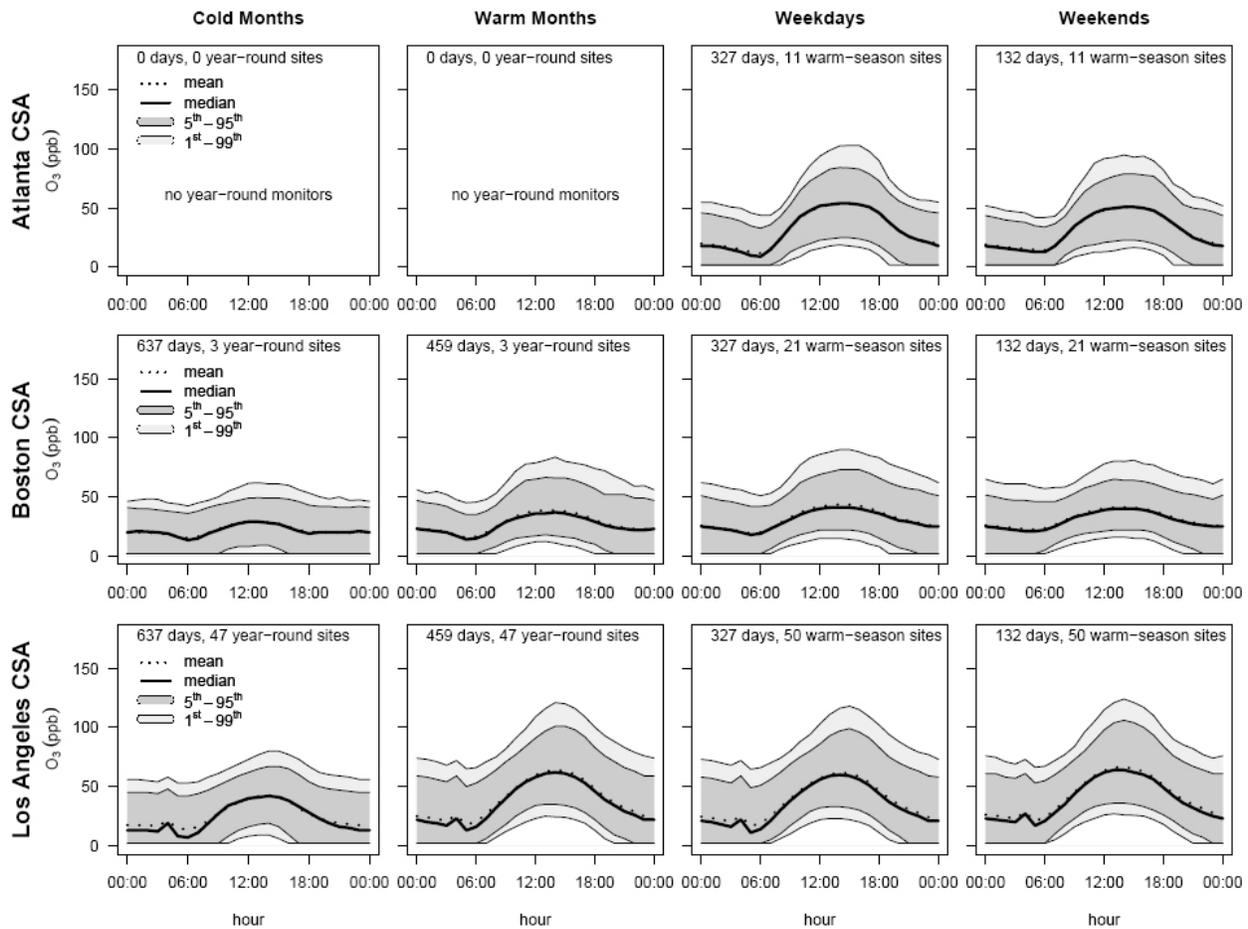
<sup>1</sup> On September 16, 2009, EPA announced it would reconsider the 2008 O<sub>3</sub> NAAQS, which, at the time, included primary and secondary standards of 0.075 ppm (8-h daily max).

1 distant sources either inside or outside of North America because of the influence of regional  
2 pollution (issues relating to background O<sub>3</sub> concentrations are discussed in Section 3.4). Trends in  
3 tropospheric O<sub>3</sub> on a global scale have been monitored around the world using ozonesondes, remote  
4 surface monitors, mountain top monitors, and satellites. Global trends in the burden of tropospheric  
5 O<sub>3</sub> as they relate to climate change are discussed in Chapter 10, Section 10.2.3.1.

### 3.6.3.2. Hourly Variations

6 Ozone concentrations show a strong degree of diel variability resulting from daily patterns in  
7 temperature, sunlight, and precursor emissions. Other factors, such as the relative importance of  
8 transport versus local photochemical production and loss rates, the timing for entrainment of air from  
9 the nocturnal residual boundary layer, and the diurnal variability in mixing layer height also play a  
10 role in daily O<sub>3</sub> patterns. The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) looked at composite urban  
11 diel variations from April to October 2000 to 2004 and found 1-h maxima to occur in mid-afternoon  
12 and 1-h minima to occur in early morning. On a national basis, however, there was a high degree of  
13 spread in these times and caution was raised in extrapolating results from one city to another in  
14 determining the time of day for O<sub>3</sub> maxima and minima.

15 A similar analysis was performed using the 1-h avg O<sub>3</sub> data from the 20 focus cities listed in  
16 Table 3-9. The year-round data set described in Table 3-5 was used to compare diel patterns during  
17 cold months (October - April) and warm months (May - September) between 2007 and 2009. The  
18 warm-season data set, also described in Table 3-5, was used to compare weekday and weekend diel  
19 patterns. Figure 3A-96 through 3A-115 show these patterns for each of the cities; examples for  
20 Atlanta, Boston and Los Angeles are shown in Figure 3-43.



**Figure 3-43. Diel patterns in 1-h avg ozone for Atlanta, Boston and Los Angeles 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). Atlanta had no year-round monitors available for the cold month/warm month comparison.**

1 In general, all the urban areas showed 1-h daily max concentrations occurring typically in the  
 2 early afternoon. In all cities, these afternoon peaks were more pronounced in the warm months than  
 3 in the cold months. However, a small peak was still present during the cold months. During warm  
 4 months, the difference between the median daily extrema varied considerably by city. For example,  
 5 in Los Angeles (Figure 3-43), the median 1-h daily min (10 ppb) at ~5:00 a.m. was 50 ppb less than  
 6 the median 1-h daily max (60 ppb) at ~2:00 p.m. By contrast, in Boston (Figure 3-43), the median  
 7 1-h daily min (13 ppb) occurred at the same time, but was only 25 ppb less than the median 1-h daily  
 8 max (38 ppb). Cities with large daily swings (>40 ppb) in median 1-h O<sub>3</sub> concentrations included  
 9 Atlanta, Birmingham, Los Angeles, Phoenix, Pittsburgh, and Salt Lake City (Figure 3A-96, 3A-98,  
 10 3A-105, 3A-109, 3A-110, and 3A-111). Cities with small daily swings (<25 ppb) in median 1-h O<sub>3</sub>  
 11 concentrations included Boston, Minneapolis, San Francisco and Seattle (Figure 3A-99, 3A-106, 3A-  
 12 113, and 3A-114). These results are very similar to those found in the 2006 O<sub>3</sub> AQCD (U.S. EPA,

1 2006, [088089](#)) where many of these same urban areas were investigated. This supports the  
2 conclusions drawn in the AQCD that diel patterns in O<sub>3</sub> have remained stable over the last 20 years,  
3 with times of occurrence of the daily maxima varying by no more than an hour from year to year.

4 Using the warm-season data, there was very little difference in the median diel profiles for  
5 weekdays compared with weekends across all cities. This result stresses the complexity of O<sub>3</sub>  
6 formation and the importance of meteorology, entrainment, biogenic precursor emissions, and  
7 transport in addition to anthropogenic precursor emissions. There was, however, a subtle deviation  
8 between weekdays and weekends in the lower percentiles (1st and 5th) of the distribution. The lower  
9 end of the distribution tended to be lower on weekdays relative to weekends. This is consistent with  
10 analyses in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) and is a result of lower traffic volumes on  
11 weekends relative to weekdays, leading to less NO emissions and O<sub>3</sub> titration on the weekends.

12 Seasonal and site-to-site variations in diel patterns within a subset of the urban focus areas  
13 presented here were investigated in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). In northern cities,  
14 there was substantial seasonal variability in the diel patterns with higher extreme values in the O<sub>3</sub>  
15 distribution during the warm season than during the cold season. In southern cities, the seasonal  
16 differences in extreme O<sub>3</sub> concentrations were much smaller, and some of the highest O<sub>3</sub>  
17 concentrations in the Houston CSA were found outside of summer. The general pattern that emerged  
18 from investigating site-to-site variability within the urban areas was that peaks in 1-h avg O<sub>3</sub>  
19 concentrations are higher and tend to occur later in the day at downwind sites relative to sites located  
20 in the urban core. Differences between sites were not only related to the distance between them, but  
21 also depend on the presence or absence of nearby O<sub>3</sub> sources or sinks.

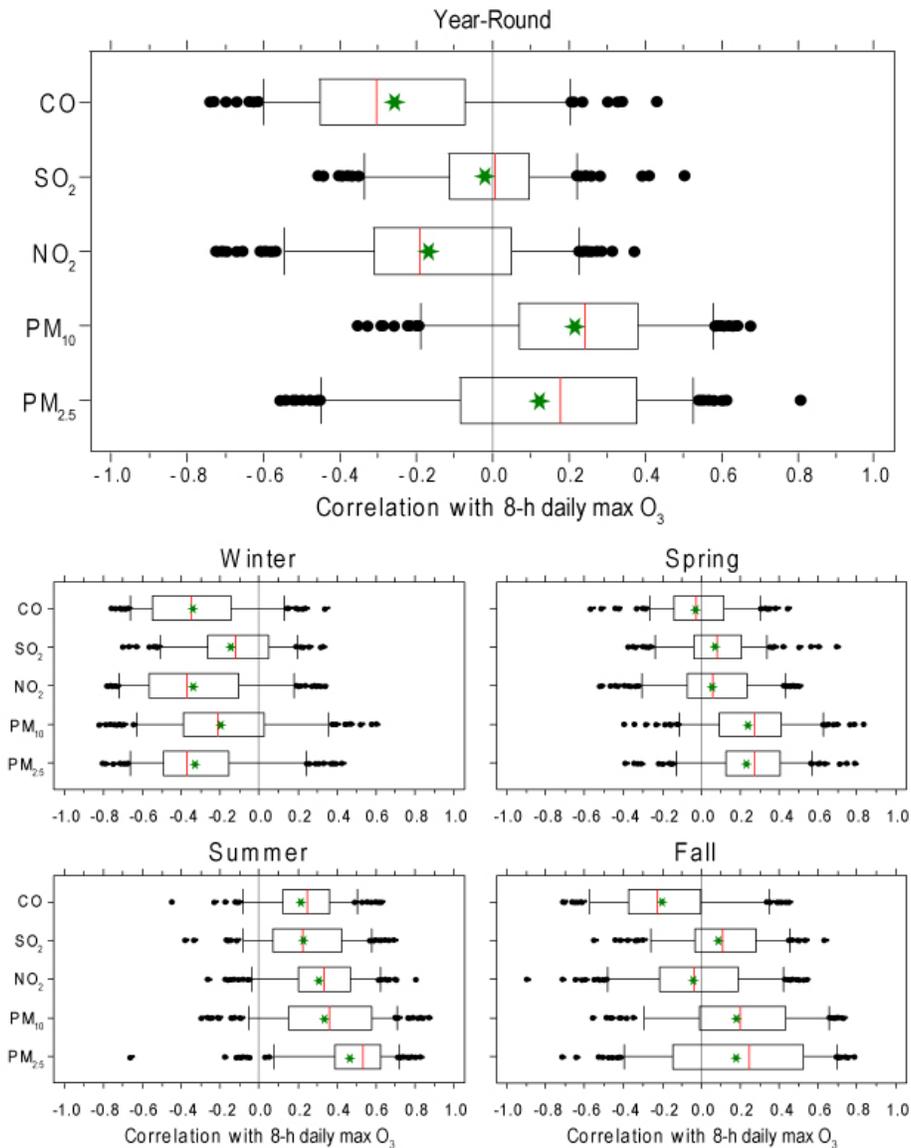
### 3.6.4. Associations with Co-pollutants

22 Correlations between O<sub>3</sub> and other criteria pollutants are discussed in this section. Since O<sub>3</sub> is  
23 a secondary pollutant formed in the atmosphere from precursor emissions, it is not expected to be  
24 highly correlated with primary pollutants such as CO and NO<sub>x</sub>. Furthermore, O<sub>3</sub> formation is  
25 strongly influenced by meteorology, entrainment, and transport of both O<sub>3</sub> and O<sub>3</sub> precursors,  
26 resulting in a broad range in correlations with other pollutants which can vary substantially with  
27 season.

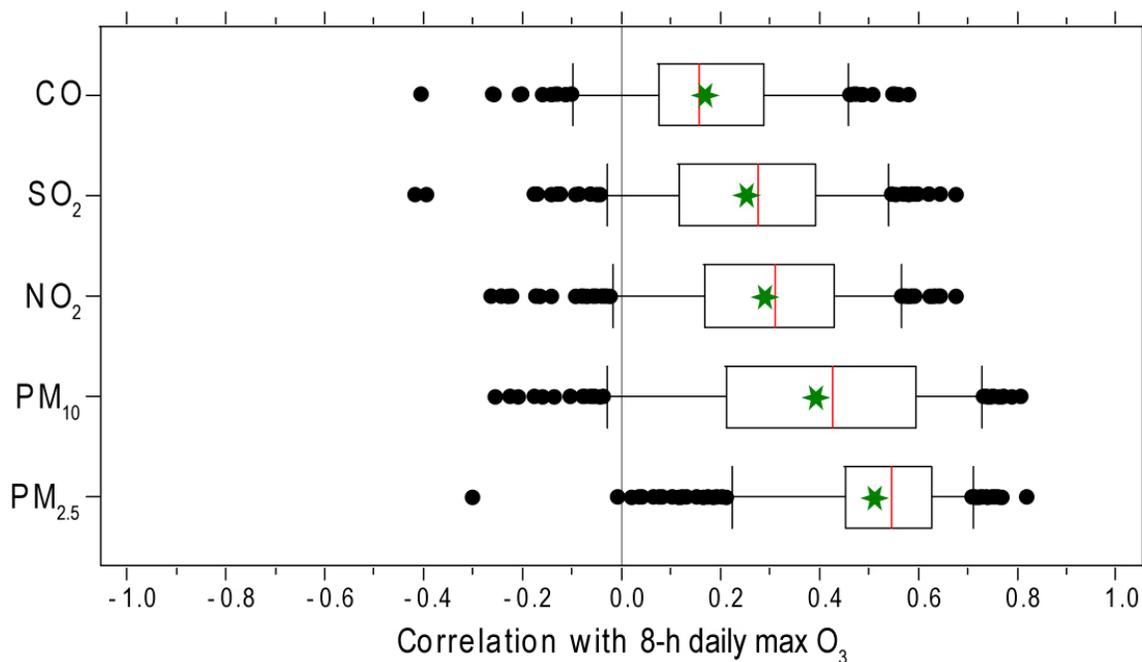
28 To investigate correlations with co-pollutants, 8-h daily max O<sub>3</sub> from the year-round and  
29 warm-season data sets (Table 3-6 and Table 3-7) were compared with co-located 24-h avg CO, SO<sub>2</sub>,  
30 NO<sub>2</sub>, PM<sub>2.5</sub> and PM<sub>10</sub> obtained from AQS for 2007-2009. Figure 3-44 and Figure 3-45 contain  
31 co-pollutant box plots of the correlation between co-located monitors for the year-round data set and  
32 the warm-season data set, respectively.

33 The year-round 8-h daily max O<sub>3</sub> data (Figure 3-44) had a very wide range in correlations with  
34 all the 24-h avg co-pollutants. A more clear pattern emerged when the data were stratified by season  
35 (bottom four plots in Figure 3-44) with mostly negative correlations in the winter and mostly  
36 positive correlations in the summer for all co-pollutants. In summer, the IQR in correlations is  
37 positive for all co-pollutants. However, the median seasonal correlations are still modest at best with

1 the highest positive correlation at 0.52 for PM<sub>2.5</sub> in the summer and the highest negative correlation  
 2 at -0.38 for PM<sub>2.5</sub> in the winter. Spring and fall lie in between with spring having a slightly narrower  
 3 distribution than fall for all co-pollutants. The warm-season 8-h daily max O<sub>3</sub> data (Figure 3-45)  
 4 shows a very similar distribution to the summer stratification of the year-round data due to their  
 5 overlap in time periods (May-Sept and Jun-Aug, respectively).



**Figure 3-44. 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, SO<sub>2</sub>, NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> from AQS, 2007-2009 (top figure) 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 dots).**



**Figure 3-45. 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, SO<sub>2</sub>, NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> from AQS, 2007-2009. Shown are the median (red line), mean (green star), inner-quartile range (box), 5th and 95th percentiles (whiskers), and extremes (black dots).**

1           The seasonal fluctuations in correlations present in Figure 3-44 result in part from the mixture  
 2 of primary and secondary sources for the co-pollutants. For example, O<sub>3</sub> is a secondary pollutant  
 3 whereas PM<sub>2.5</sub> has both primary and secondary origins and these two pollutants show the largest  
 4 summertime/wintertime swing in correlation distributions. This situation arises because the  
 5 secondary component to PM<sub>2.5</sub> is larger during the summer and is formed in conditions conducive to  
 6 secondary O<sub>3</sub> formation. The result is positive correlations between O<sub>3</sub> and PM<sub>2.5</sub> during the summer.  
 7 During the winter, photochemical production of O<sub>3</sub> is much smaller than during summer and O<sub>3</sub>  
 8 comes mainly from aloft, i.e., the free troposphere (see Section 3.4 for further details). In addition,  
 9 concentrations of PM<sub>2.5</sub> are much lower aloft. On relatively clean days, this can lead to high  
 10 concentrations of O<sub>3</sub> and lower concentrations of primary pollutants such as PM<sub>2.5</sub> or NO. On  
 11 relatively dirty days with elevated NO and PM<sub>2.5</sub>, the intruding O<sub>3</sub> is readily titrated by NO in the  
 12 boundary layer. These processes result in negative correlations between O<sub>3</sub> and PM<sub>2.5</sub> during the  
 13 winter.

## 3.7. Chapter 3 References

A list of all references considered for inclusion in this chapter can be found at

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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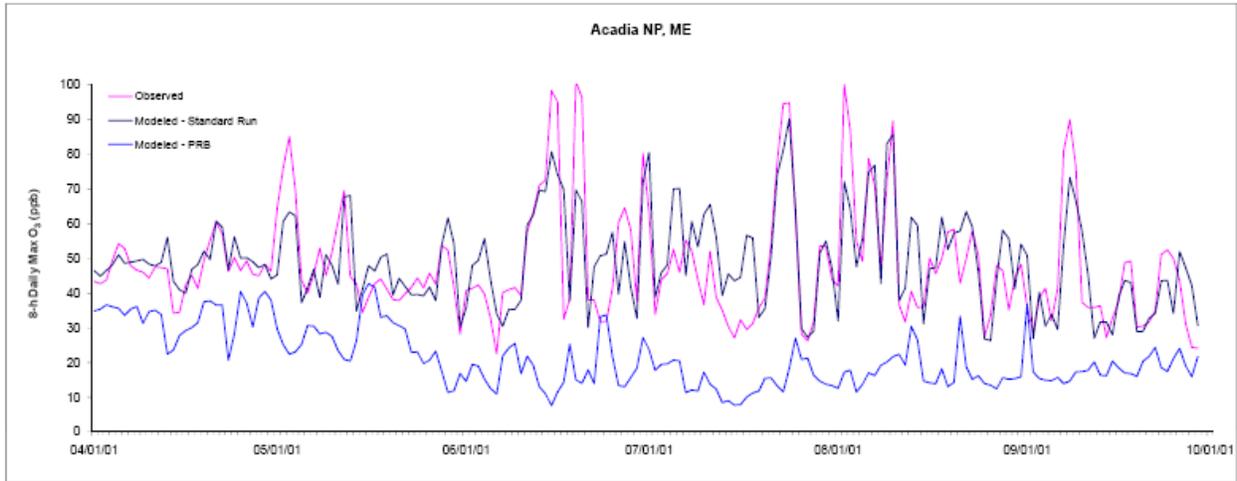
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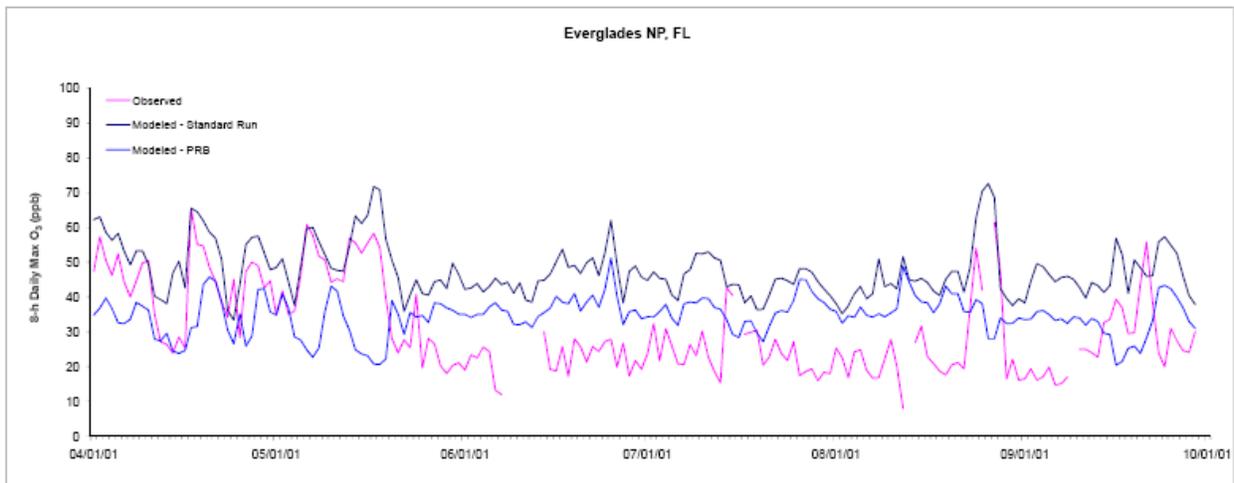
## 3.8. Chapter 3 Appendix – Supplemental Figures and Tables

### 3.8.1. Time Series of GEOS-Chem Model Predictions and Observations at Selected CASTNET Sites

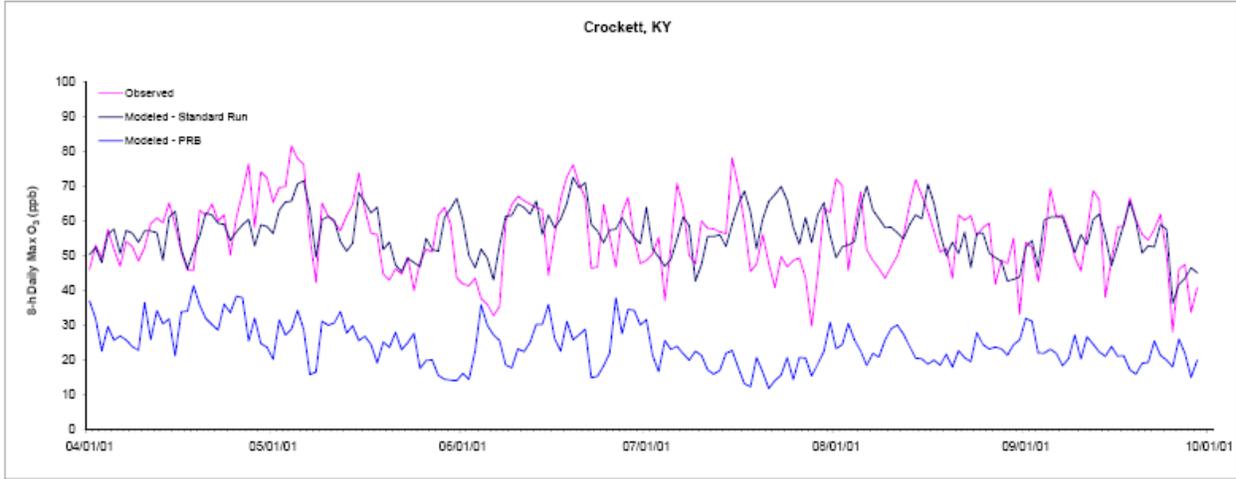
1            This section contains time series plots of 8-h daily max O<sub>3</sub> concentrations observed at 14  
 2 CASTNET sites during 2001 and corresponding GEOS-Chem predictions for the base model (i.e.,  
 3 model including all anthropogenic and natural sources) and the PRB model (i.e., model including  
 4 natural sources everywhere in the world and anthropogenic sources outside the U.S., Canada, and  
 5 Mexico). Further details on these predictions can be found in Section 3.4.3.



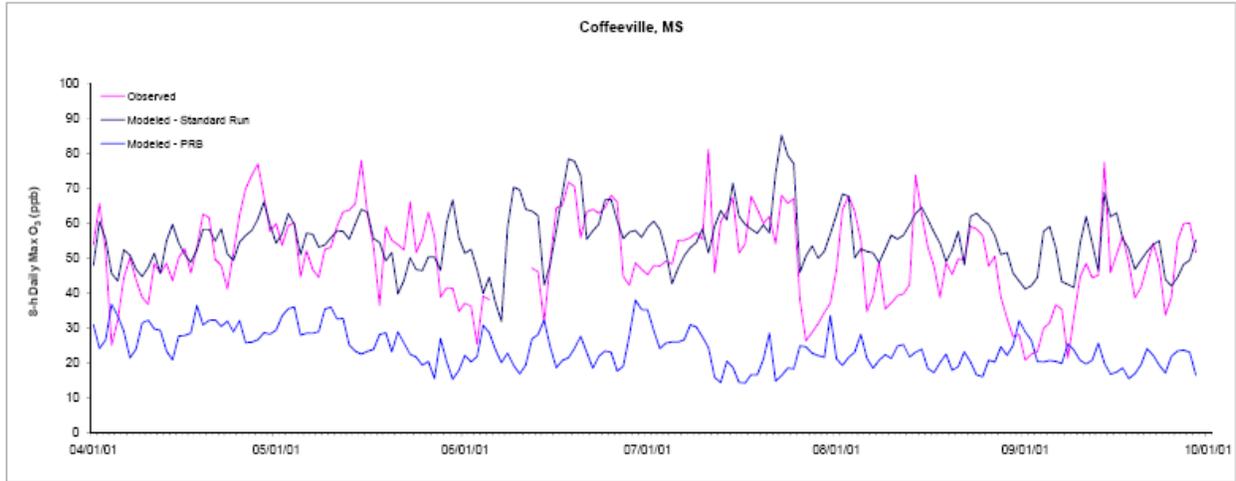
**Figure 3A-1. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Acadia NP, ME.**



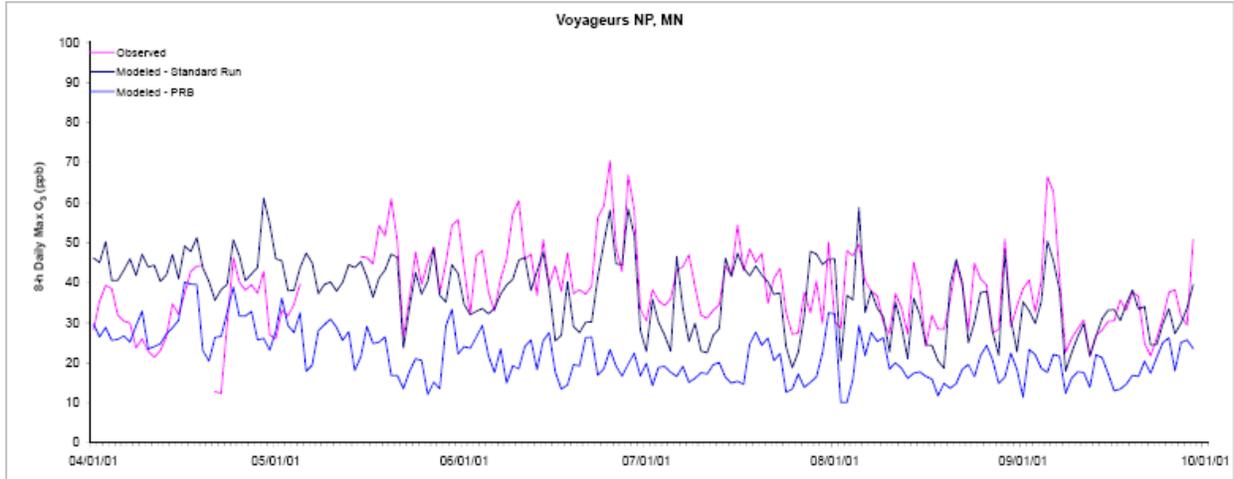
**Figure 3A-2. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Everglades NP, FL.**



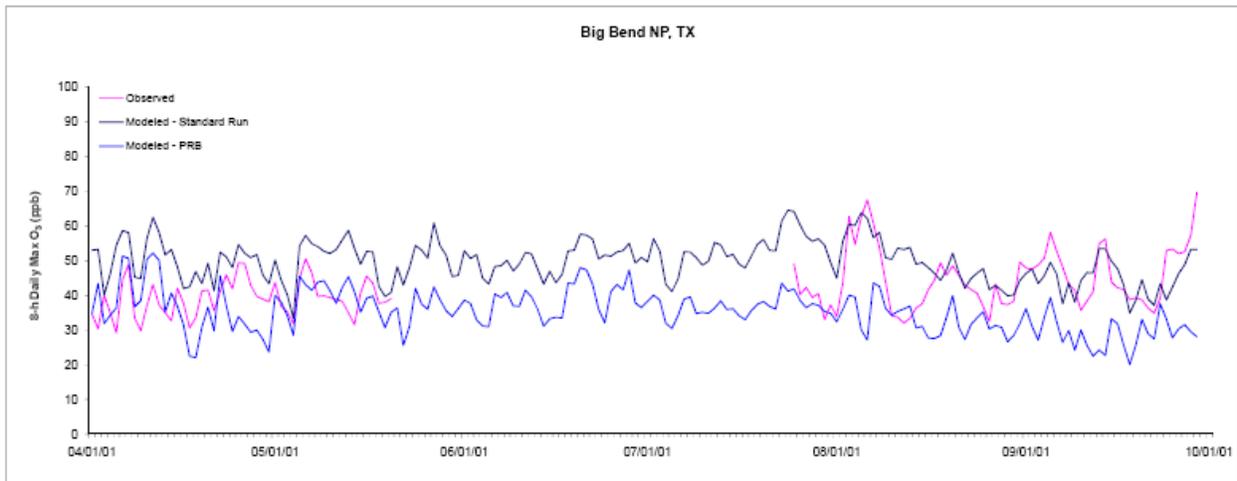
**Figure 3A-3. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Crockett, KY.**



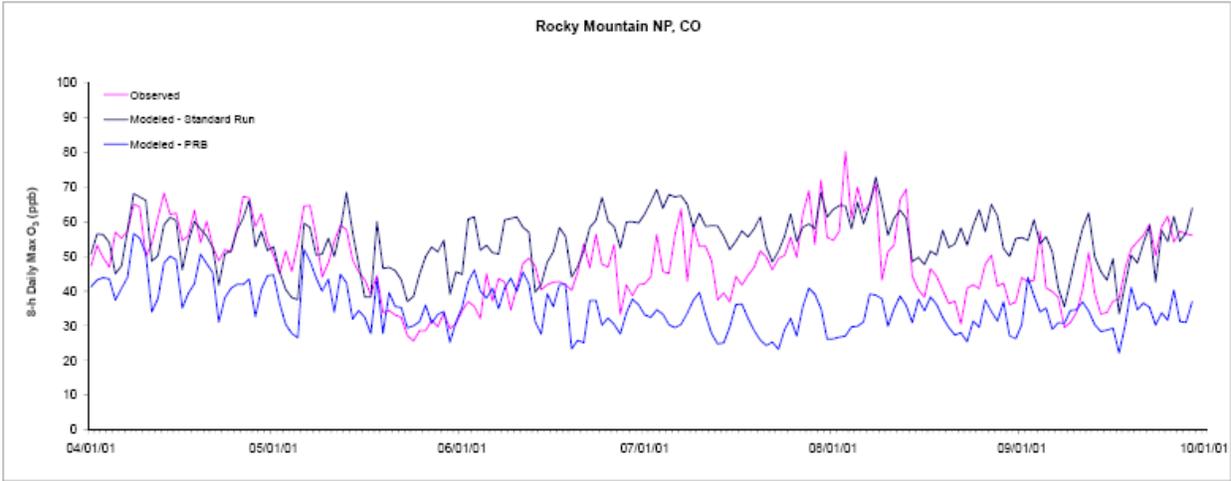
**Figure 3A-4. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Coffeeville, MS.**



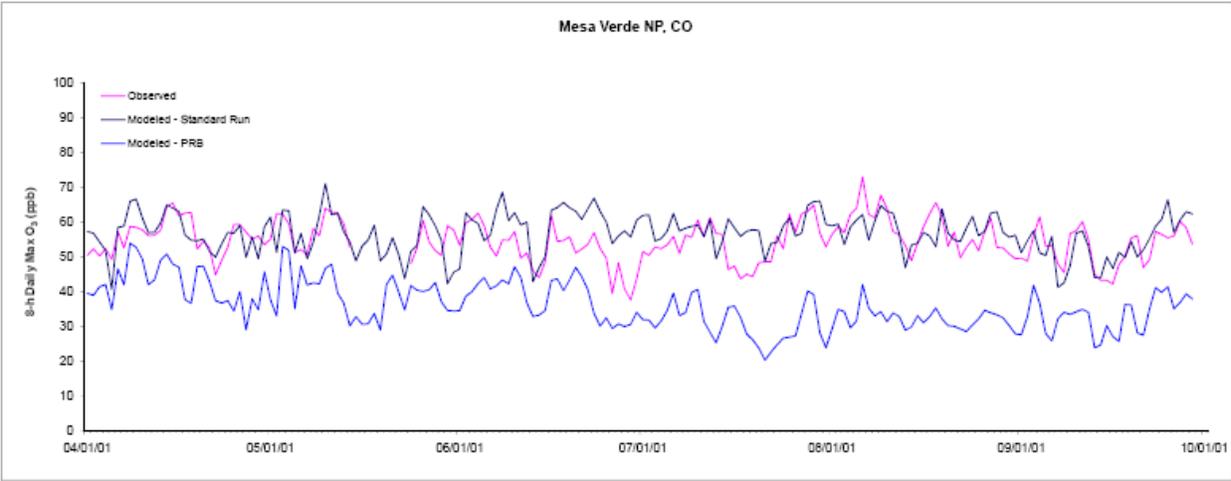
**Figure 3A-5. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Voyageurs NP, MN.**



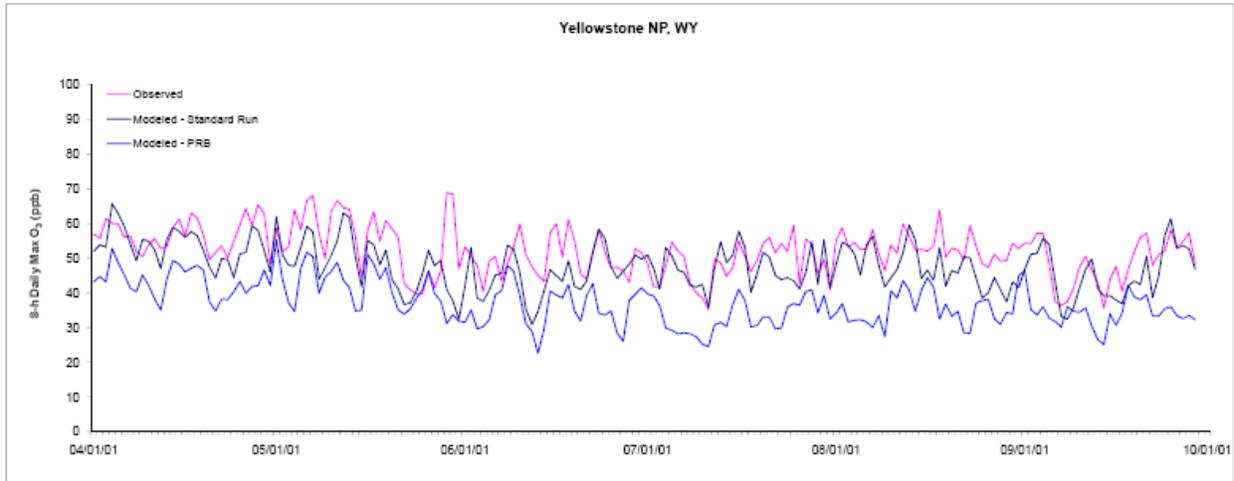
**Figure 3A-6. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Big Bend NP, TX.**



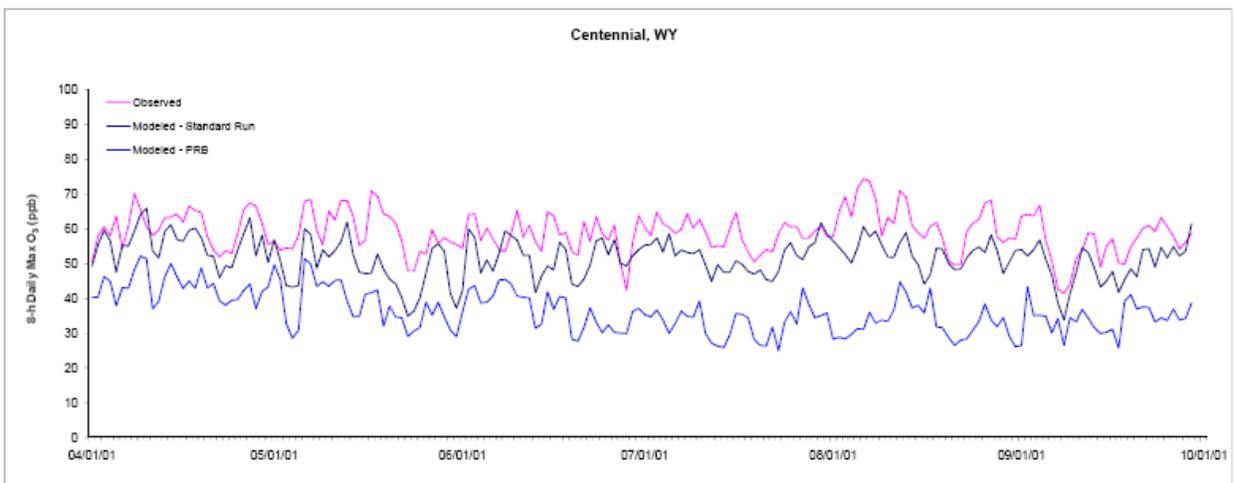
**Figure 3A-7. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Rocky Mountain NP, CO.**



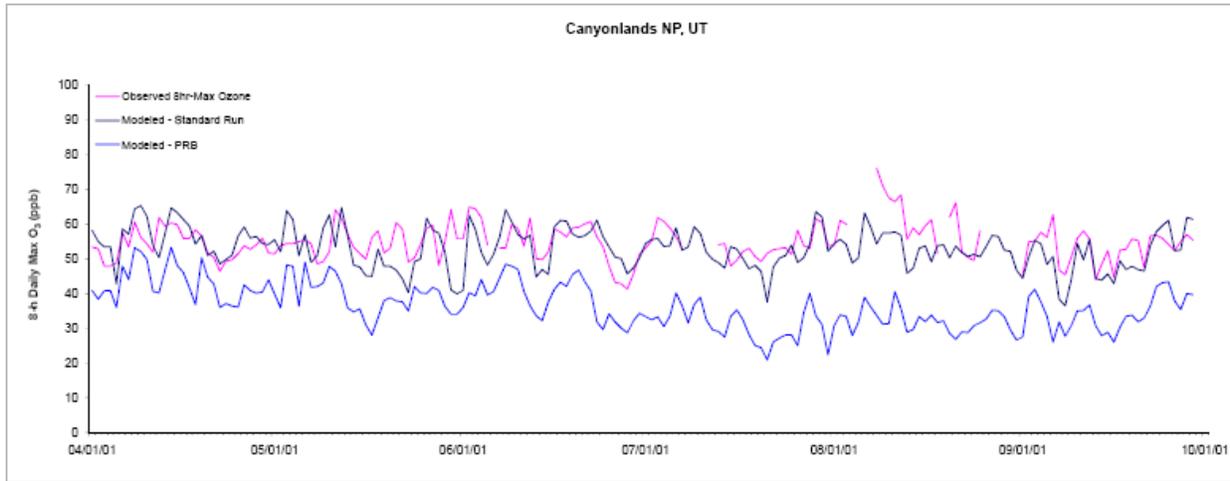
**Figure 3A-8. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Mesa Verde NP, CO.**



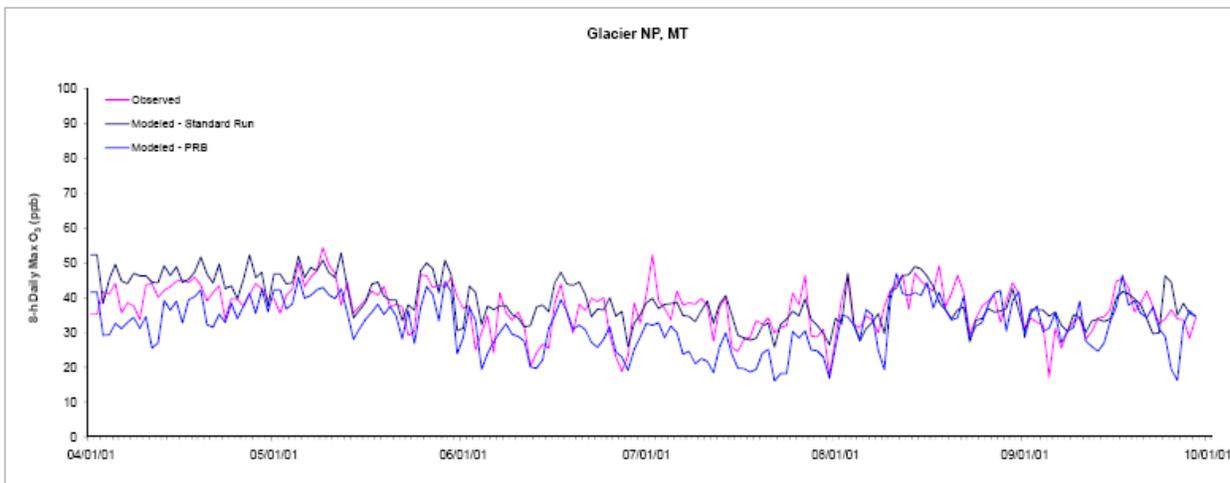
**Figure 3A-9. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Yellowstone NP, WY.**



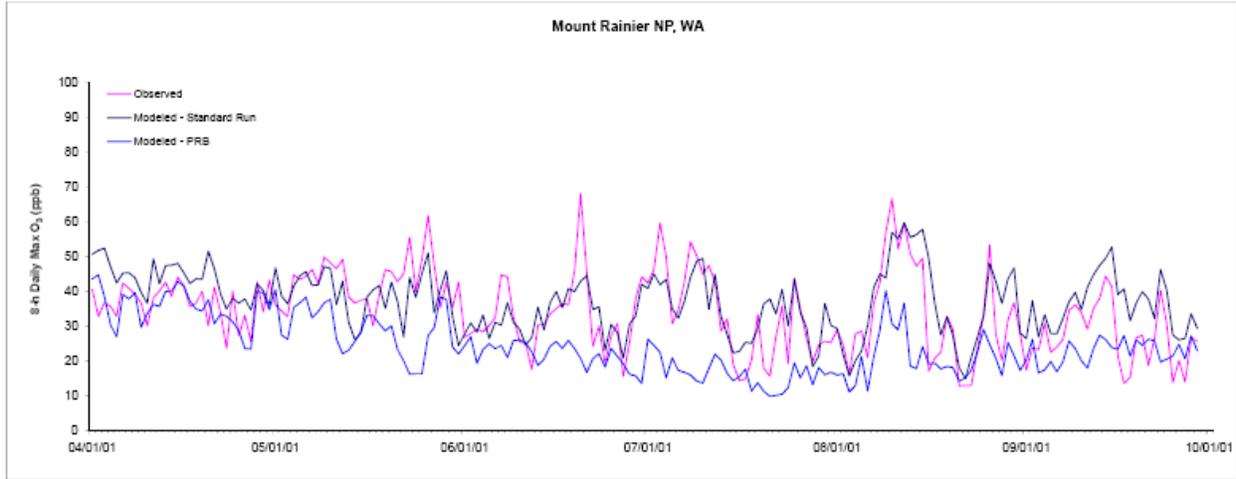
**Figure 3A-10. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Centennial, WY.**



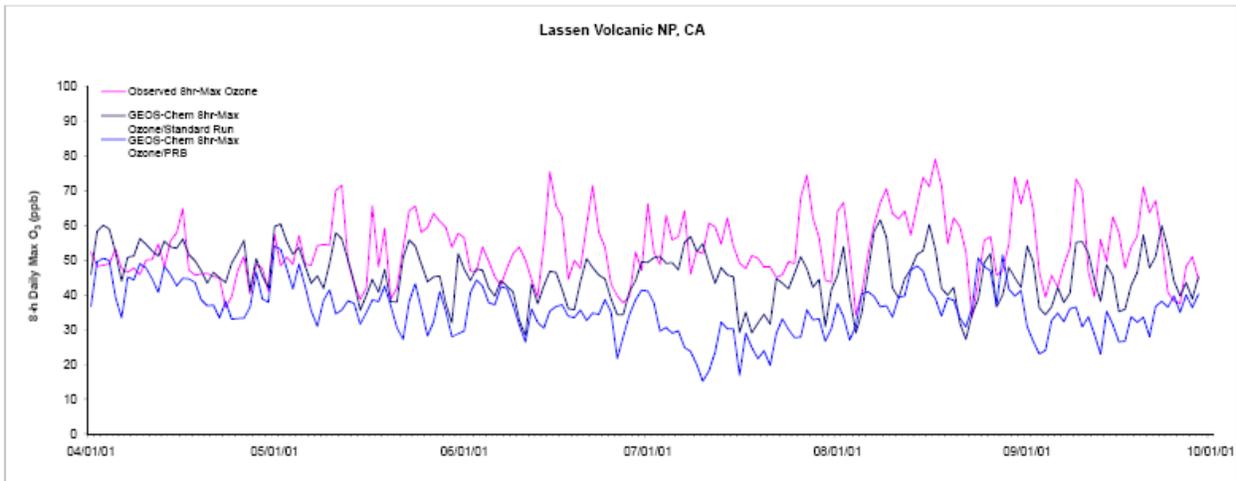
**Figure 3A-11. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Canyonlands NP, UT.**



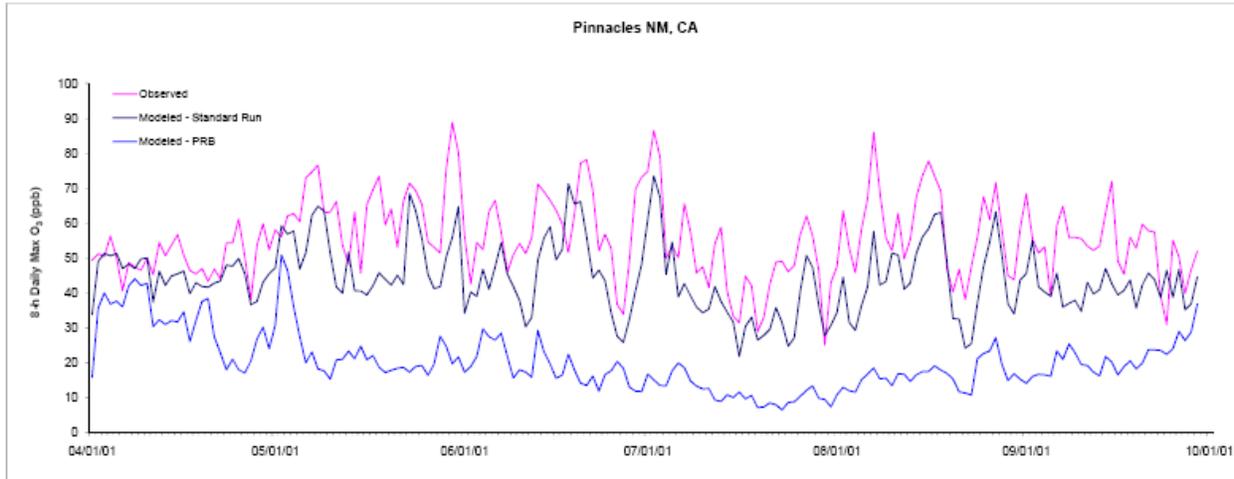
**Figure 3A-12. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Glacier NP, MT.**



**Figure 3A-13. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Mt. Rainier NP, WA.**



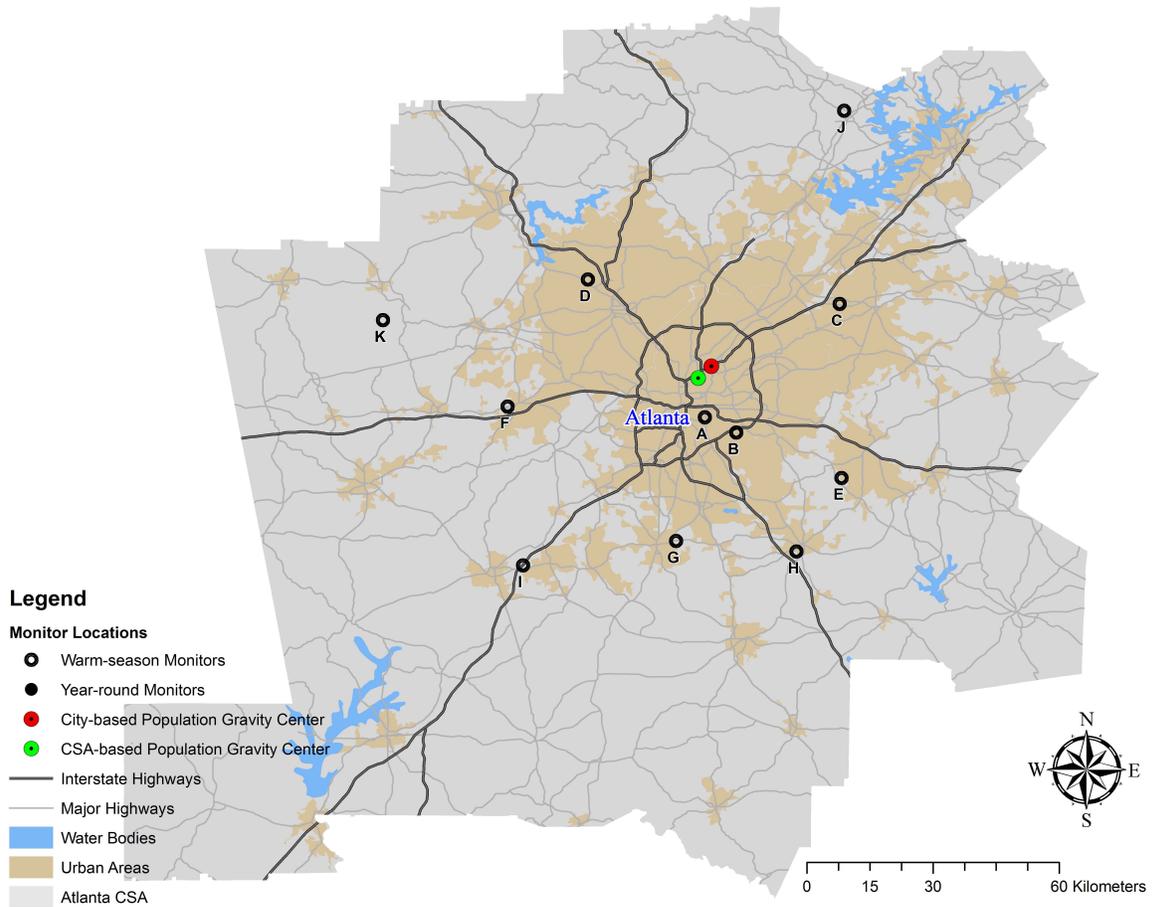
**Figure 3A-14. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Lassen Volcanic NP, CA.**



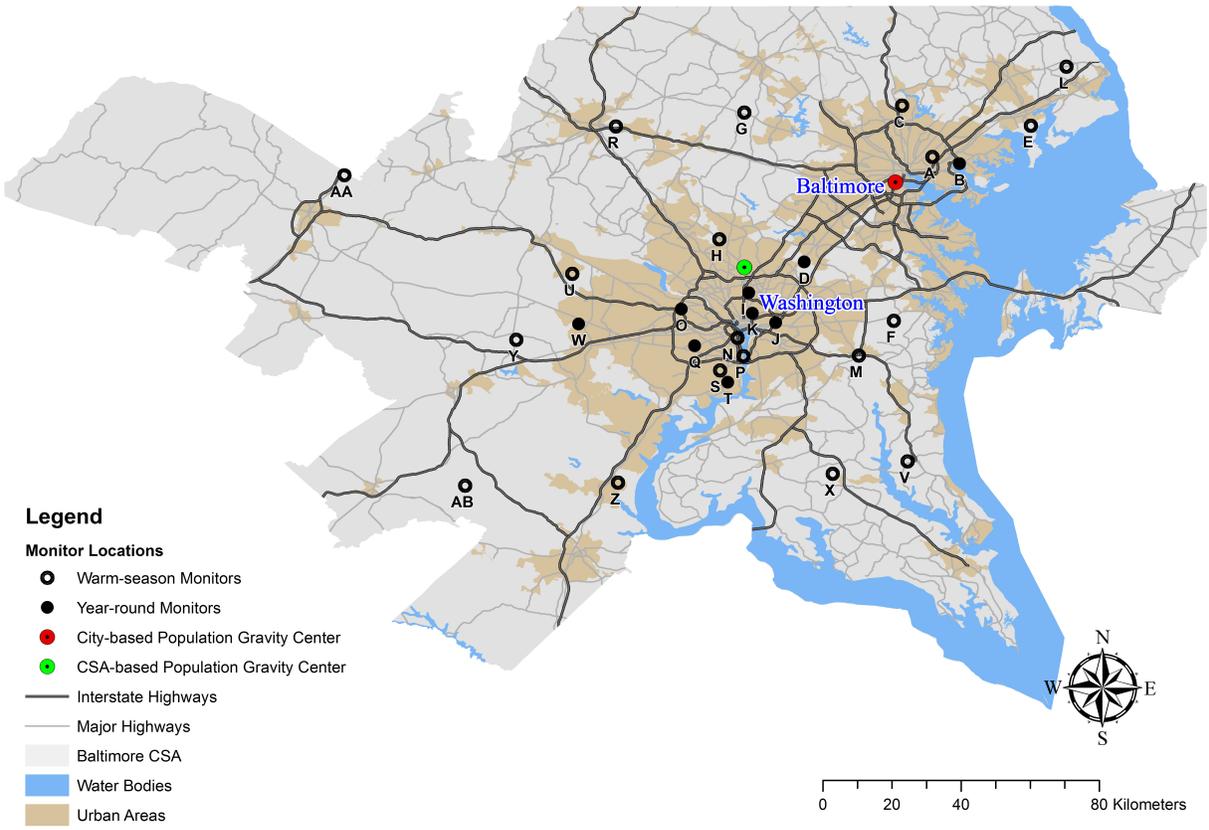
**Figure 3A-15. Time series of observed and GEOS-Chem base model and PRB model 8-h daily max ozone concentrations (ppb) with PRB estimates for Pinnacles NM, CA.**

### 3.8.2. Ozone Monitor Maps for the Urban Focus Cities

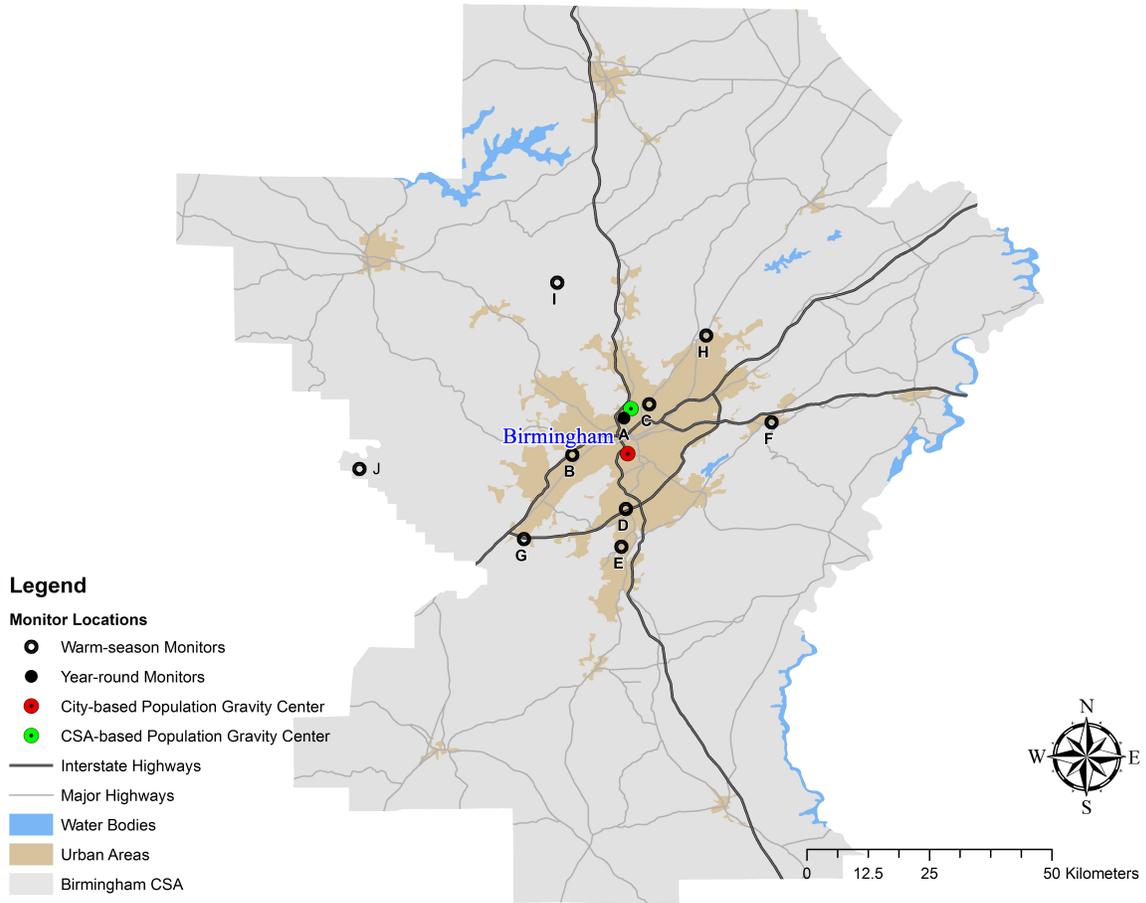
1 This section contains supplemental maps showing the location of O<sub>3</sub> monitors reporting to  
 2 AQS for each of the 20 urban focus cities introduced in Section 3.6.2.1. The monitors are delineated  
 3 in the maps as year-round or warm-season based on their inclusion in the year-round data set and the  
 4 warm-season data set discussed in Section 3.6.2.1. The maps also include the CSA/CBSA boundary  
 5 selected for monitor inclusion, the location of urban areas and water bodies, the major roadway  
 6 network, as well as the population gravity center based on the entire CSA/CBSA and the individual  
 7 focus city boundaries. Population gravity center is calculated from the average longitude and latitude  
 8 values for the input census tract centroids and represents the mean center of the population in a given  
 9 area. Census tract centroids are weighted by their population during this calculation.



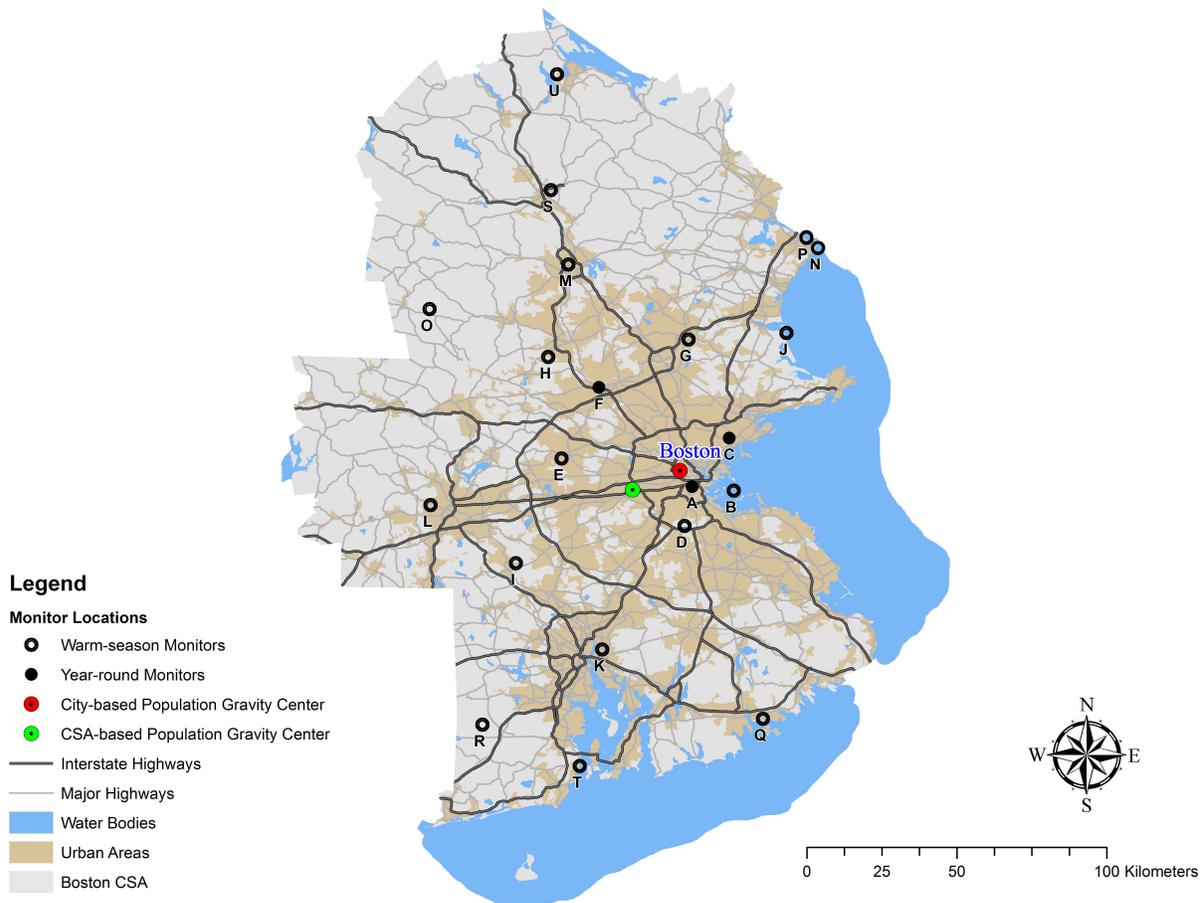
**Figure 3A-16. Map of the Atlanta CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



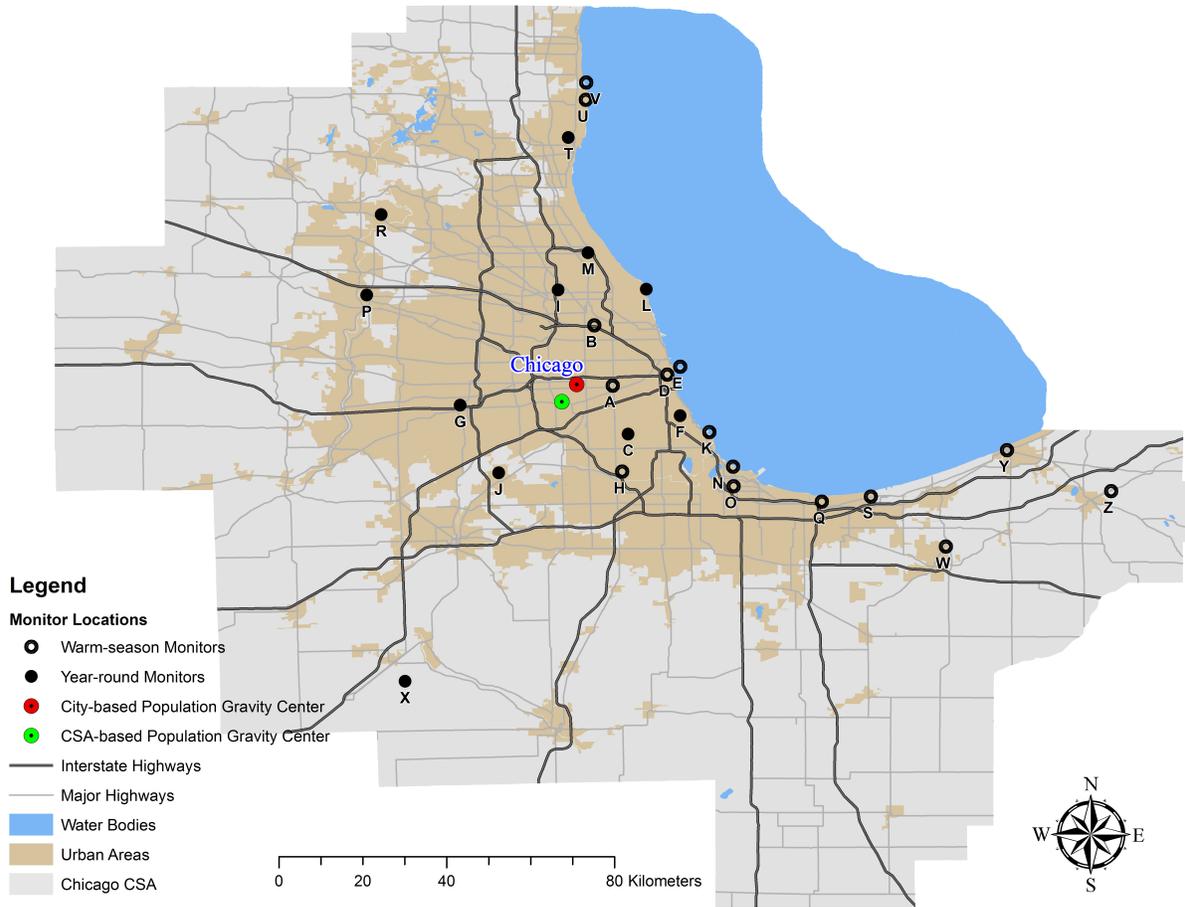
**Figure 3A-17. Map of the Baltimore CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



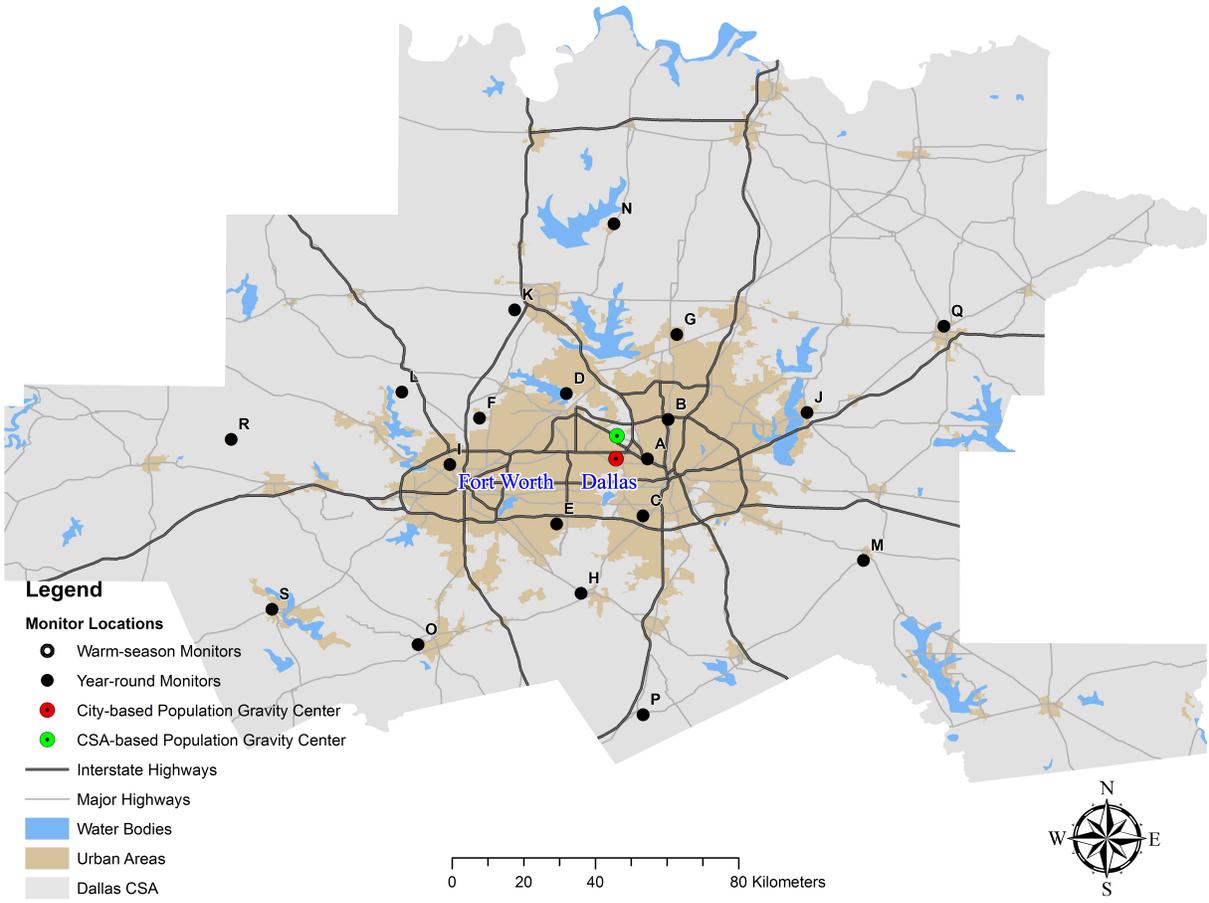
**Figure 3A-18. Map of the Birmingham CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



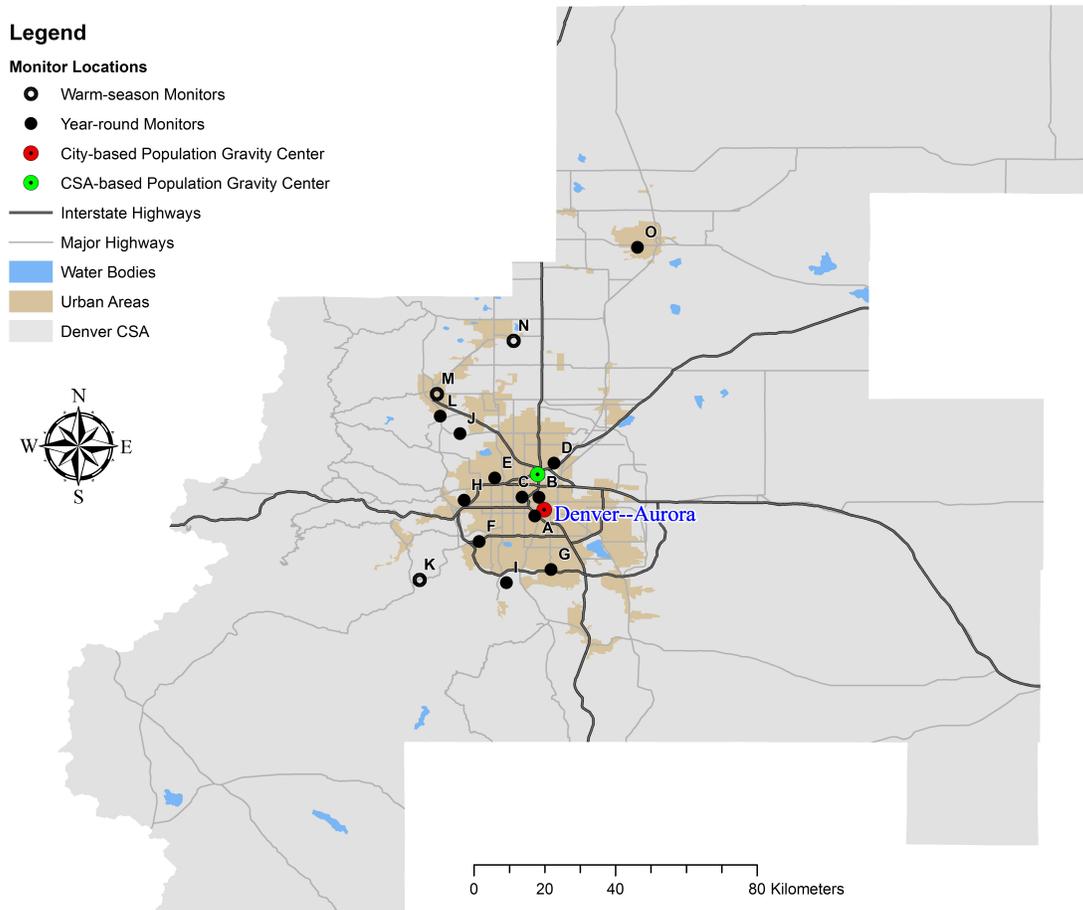
**Figure 3A-19. Map of the Boston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



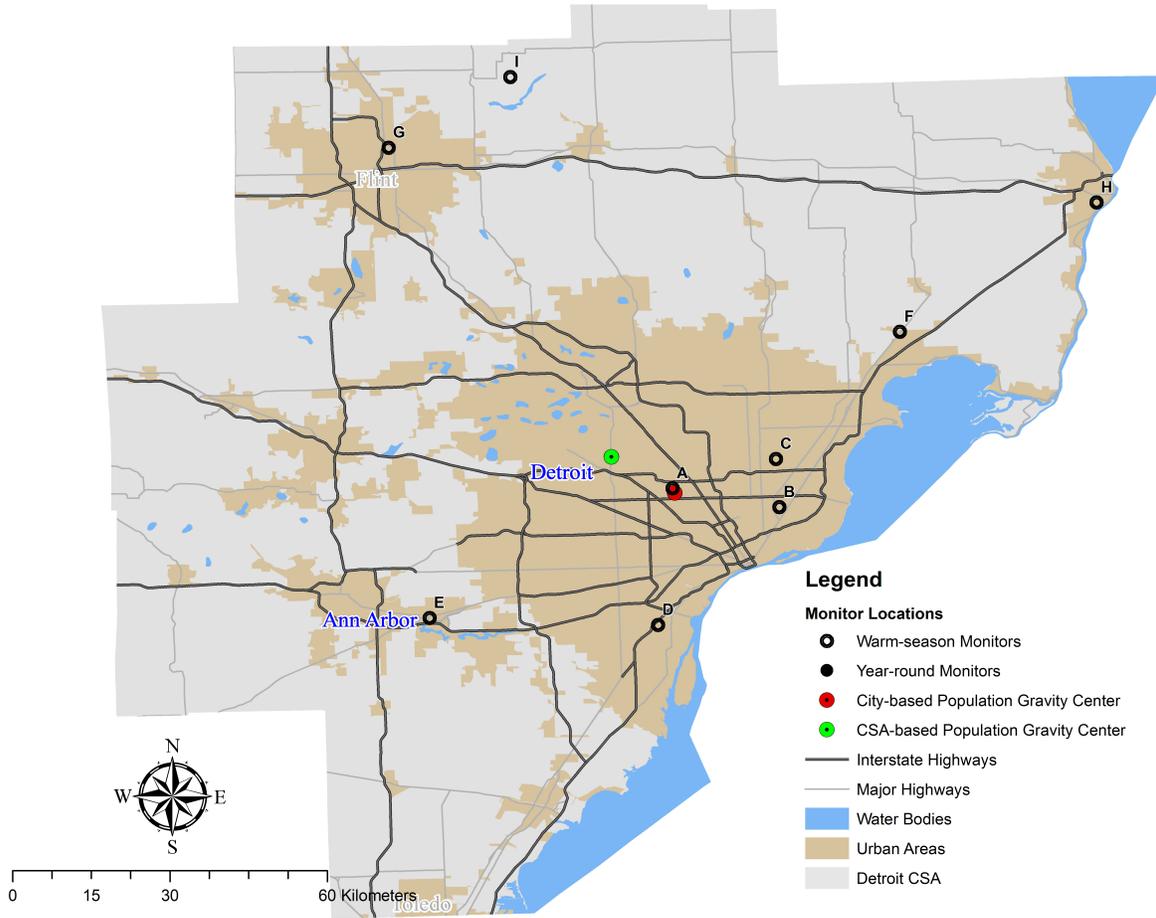
**Figure 3A-20. Map of the Chicago CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



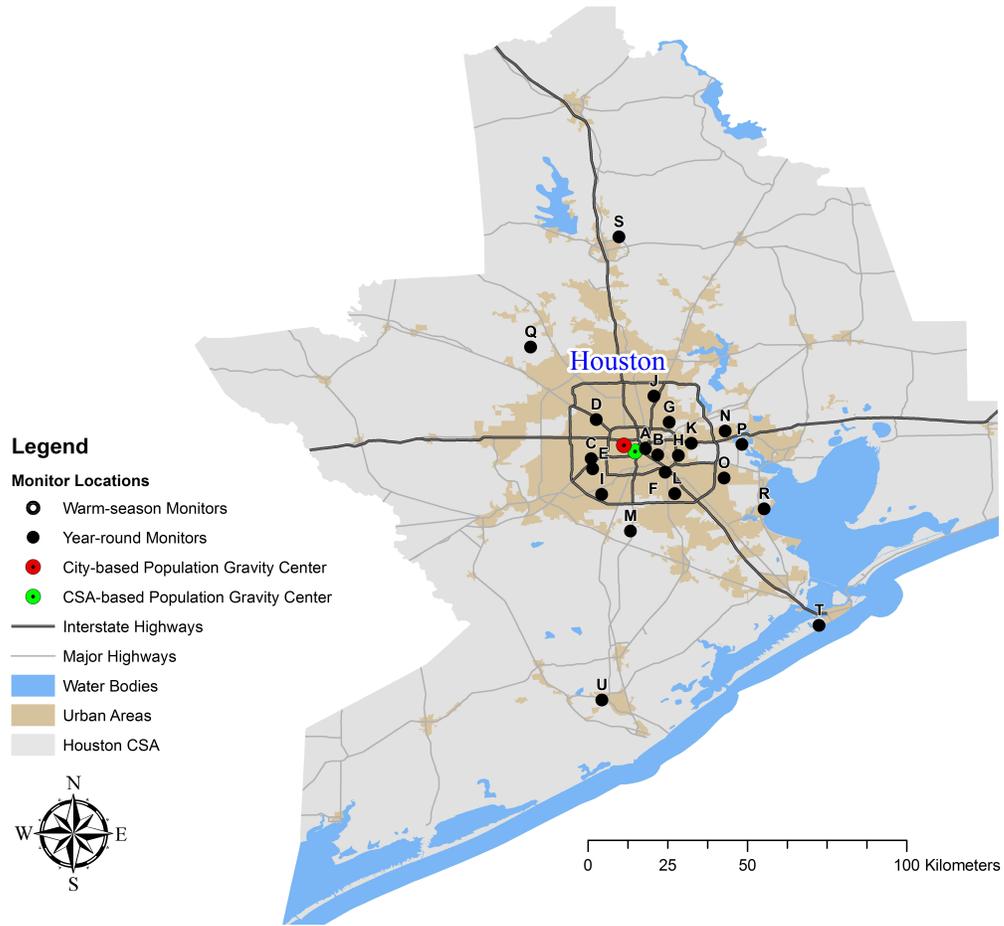
**Figure 3A-21. Map of the Dallas CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



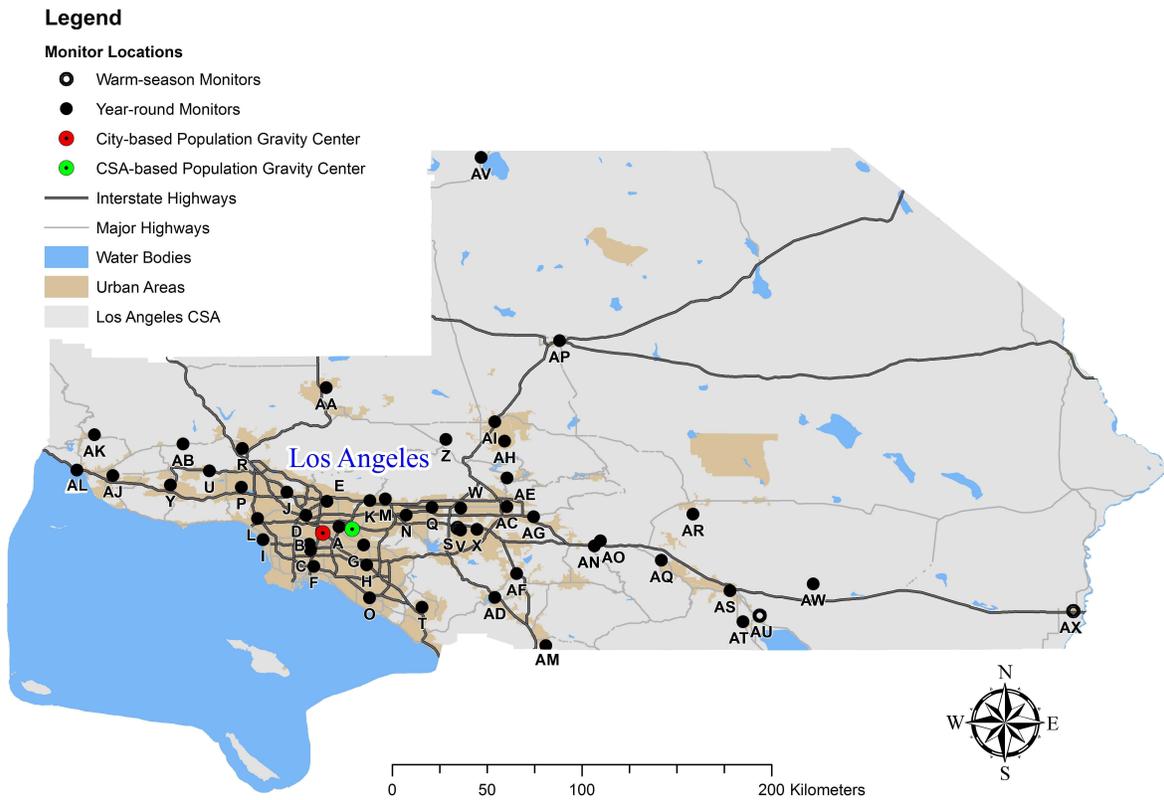
**Figure 3A-22. Map of the Denver CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



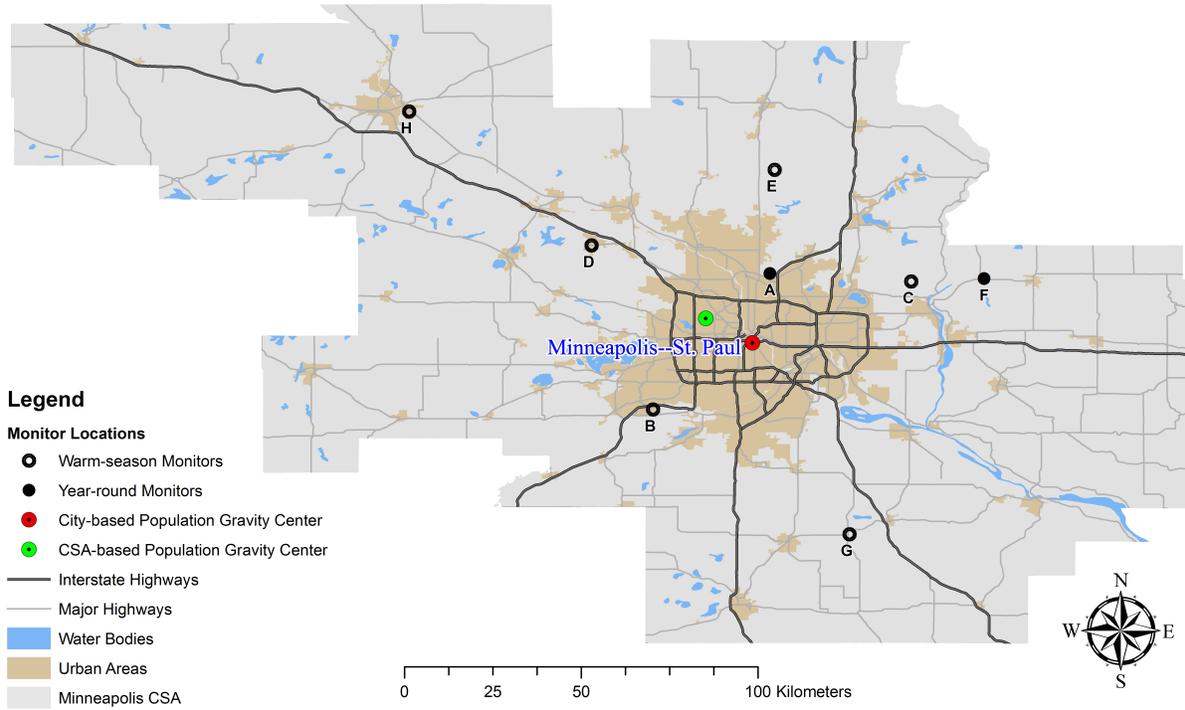
**Figure 3A-23. Map of the Detroit CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



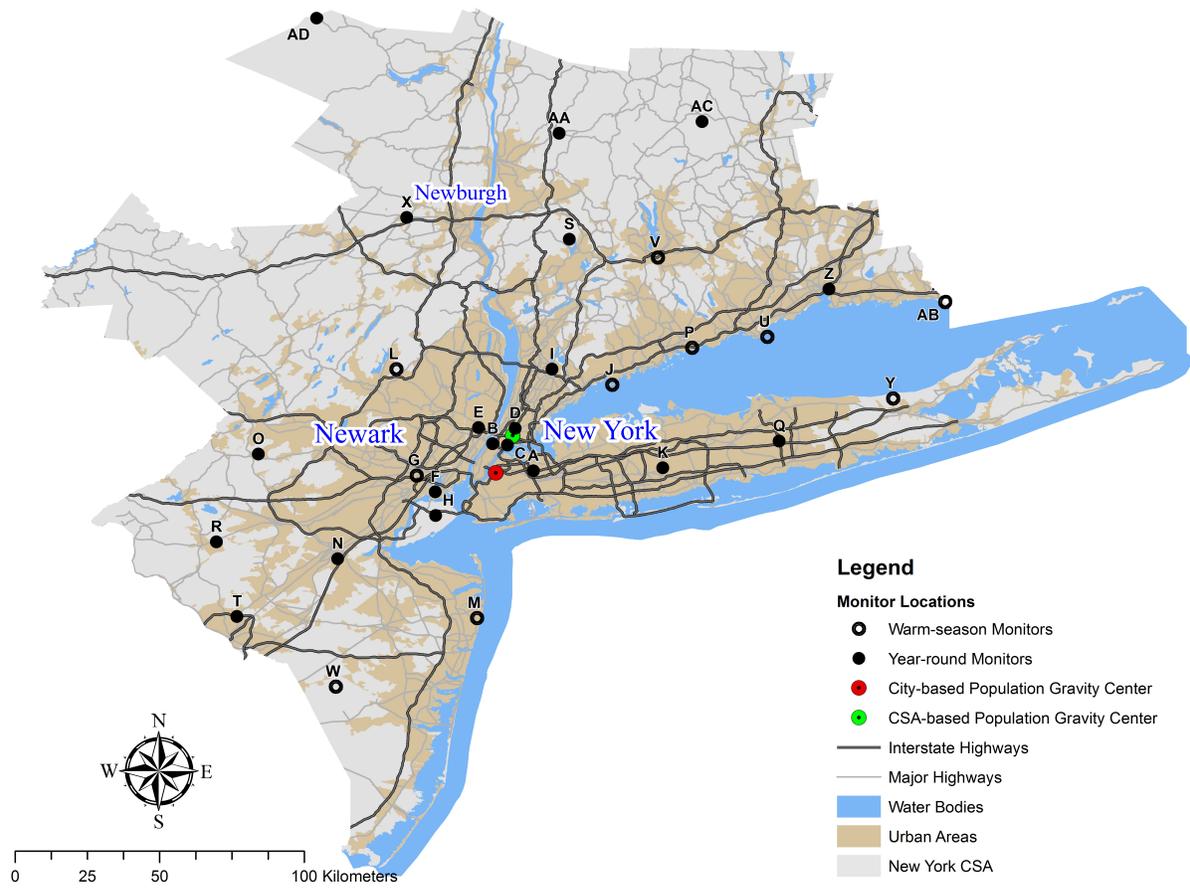
**Figure 3A-24. Map of the Houston CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



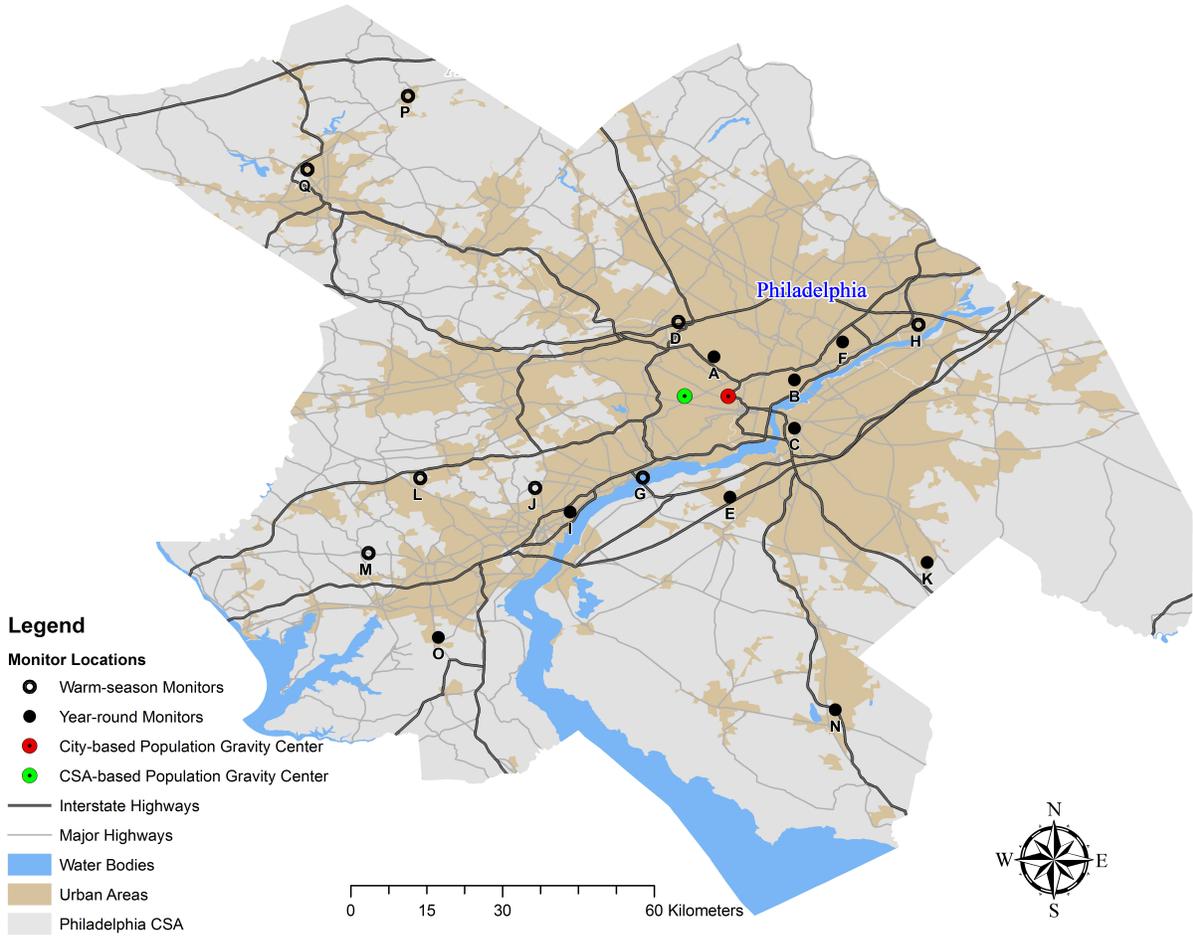
**Figure 3A-25. Map of the Los Angeles CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



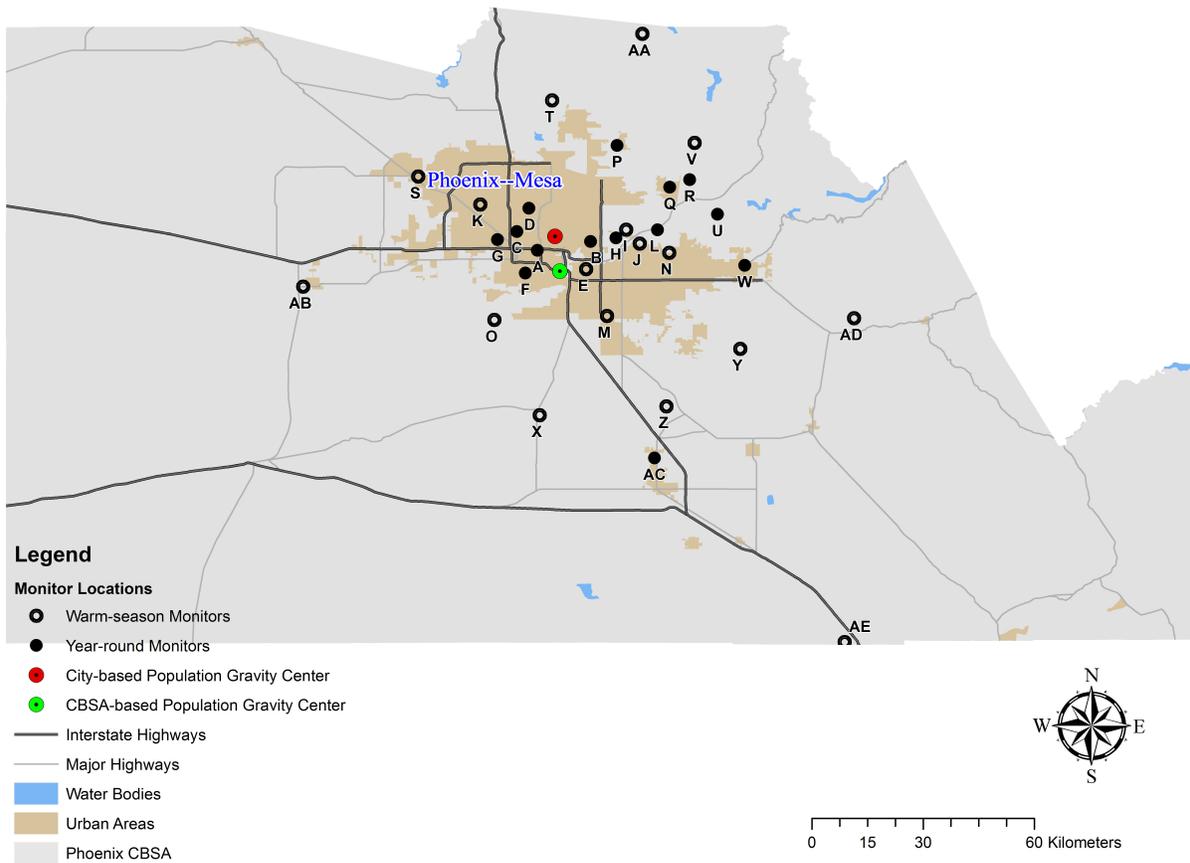
**Figure 3A-26. Map of the Minneapolis CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



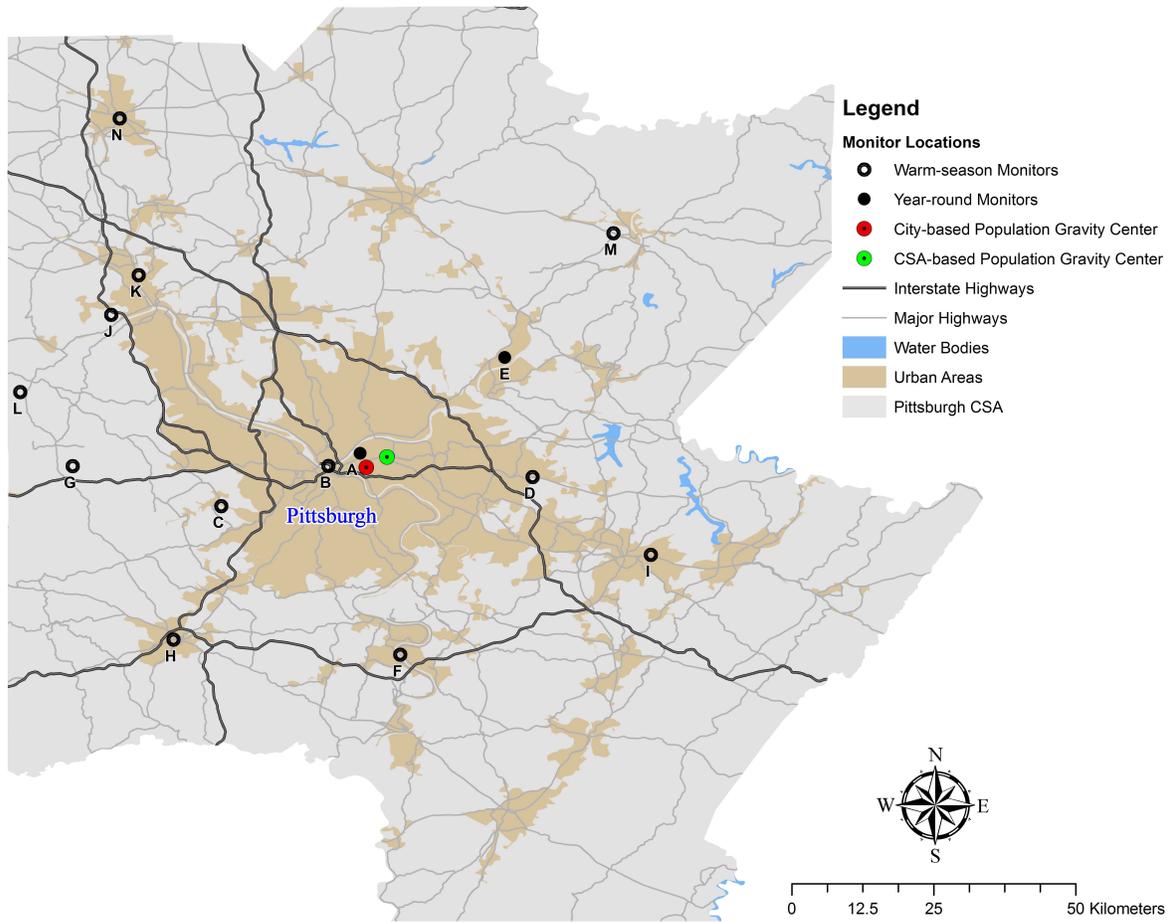
**Figure 3A-27. Map of the New York CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



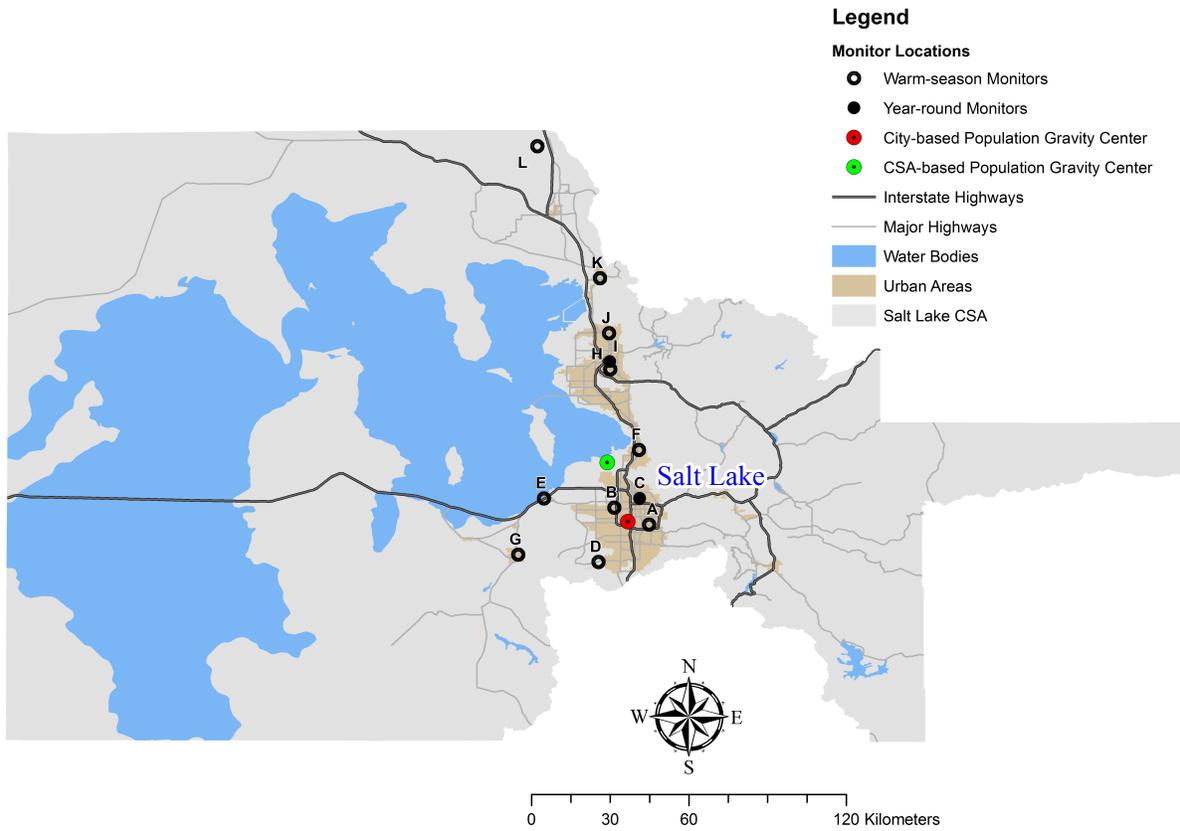
**Figure 3A-28. Map of the Philadelphia CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



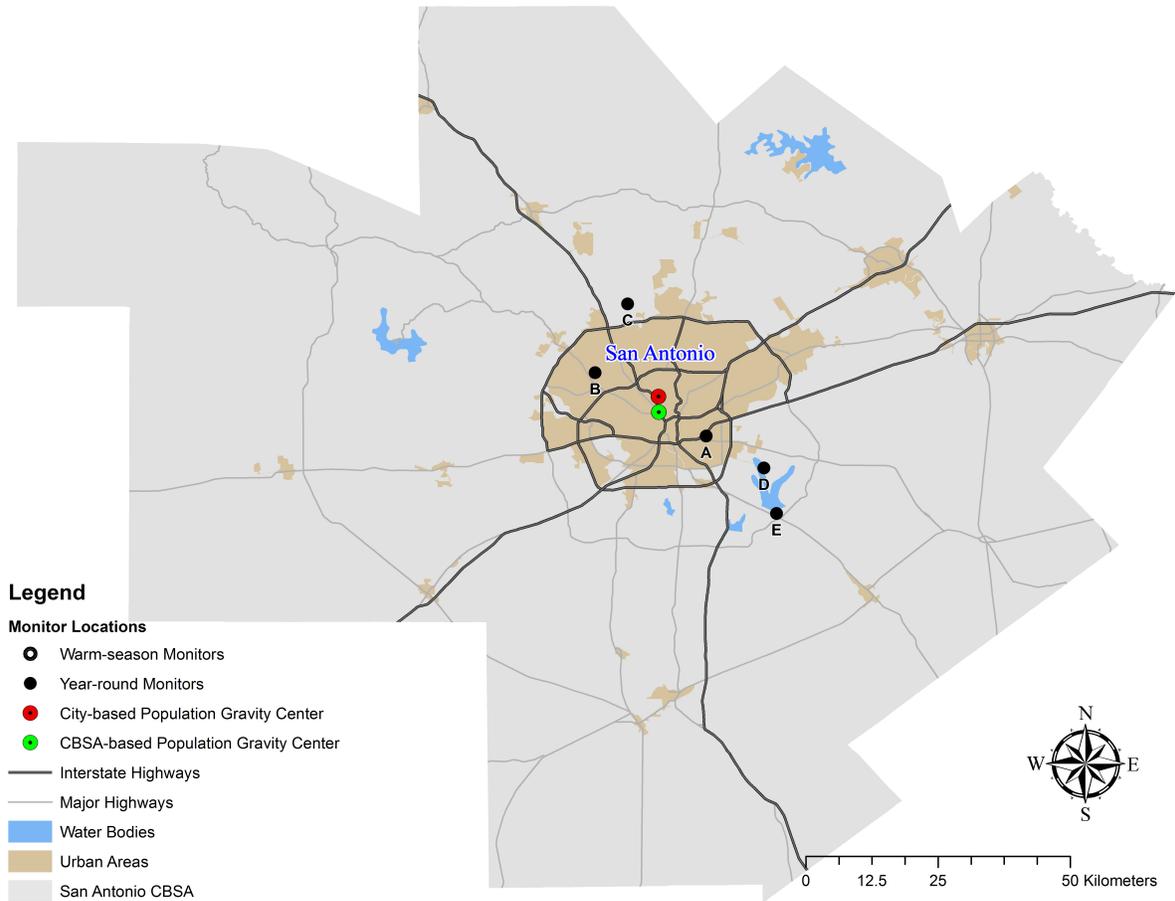
**Figure 3A-29. Map of the Phoenix CBSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



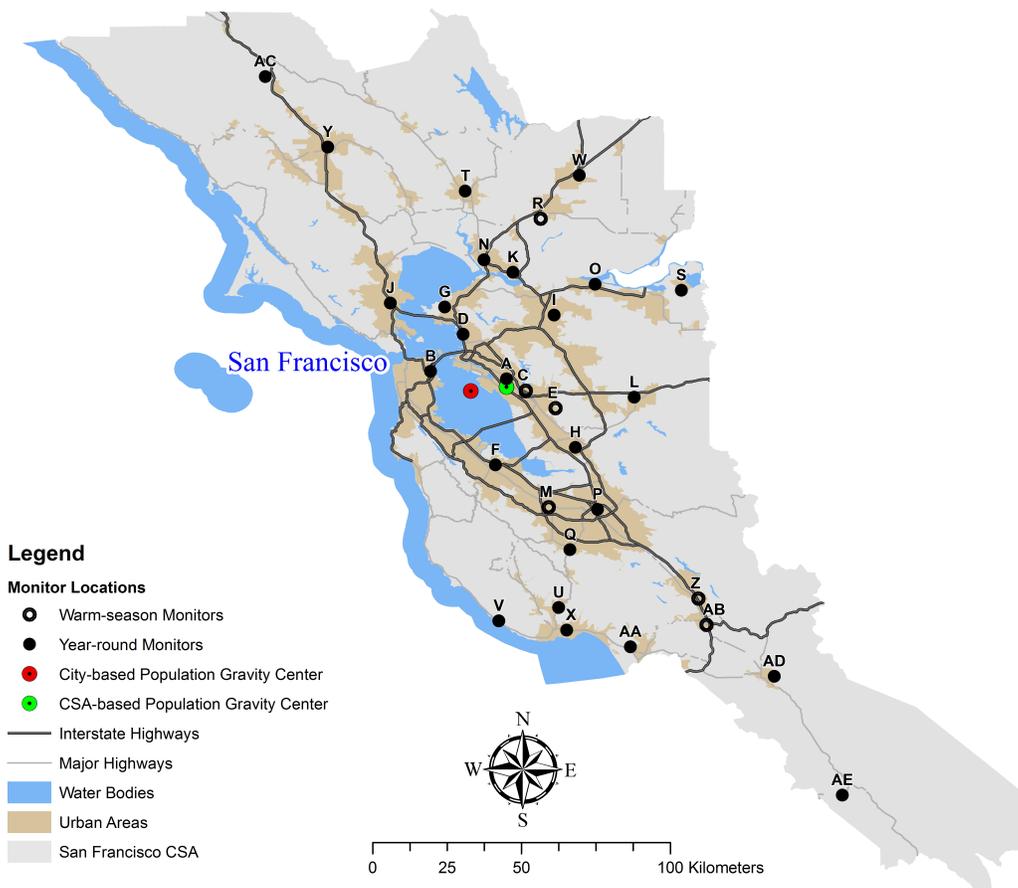
**Figure 3A-30. Map of the Pittsburgh CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



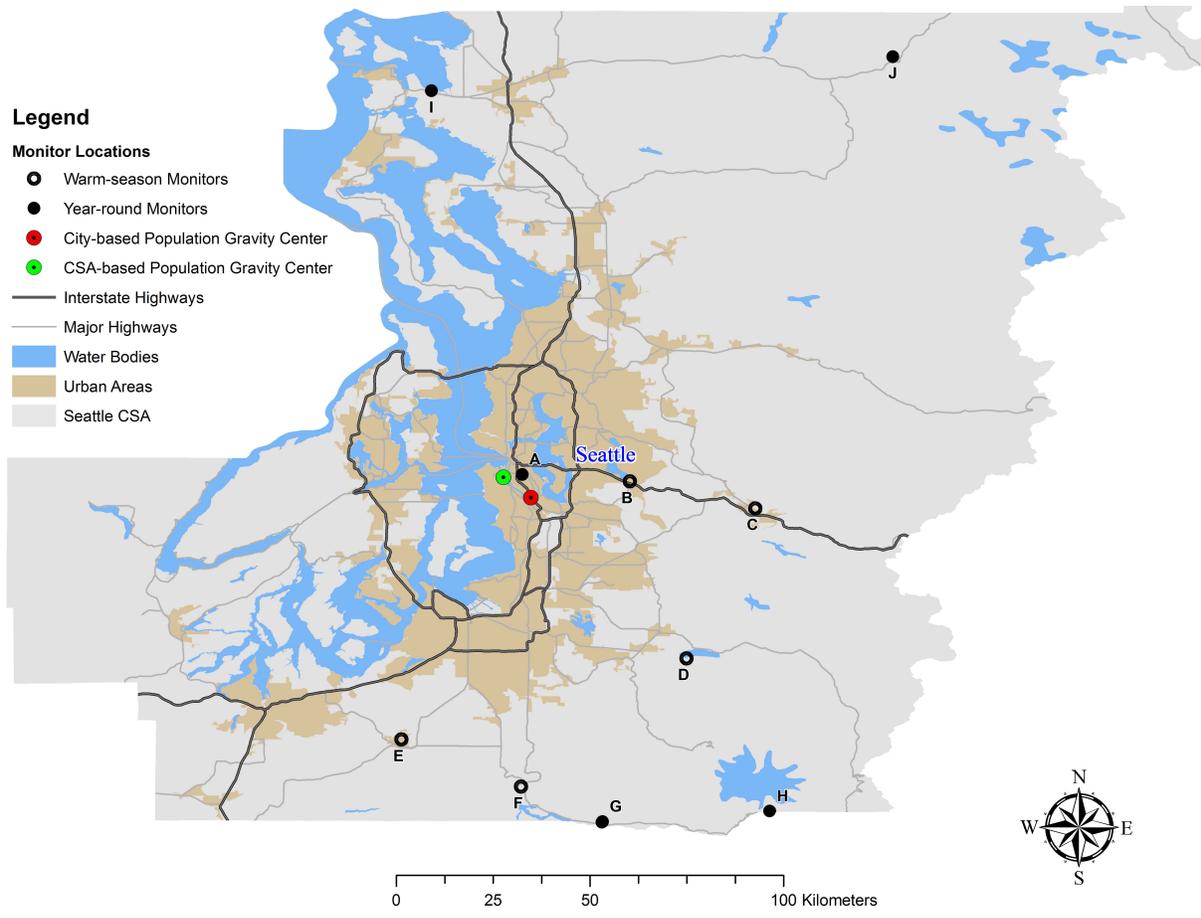
**Figure 3A-31. Map of the Salt Lake City CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



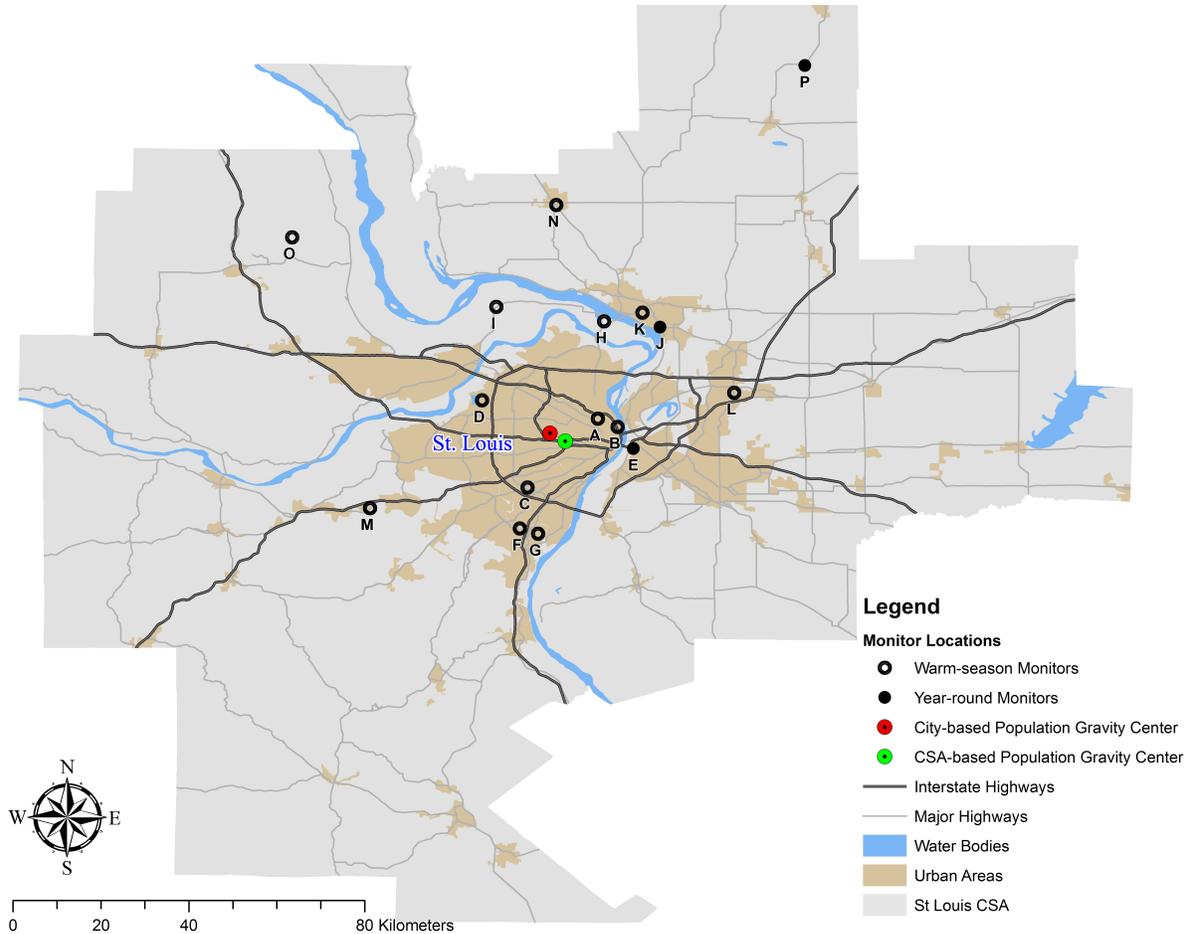
**Figure 3A-32. Map of the San Antonio CBSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



**Figure 3A-33. Map of the San Francisco CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



**Figure 3A-34. Map of the Seattle CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**



**Figure 3A-35. Map of the St. Louis CSA including ozone monitor locations, population gravity centers, urban areas, and major roadways.**

### 3.8.3. 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 daily  
 2 max O<sub>3</sub> data from each individual monitor in the 20 urban focus cities introduced in Section 3.6.2.1.  
 3 Monitor information including the AQS site id, the years containing qualifying data between 2007  
 4 and 2009, and the number of 8-h daily max O<sub>3</sub> observations included in the data set are listed next to  
 5 the box plot. Statistics including the mean, standard deviation (SD), median and inner quartile range  
 6 (IQR) are also shown for each monitor with the site letter corresponding to the sites listed in the  
 7 figures above.

### Atlanta CSA

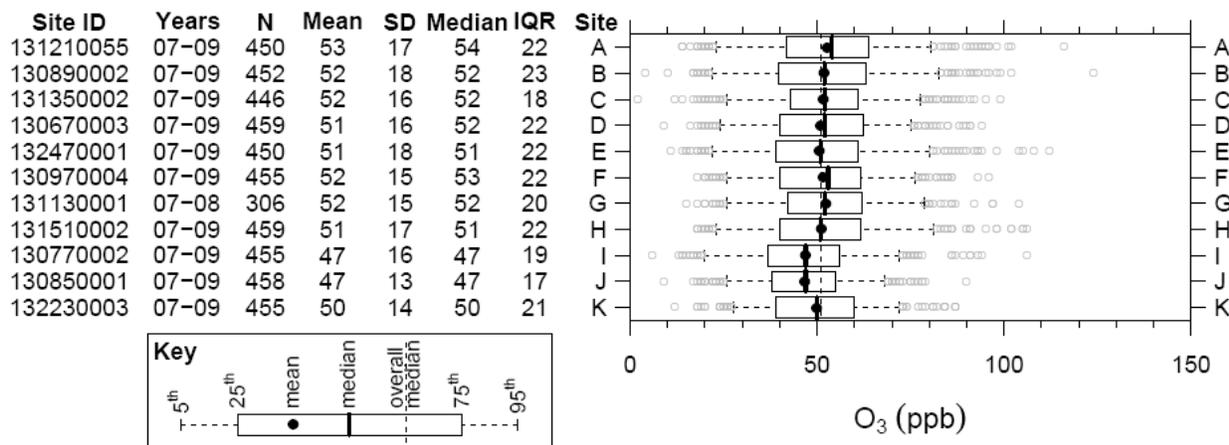


Figure 3A-36. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Atlanta CSA.

### Baltimore CSA

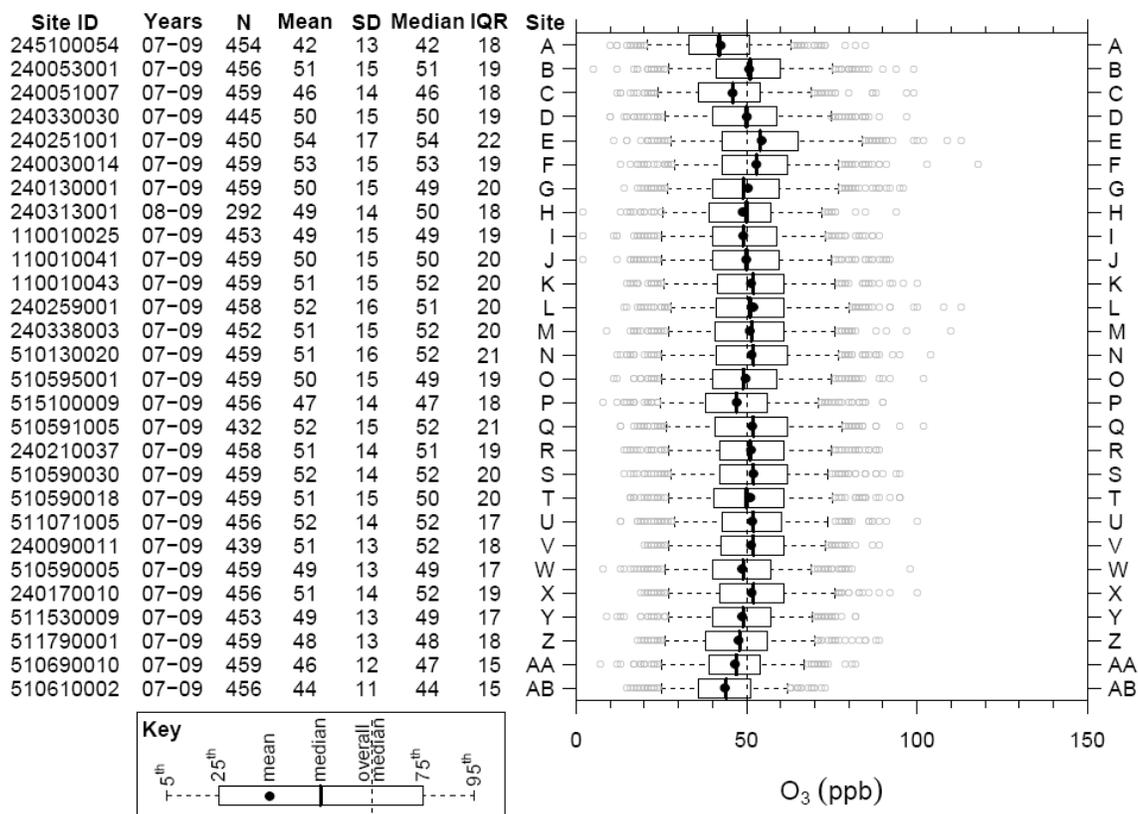


Figure 3A-37. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Baltimore CSA.

### Birmingham CSA

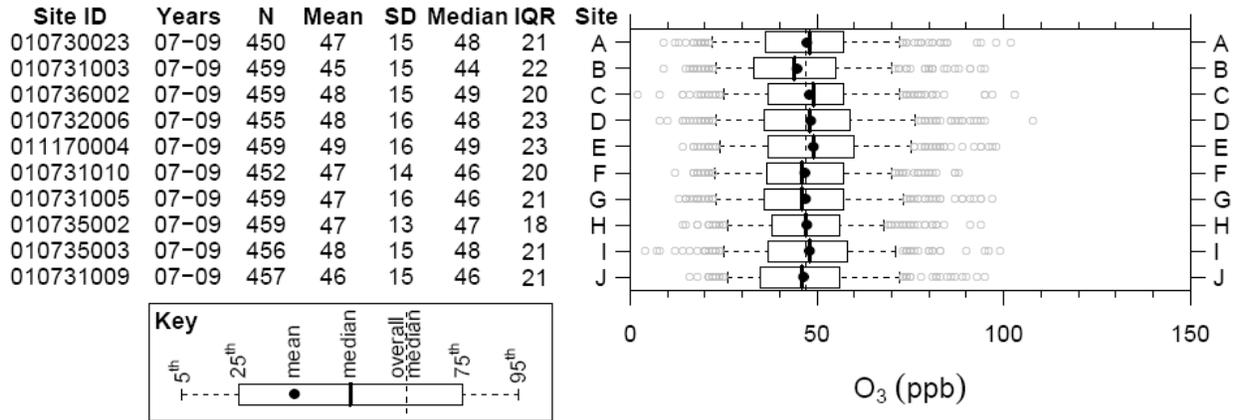


Figure 3A-38. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Birmingham CSA.

### Boston CSA

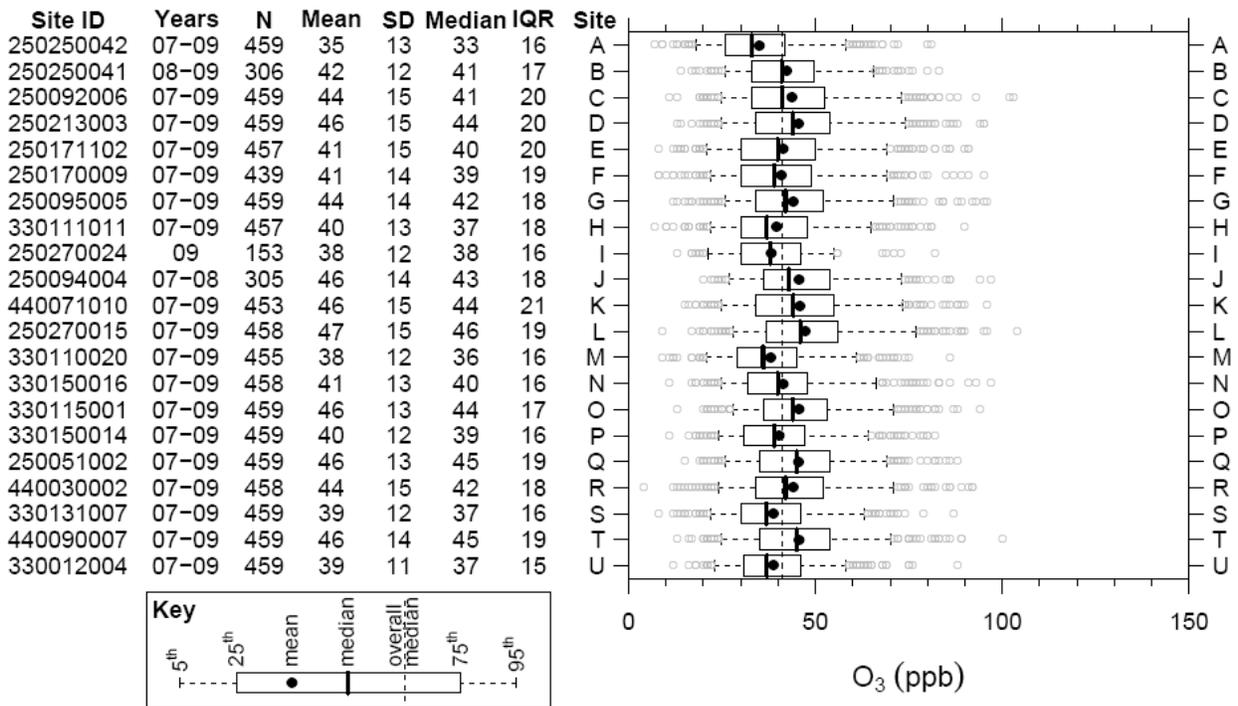


Figure 3A-39. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Boston CSA.

### Chicago CSA

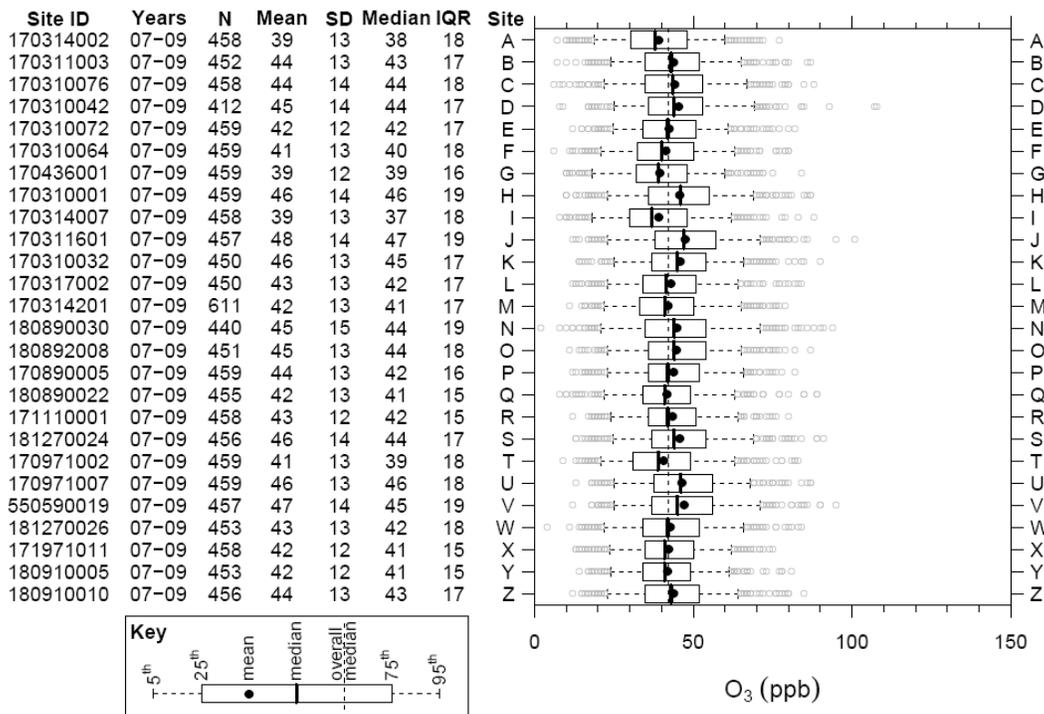


Figure 3A-40. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Chicago CSA.

### Dallas CSA

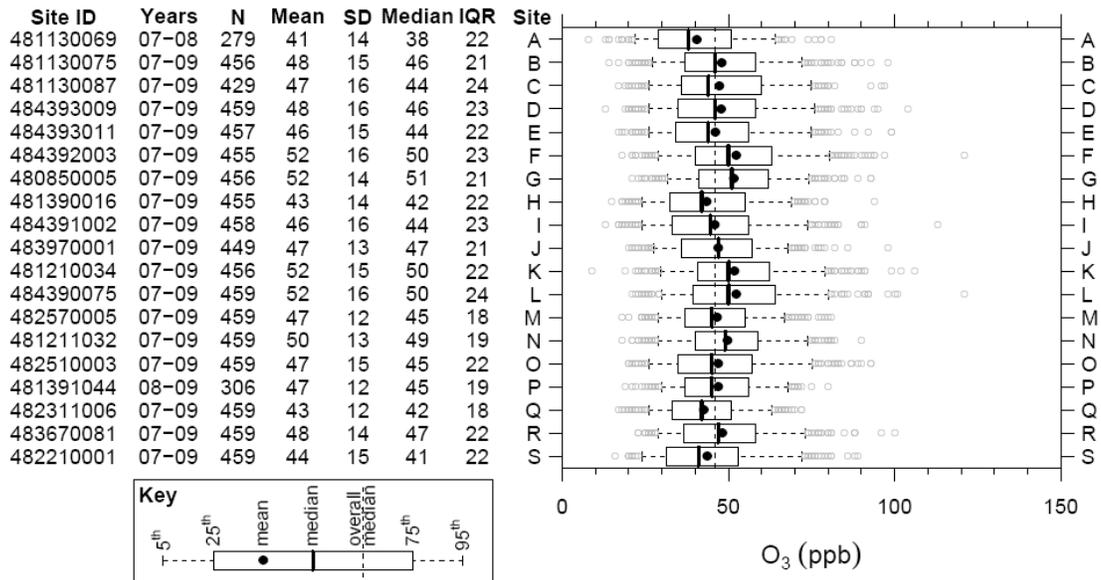
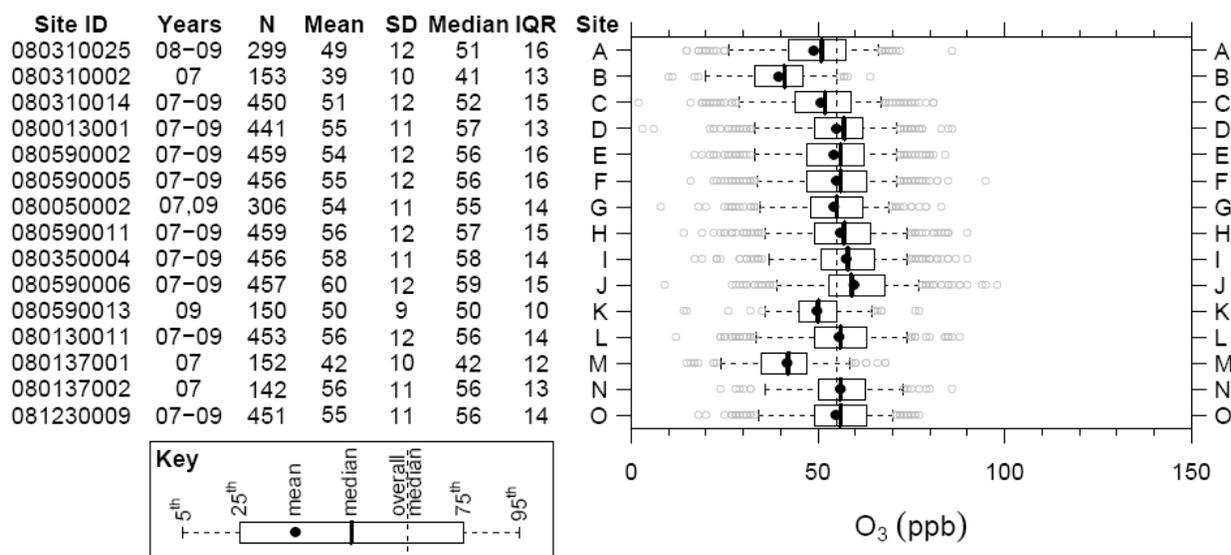


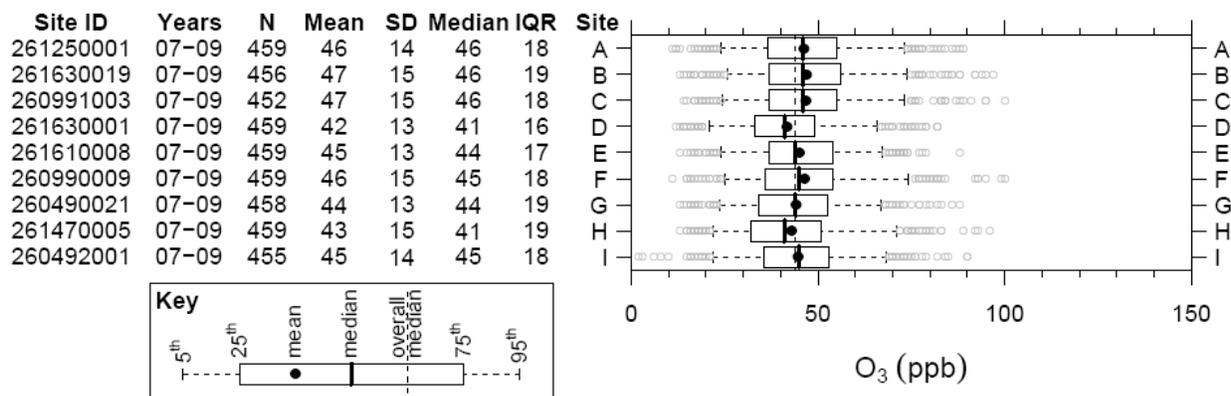
Figure 3A-41. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Dallas CSA.

### Denver CSA



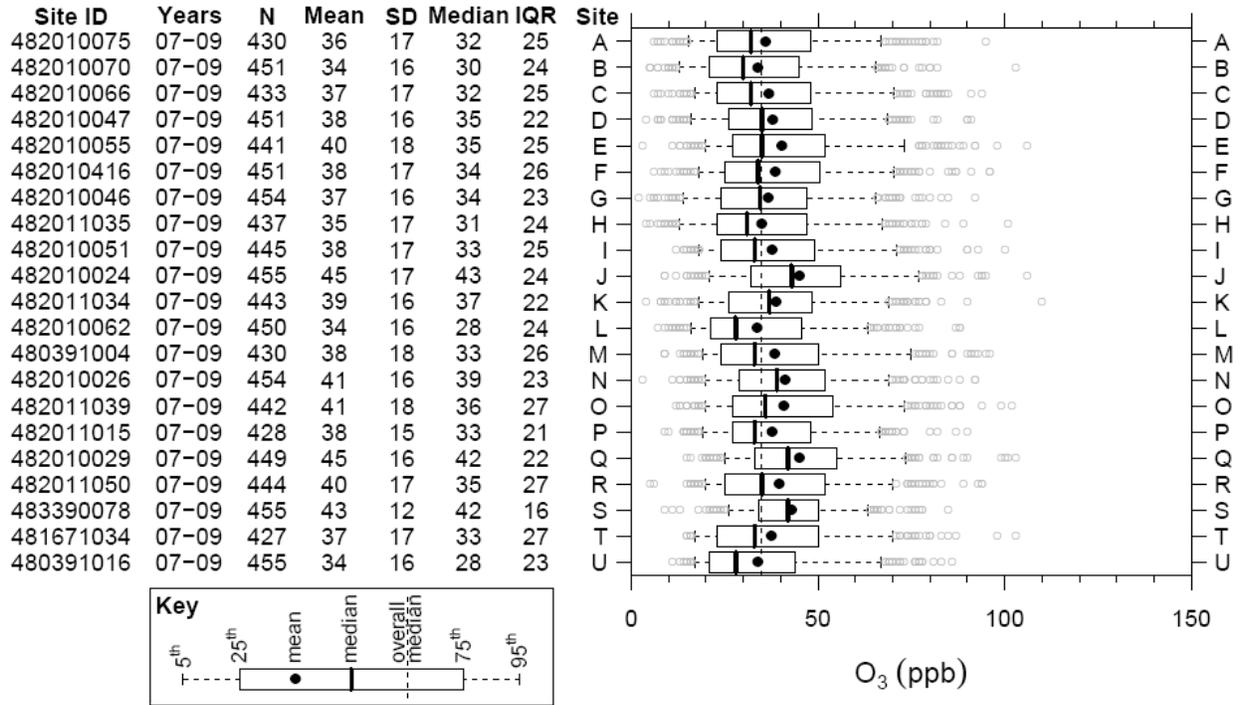
**Figure 3A-42. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Denver CSA.**

### Detroit CSA



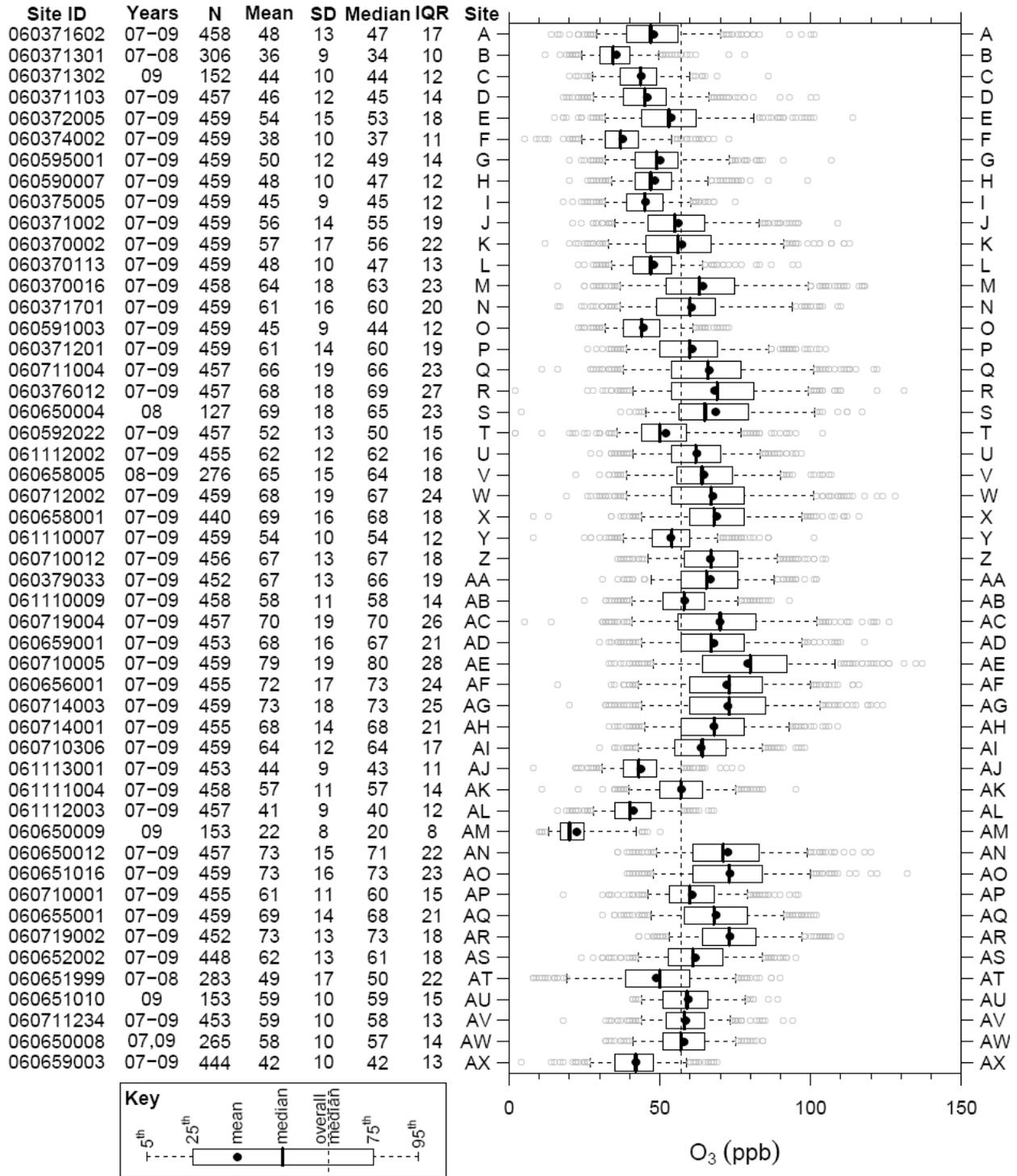
**Figure 3A-43. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Detroit CSA.**

## Houston CSA



**Figure 3A-44. 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 3A-45. 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

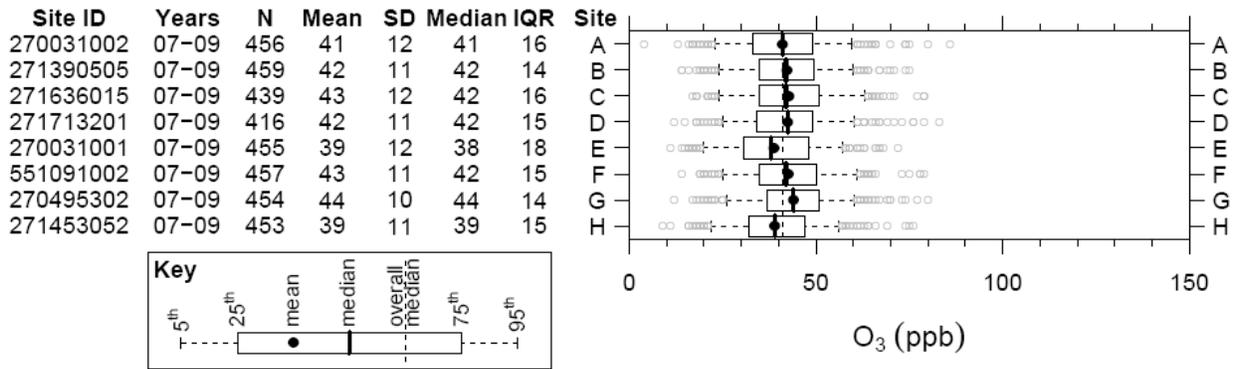


Figure 3A-46. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Minneapolis CSA.

### New York CSA

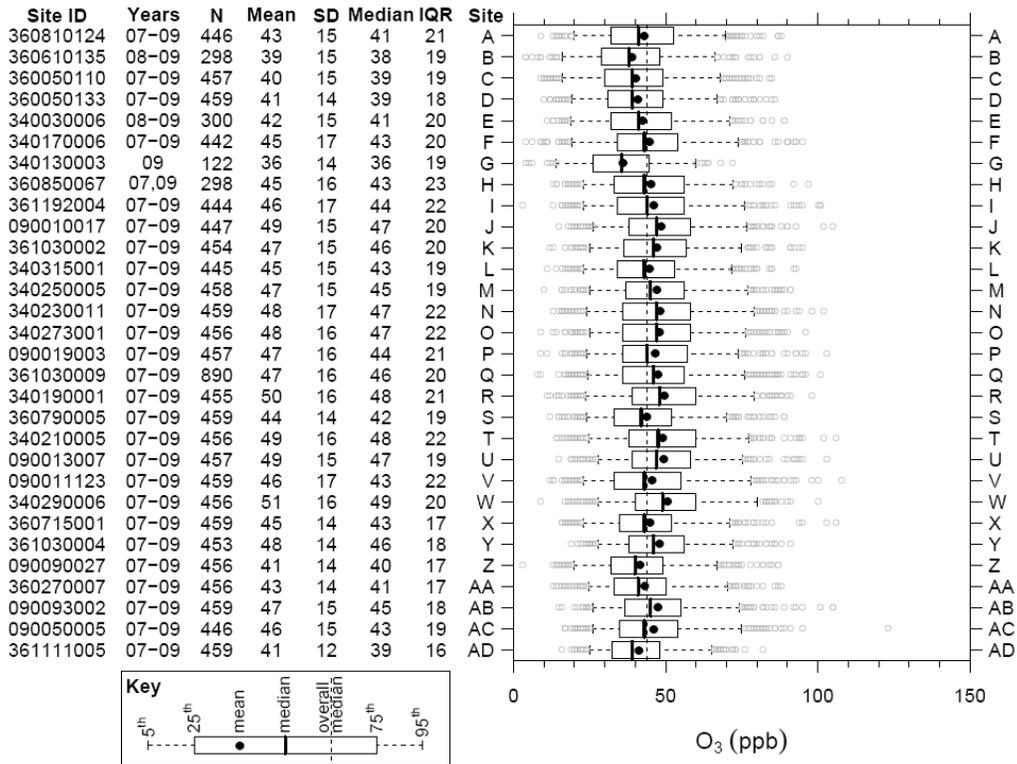
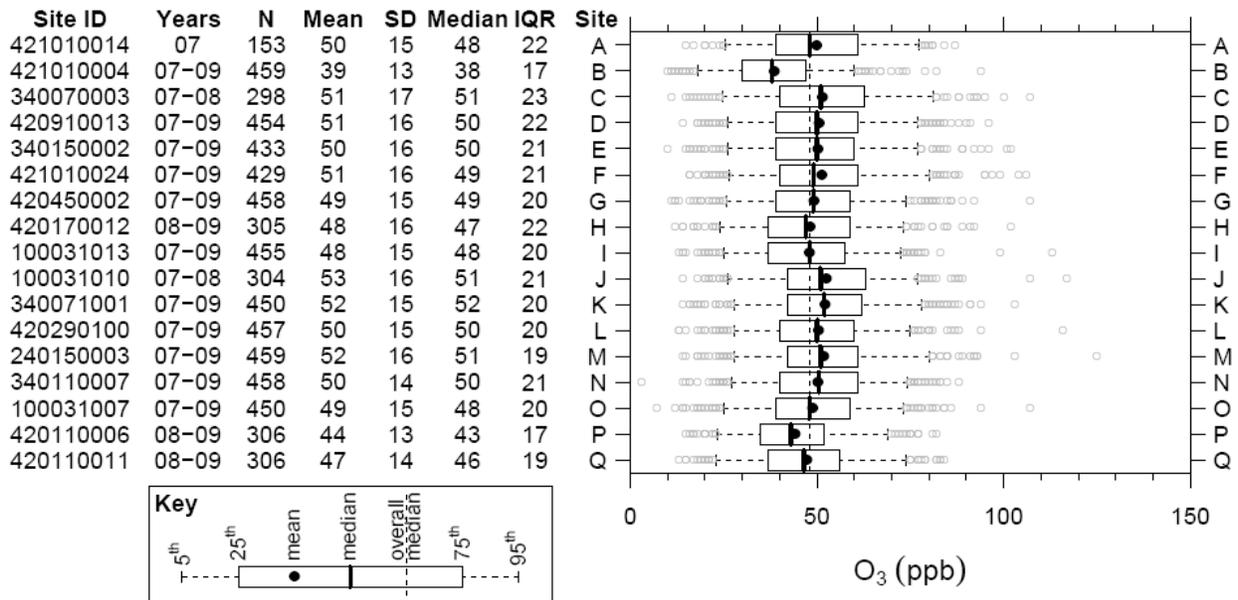


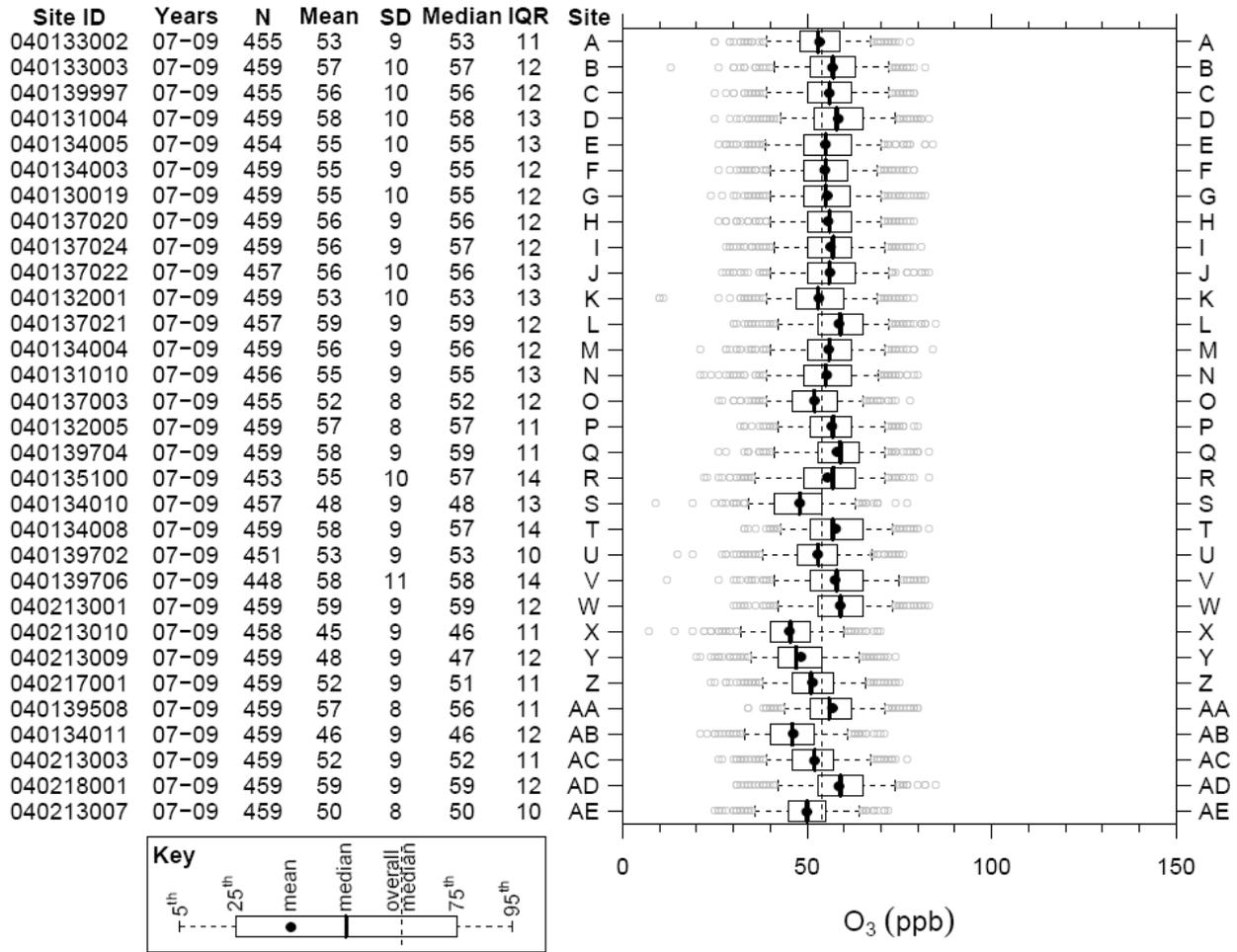
Figure 3A-47. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the New York CSA.

## Philadelphia CSA



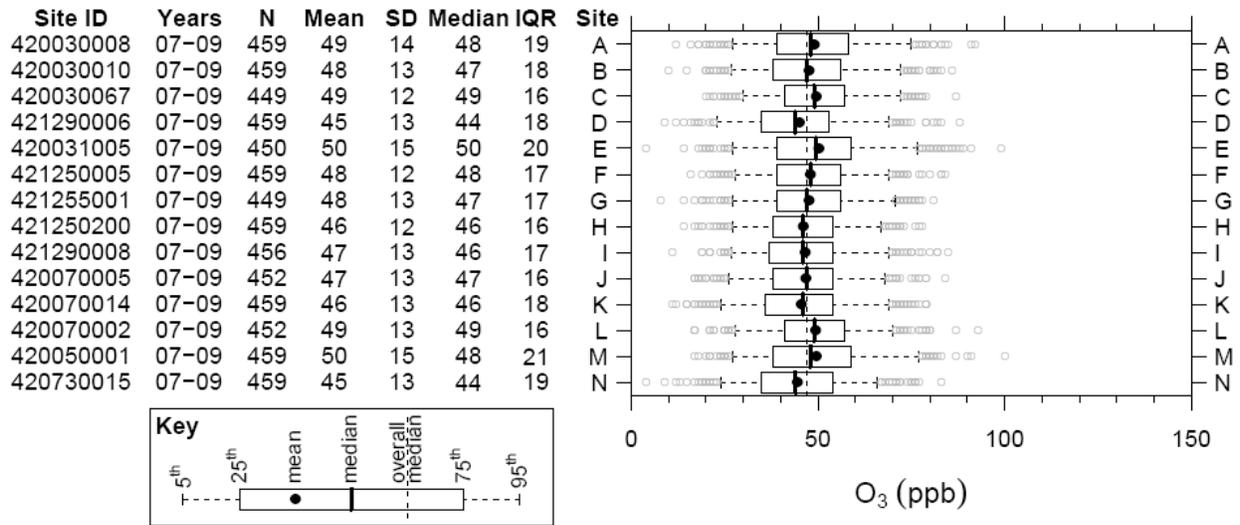
**Figure 3A-48. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Philadelphia CSA.**

## Phoenix CBSA



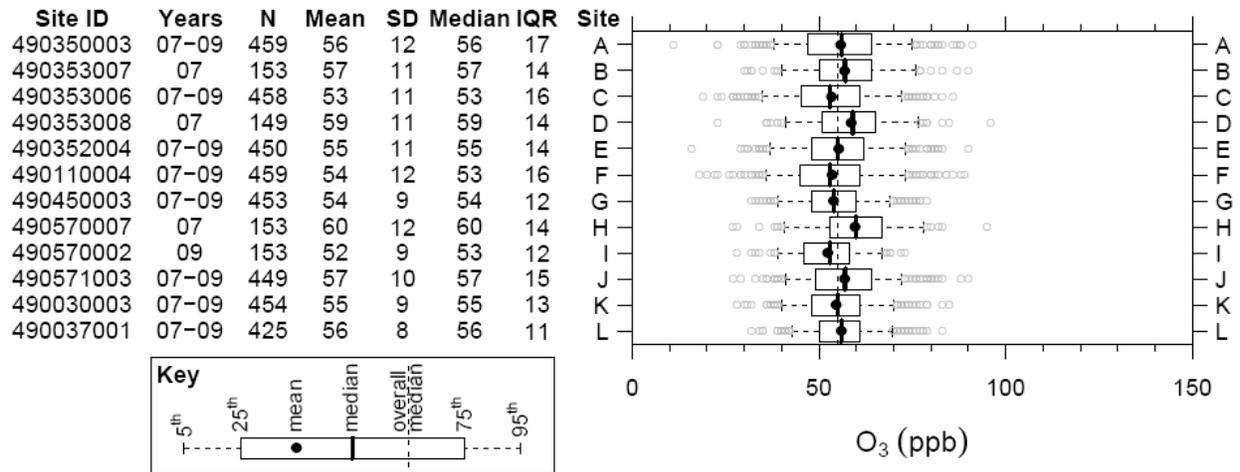
**Figure 3A-49. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Phoenix CBSA.**

### Pittsburgh CSA



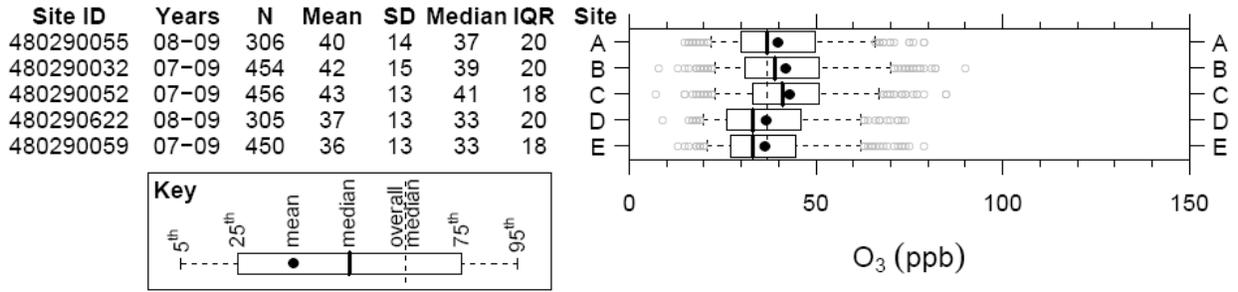
**Figure 3A-50. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Pittsburgh CSA.**

### Salt Lake City CSA



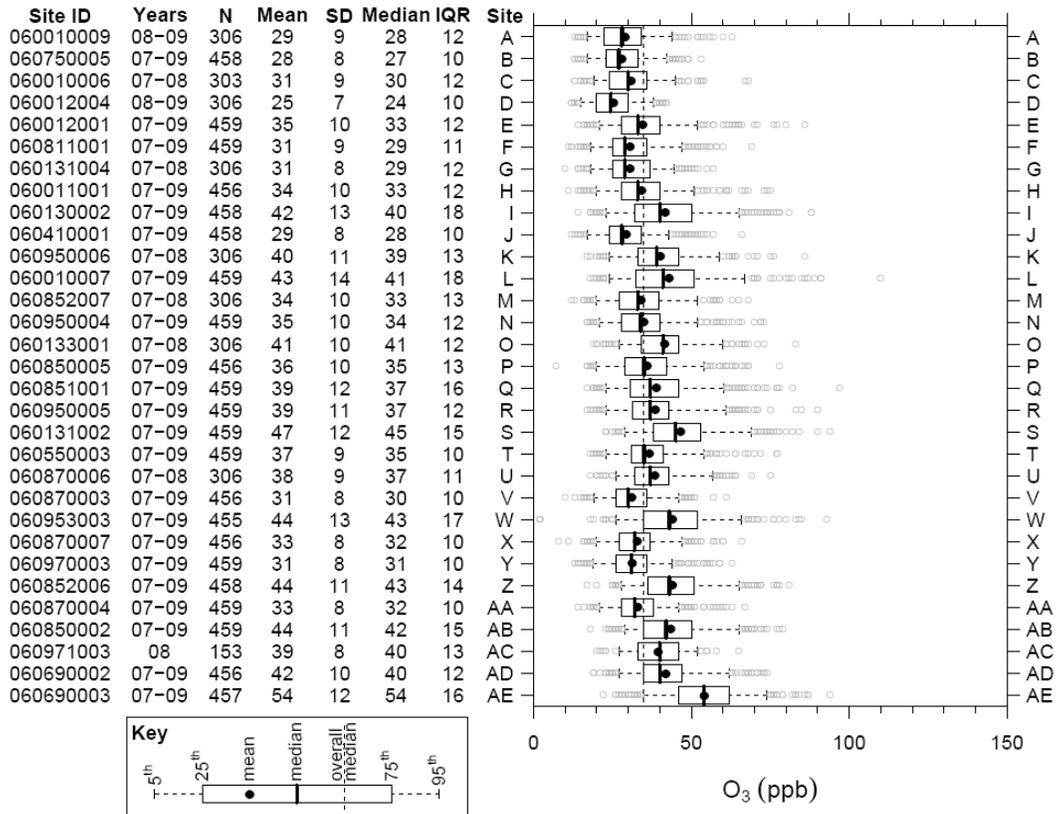
**Figure 3A-51. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Salt Lake City CSA.**

### San Antonio CBSA



**Figure 3A-52. 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.**

### San Francisco CSA



**Figure 3A-53. 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

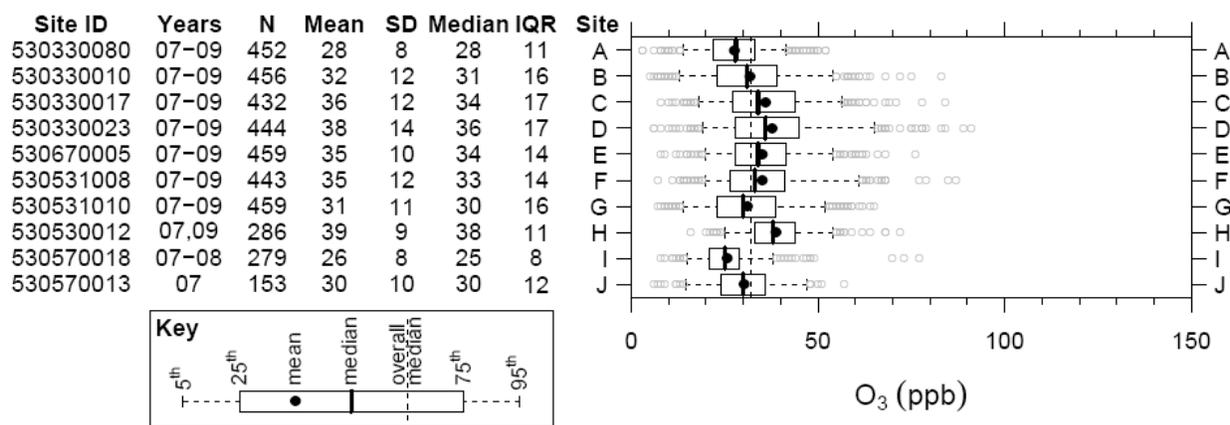


Figure 3A-54. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the Seattle CSA.

### St. Louis CSA

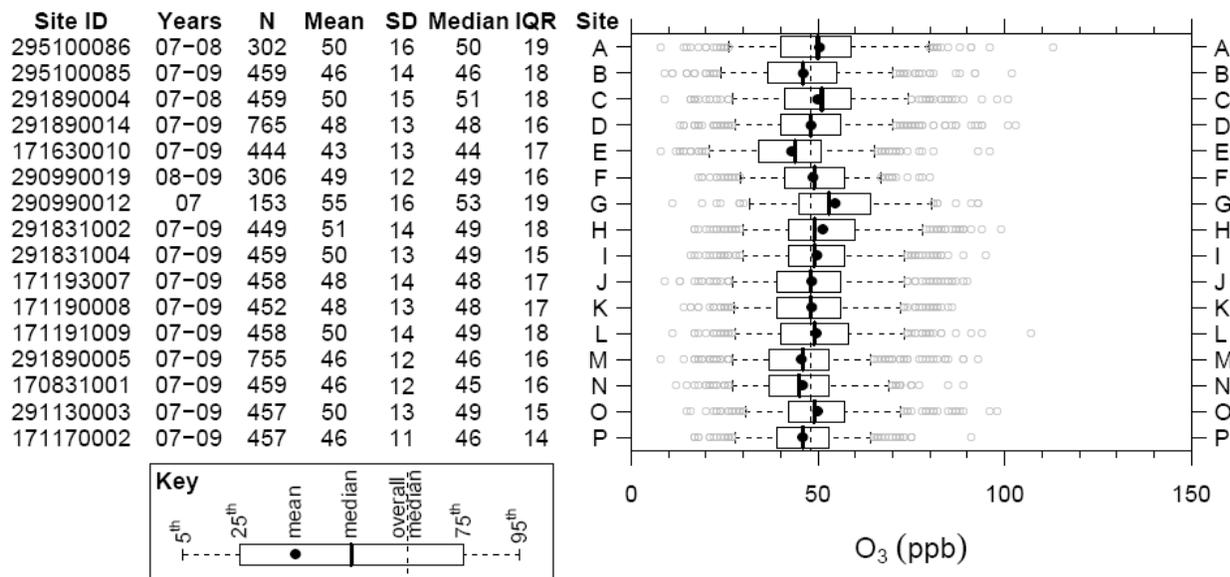
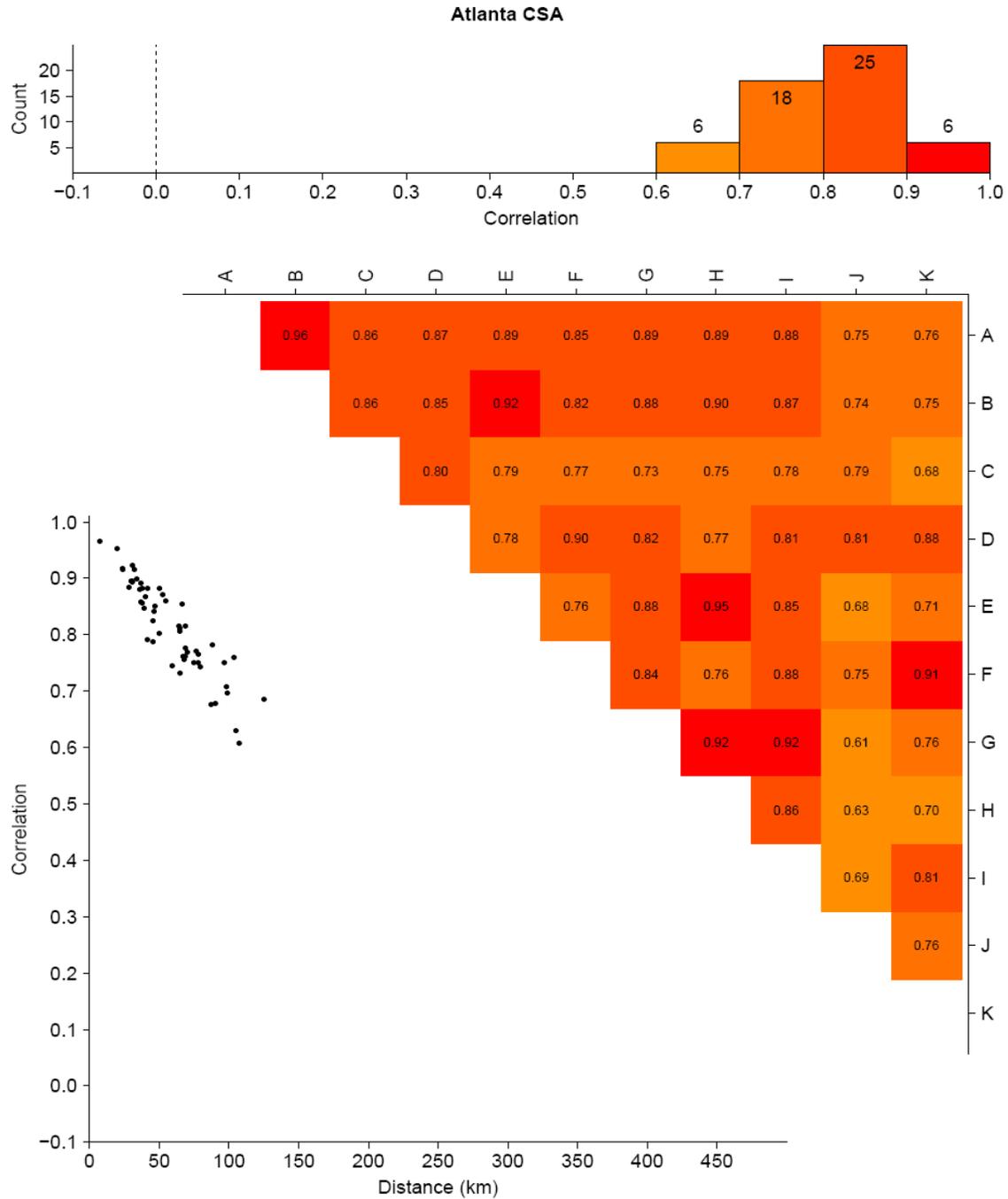


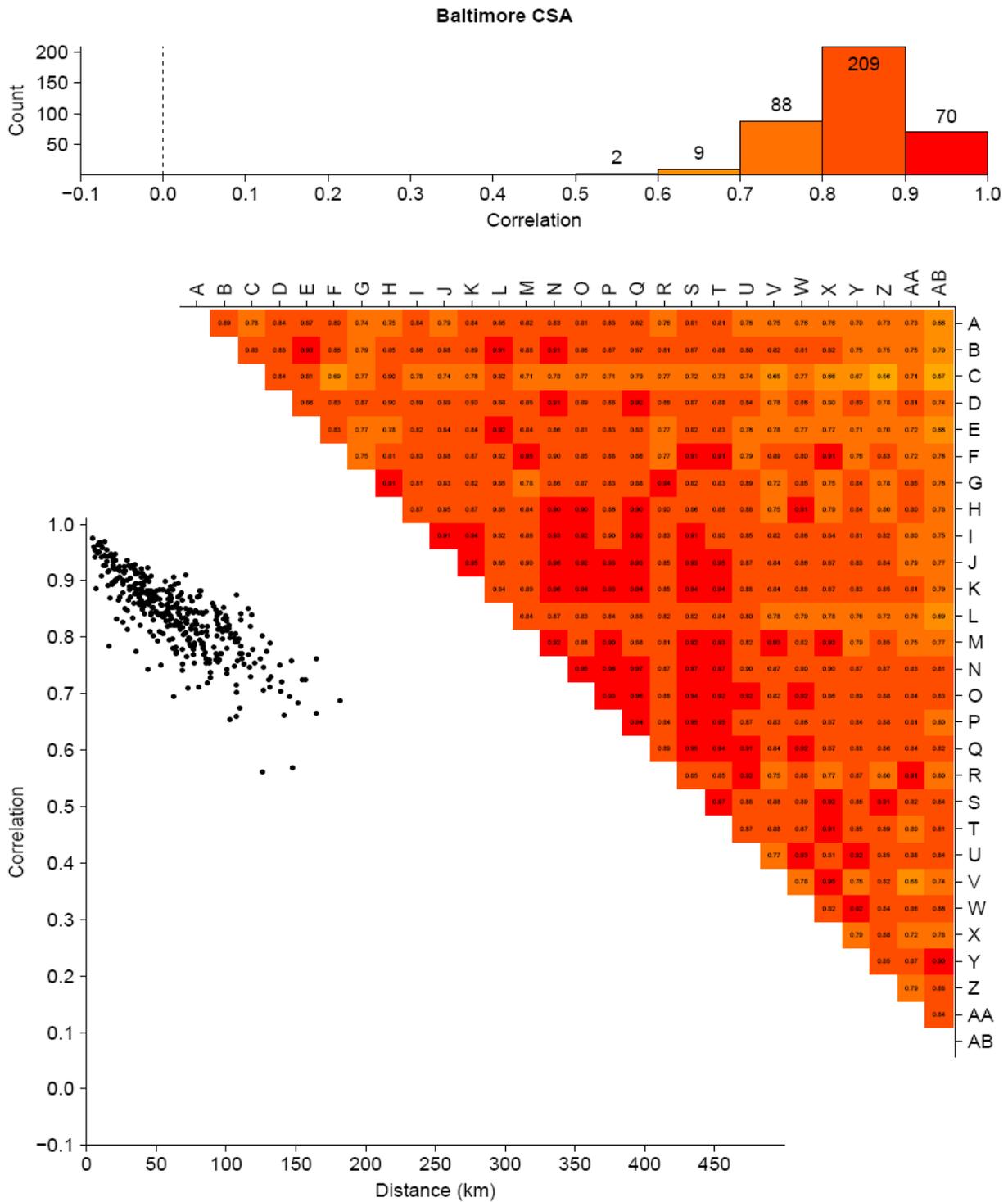
Figure 3A-55. Site information, statistics and box plots for 8-h daily max ozone from AQS monitors meeting the warm-season data set inclusion criteria within the St. Louis CSA.

### 3.8.4. Ozone Concentration Relationships for the Urban Focus Cities

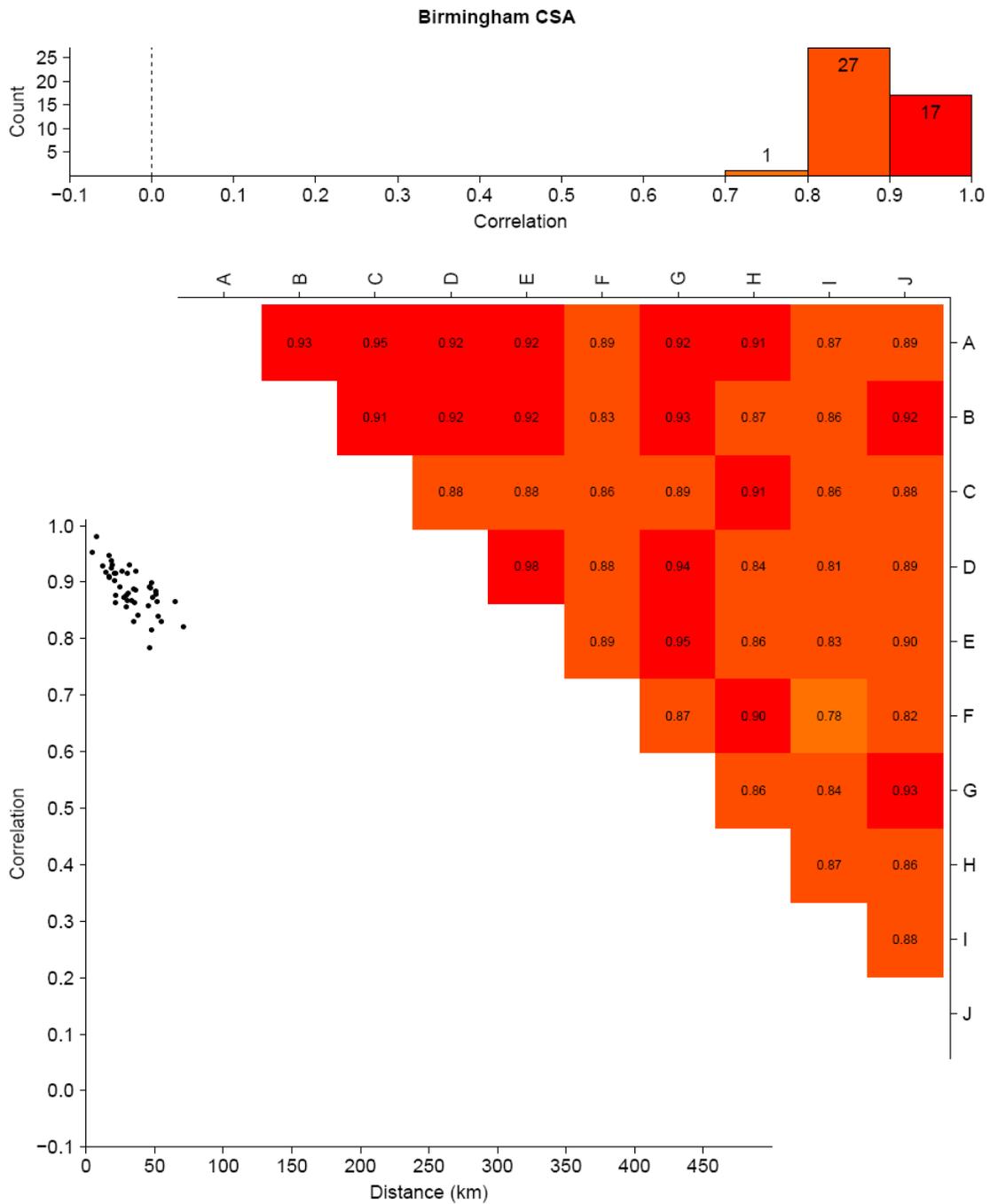
1            This section contains histograms and contour matrices of the Pearson correlation coefficient  
2 and the coefficient of divergence (COD) between 8-h daily max O<sub>3</sub> concentrations from each  
3 monitor pair within the 20 urban focus cities discussed in Section 3.6.2.1. These figures also contain  
4 scatter plots of the correlation and COD as a function of straight-line distance between monitor pairs.



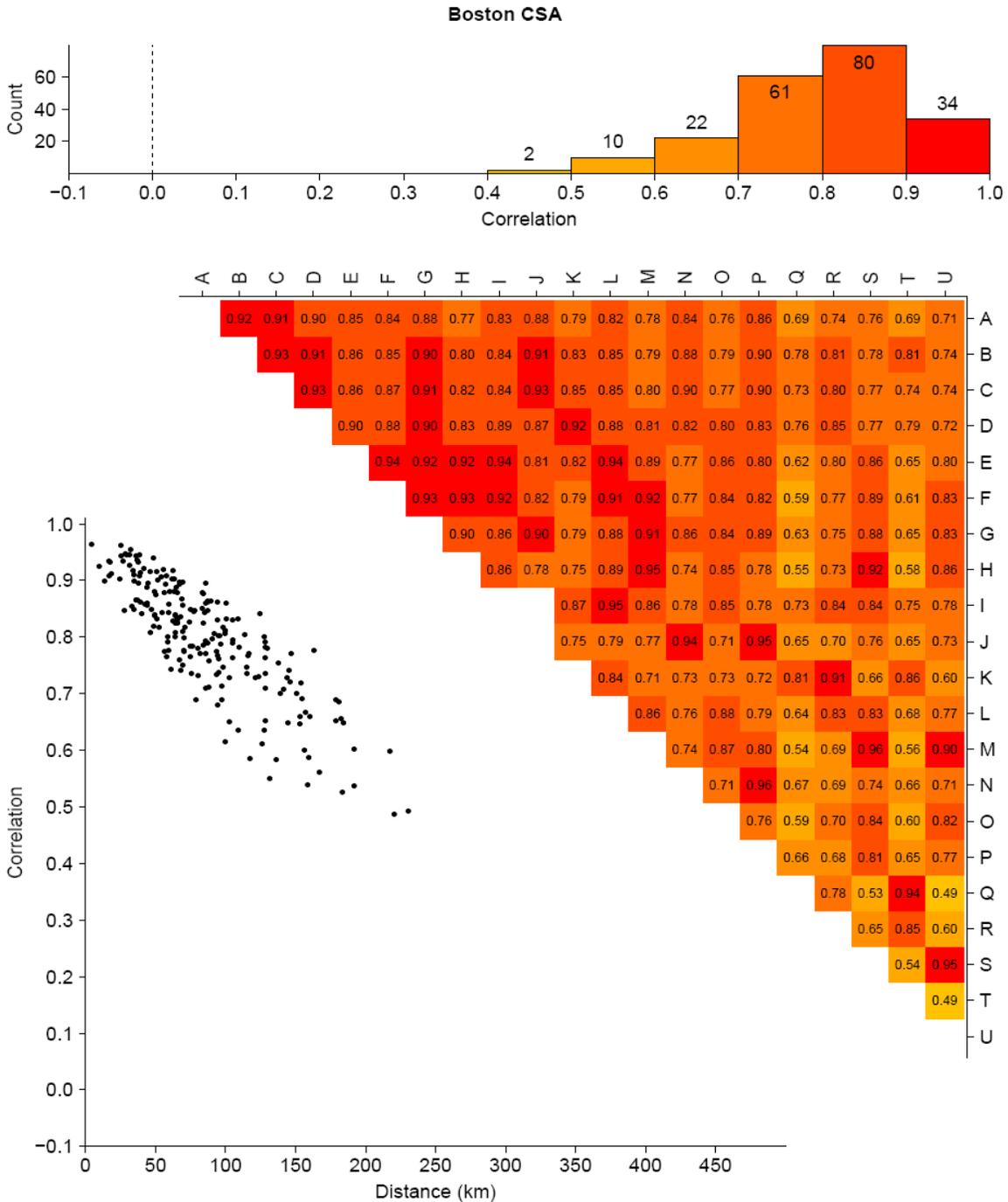
**Figure 3A-56. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



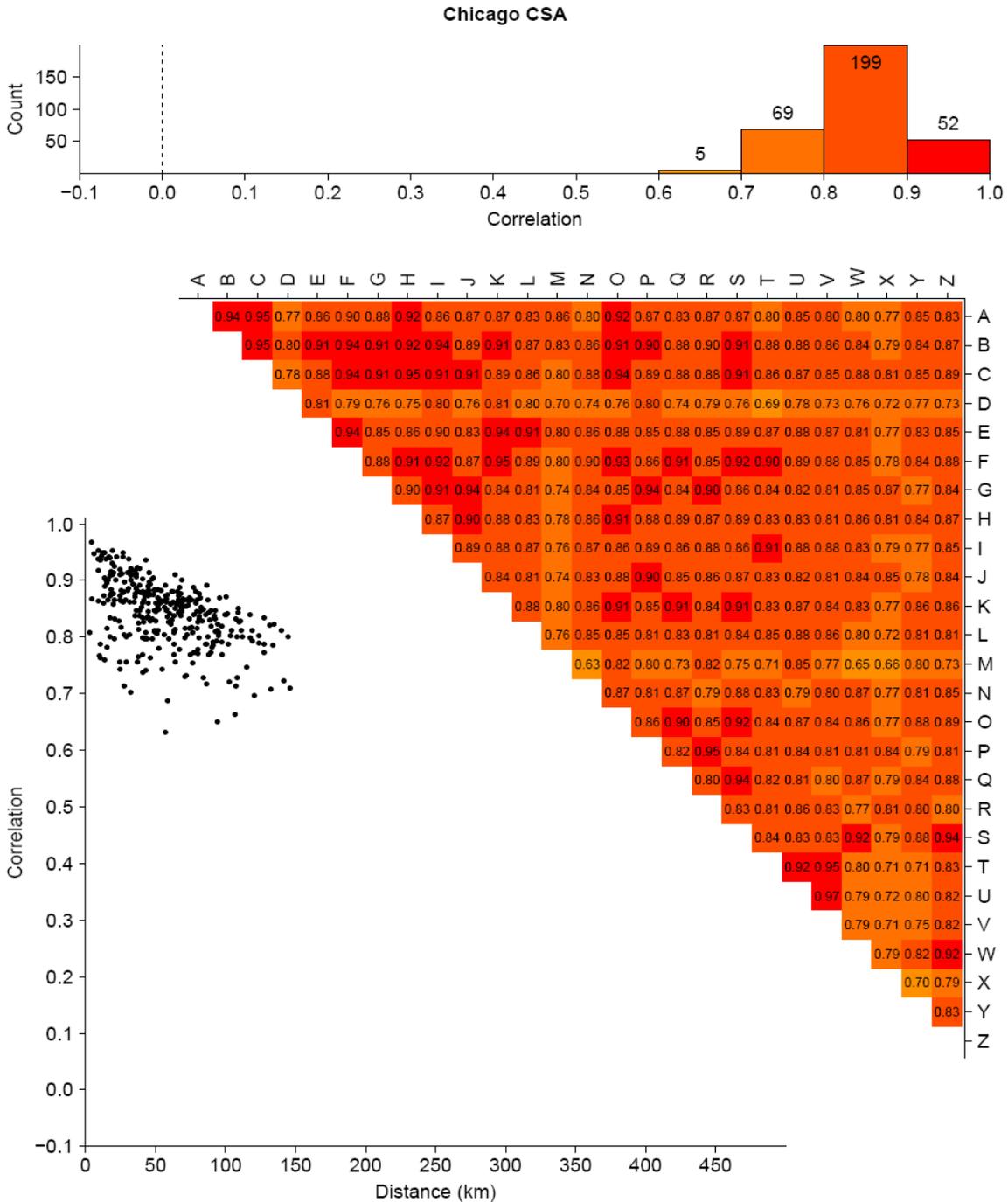
**Figure 3A-57. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Baltimore CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



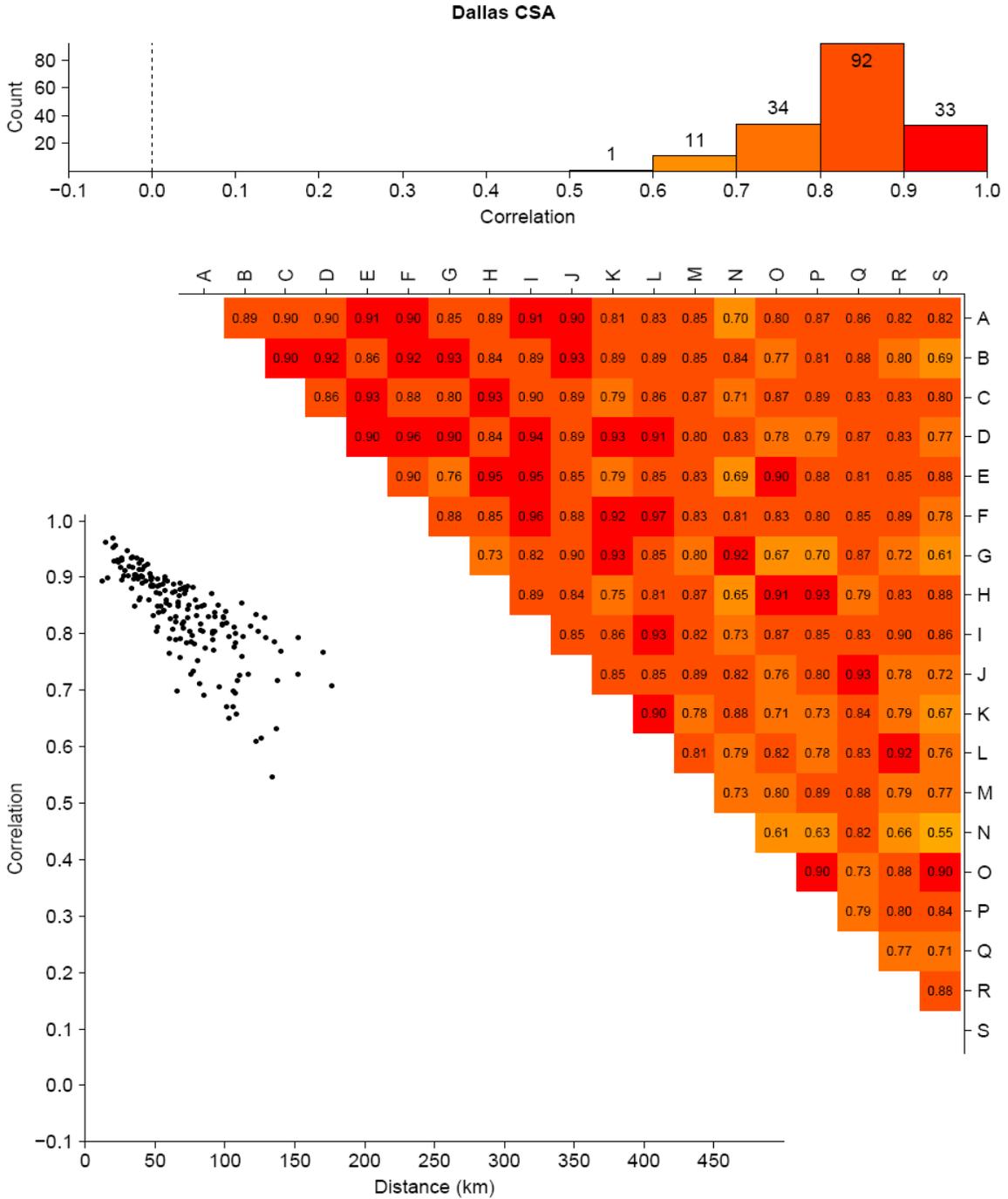
**Figure 3A-58. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Birmingham CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



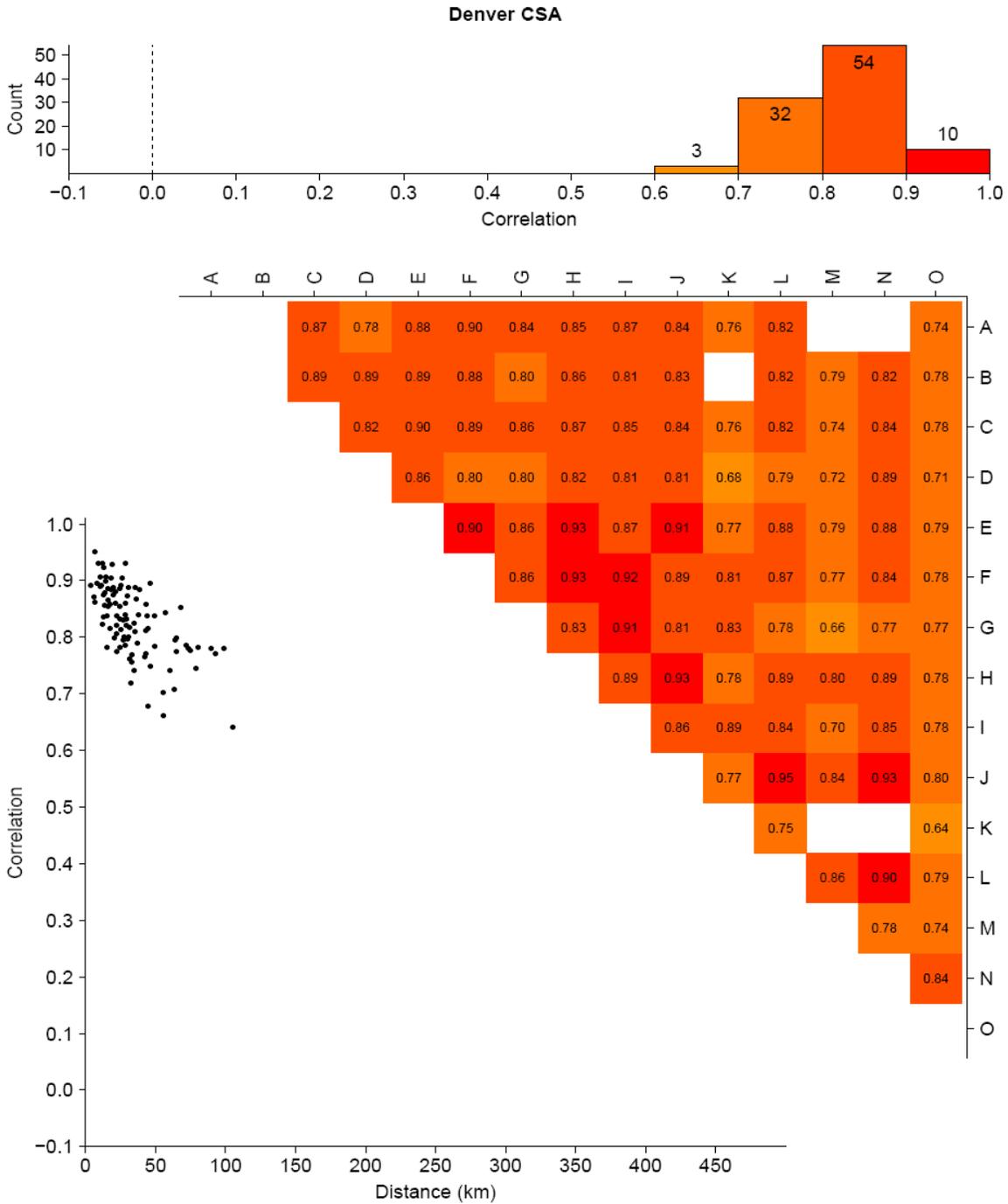
**Figure 3A-59. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



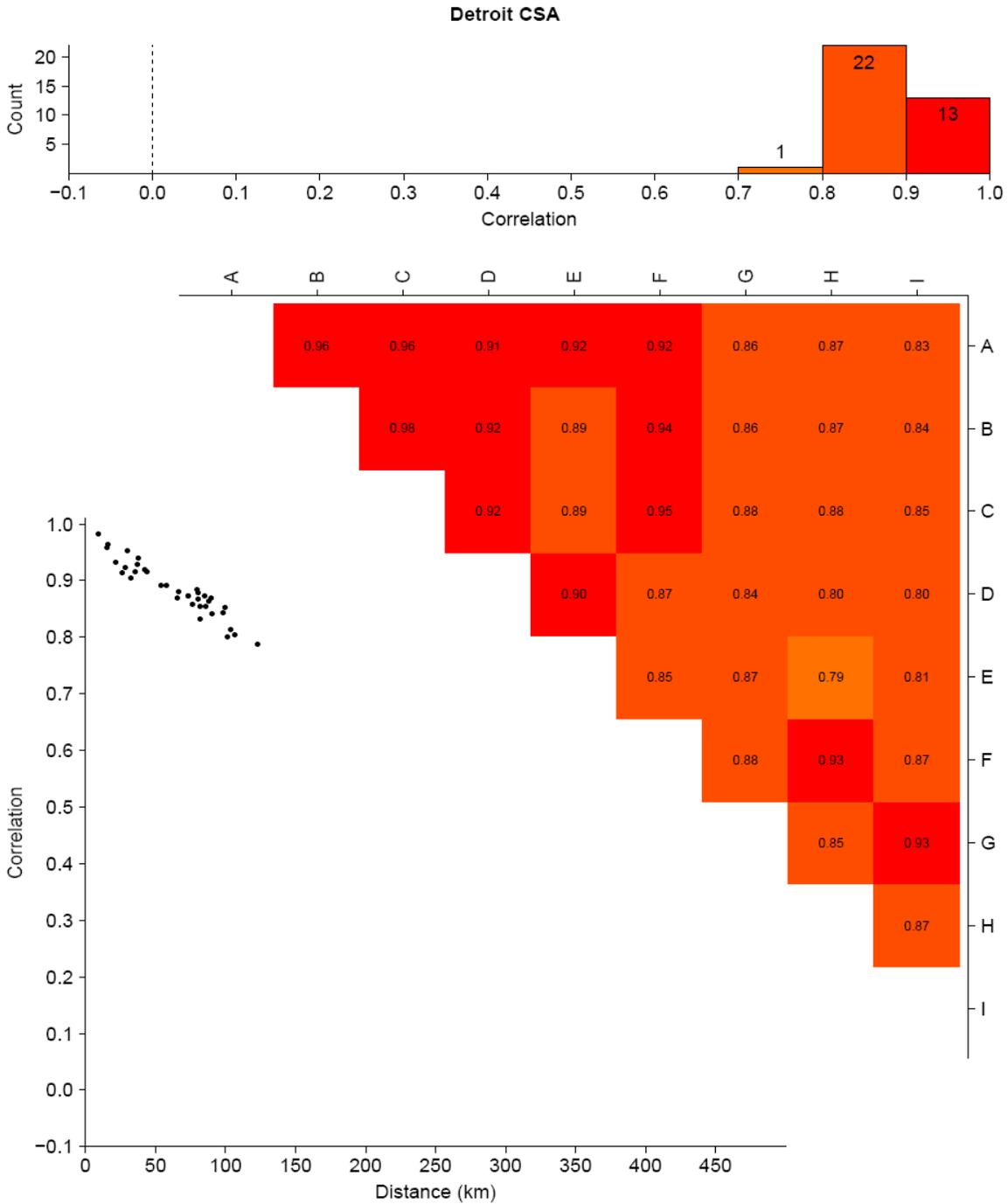
**Figure 3A-60. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Chicago CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



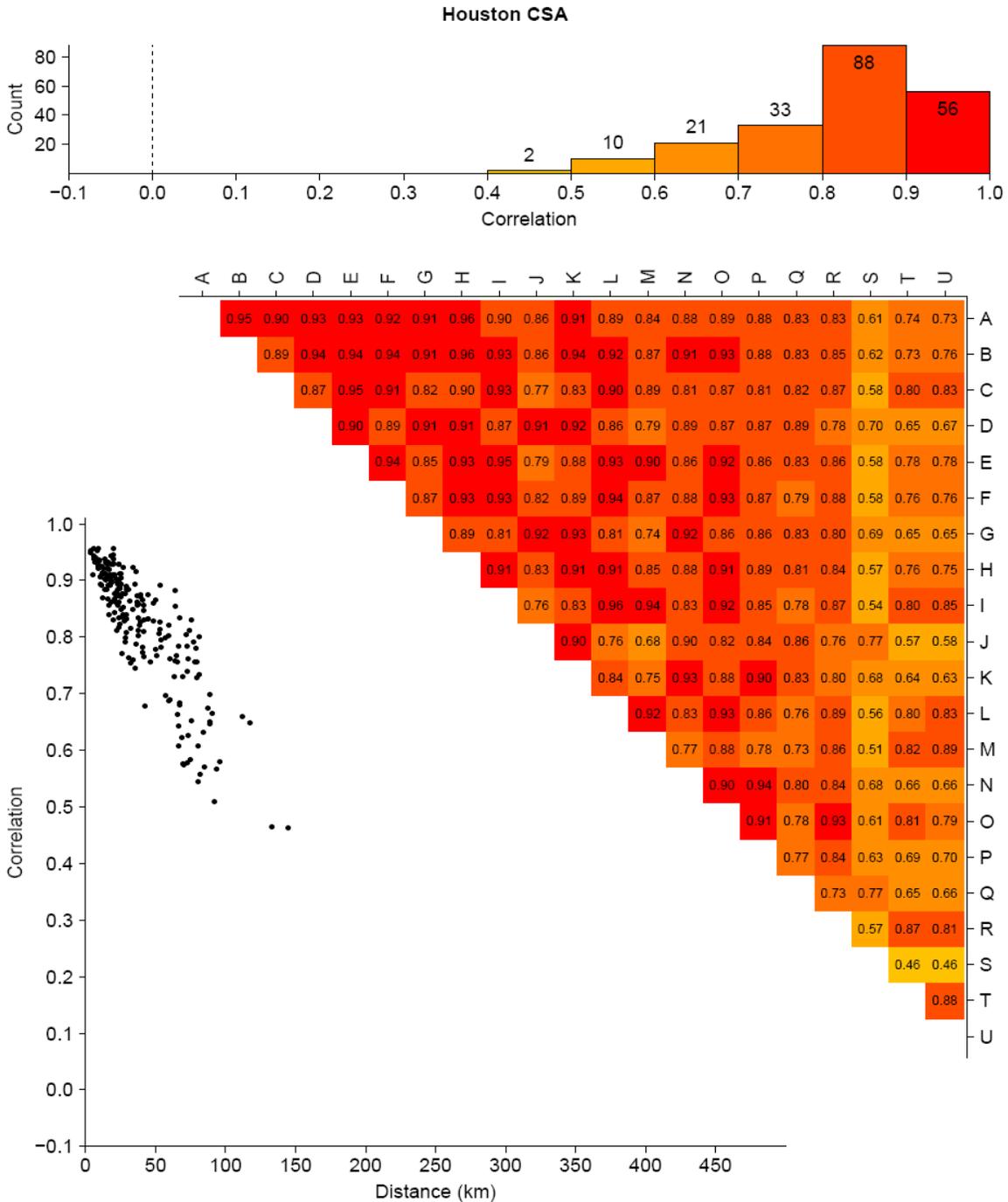
**Figure 3A-61. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Dallas CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



**Figure 3A-62. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Denver CSA. 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 3A-63. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Detroit CSA. 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 3A-64. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Houston CSA. 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.**

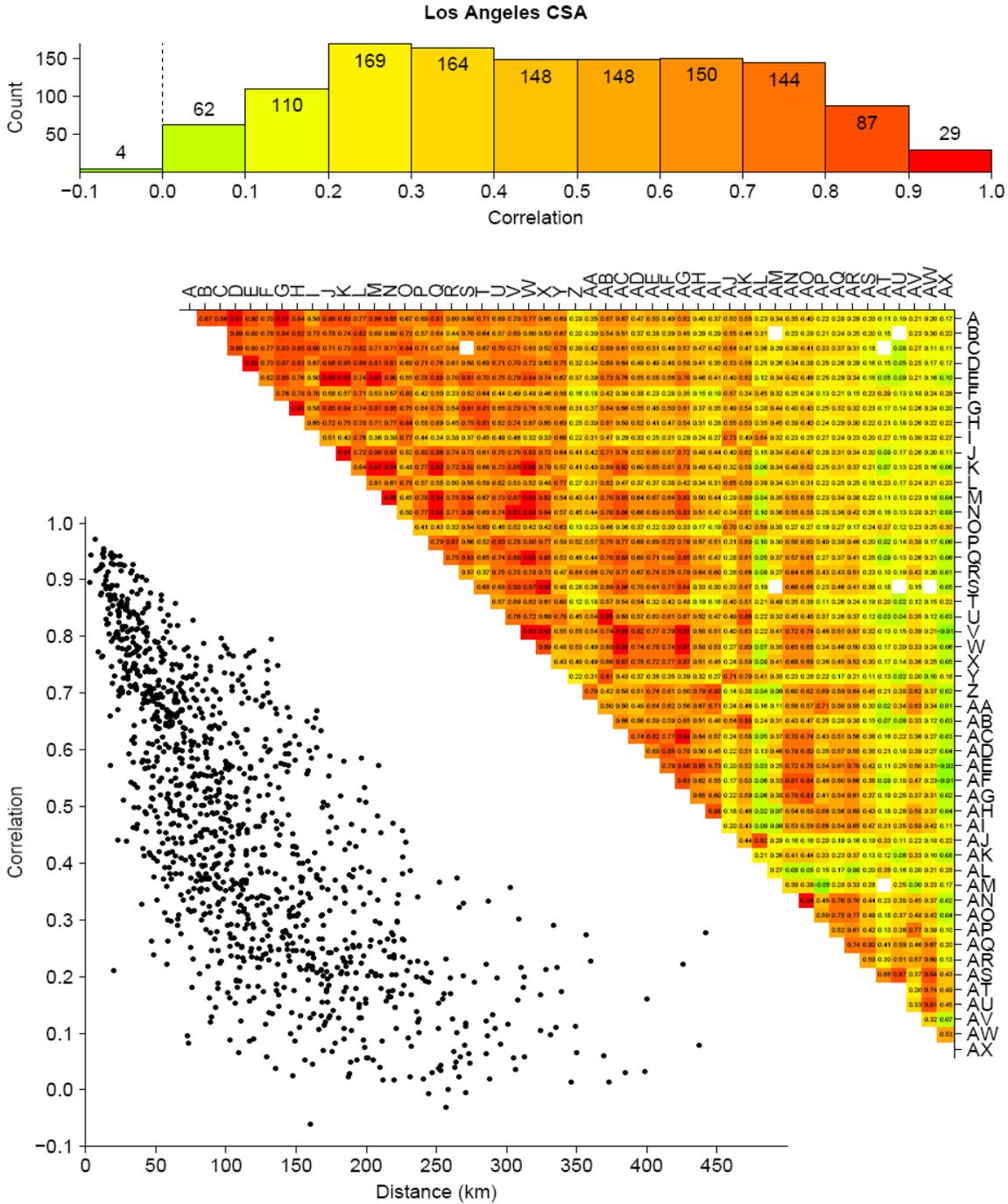
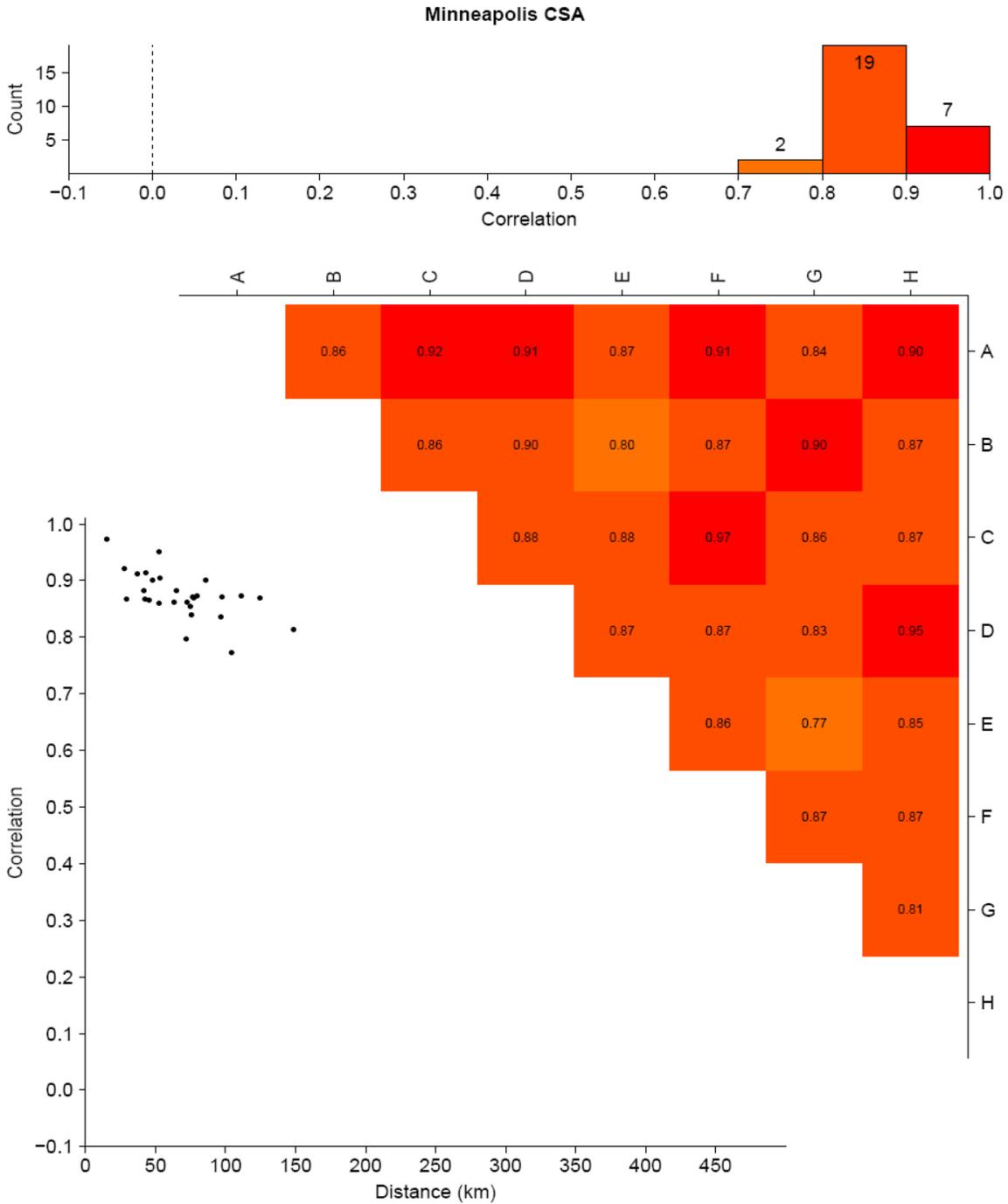
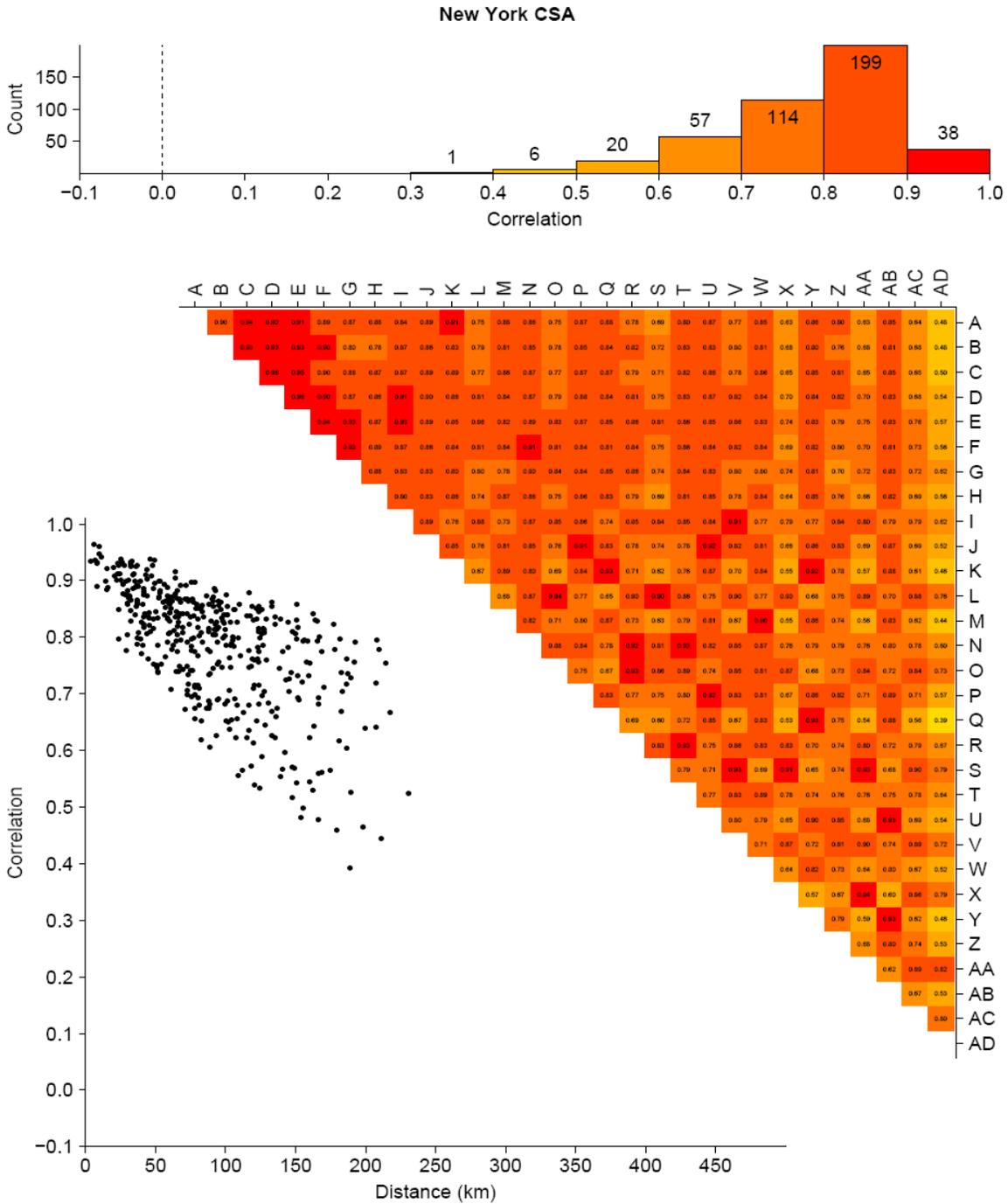


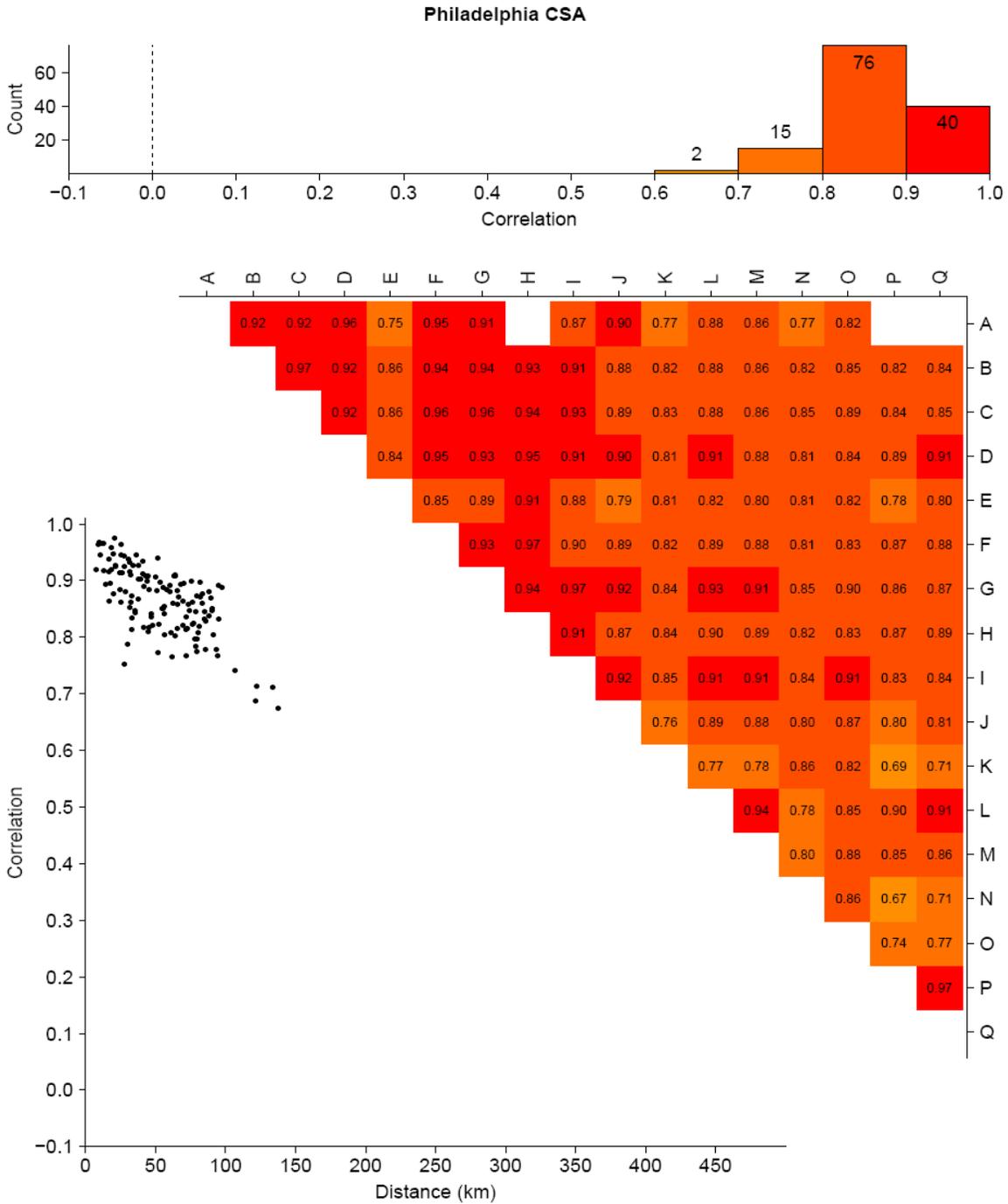
Figure 3A-65. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Los Angeles CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.



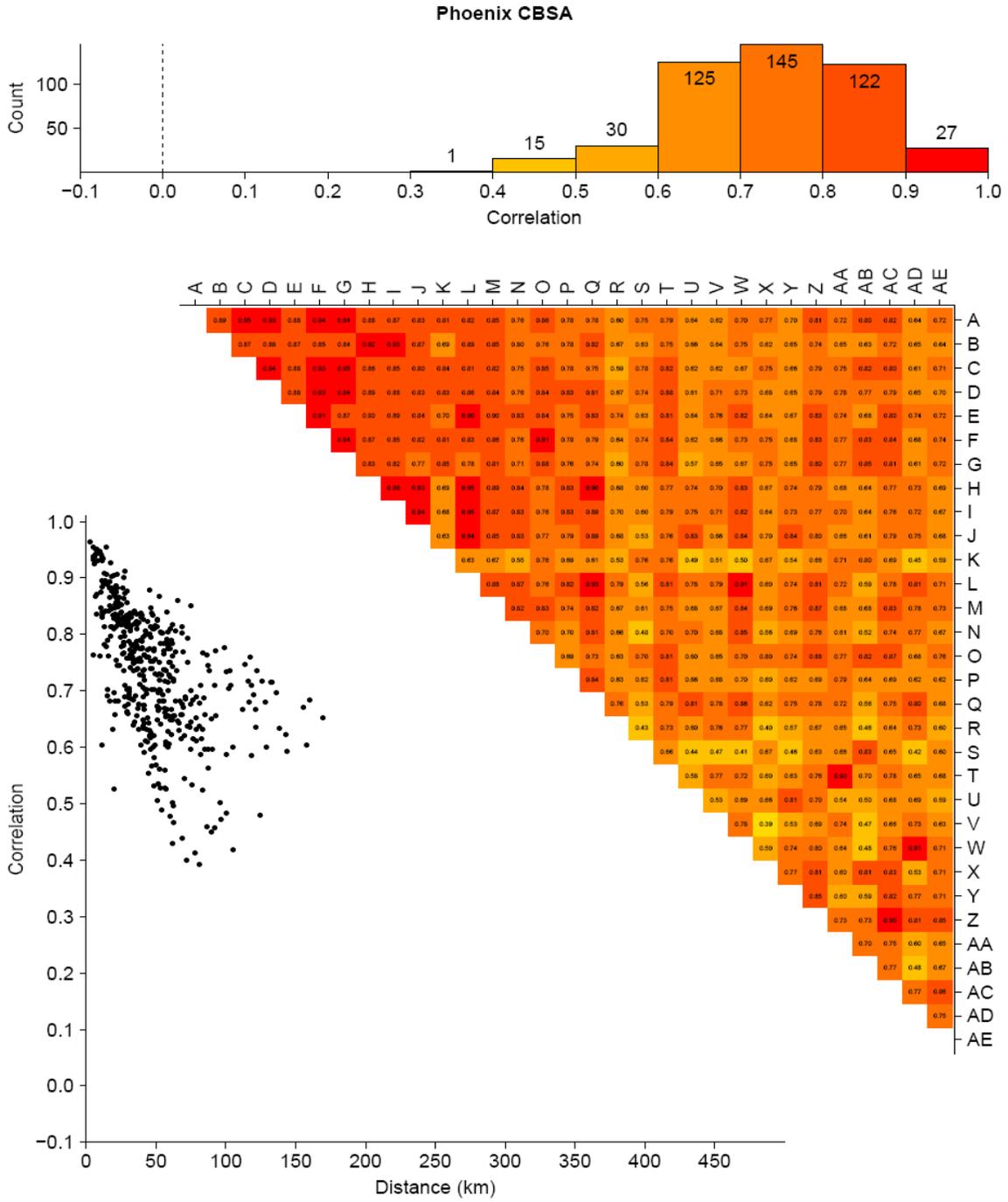
**Figure 3A-66. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Minneapolis CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



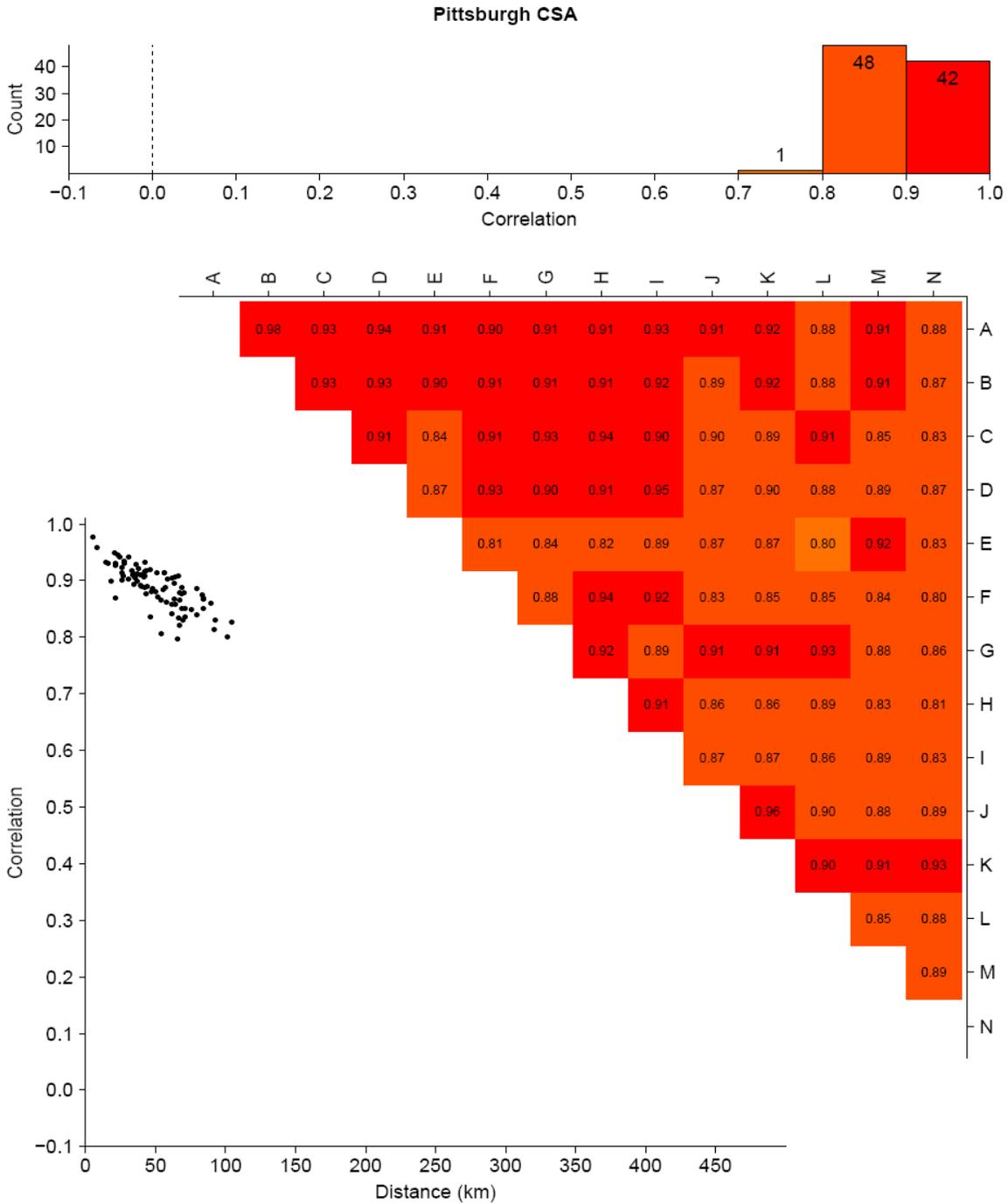
**Figure 3A-67. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the New York CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



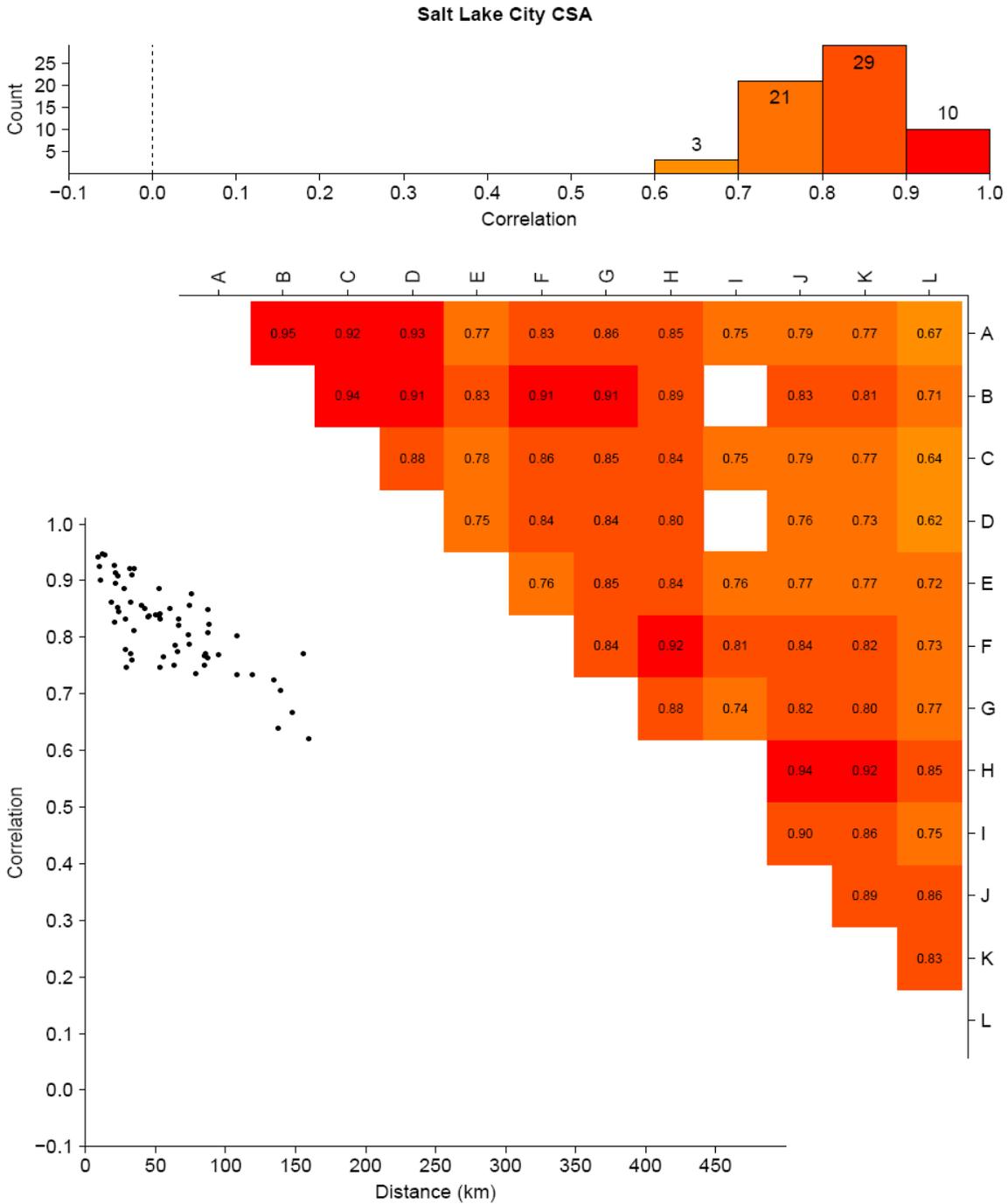
**Figure 3A-68. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Philadelphia CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



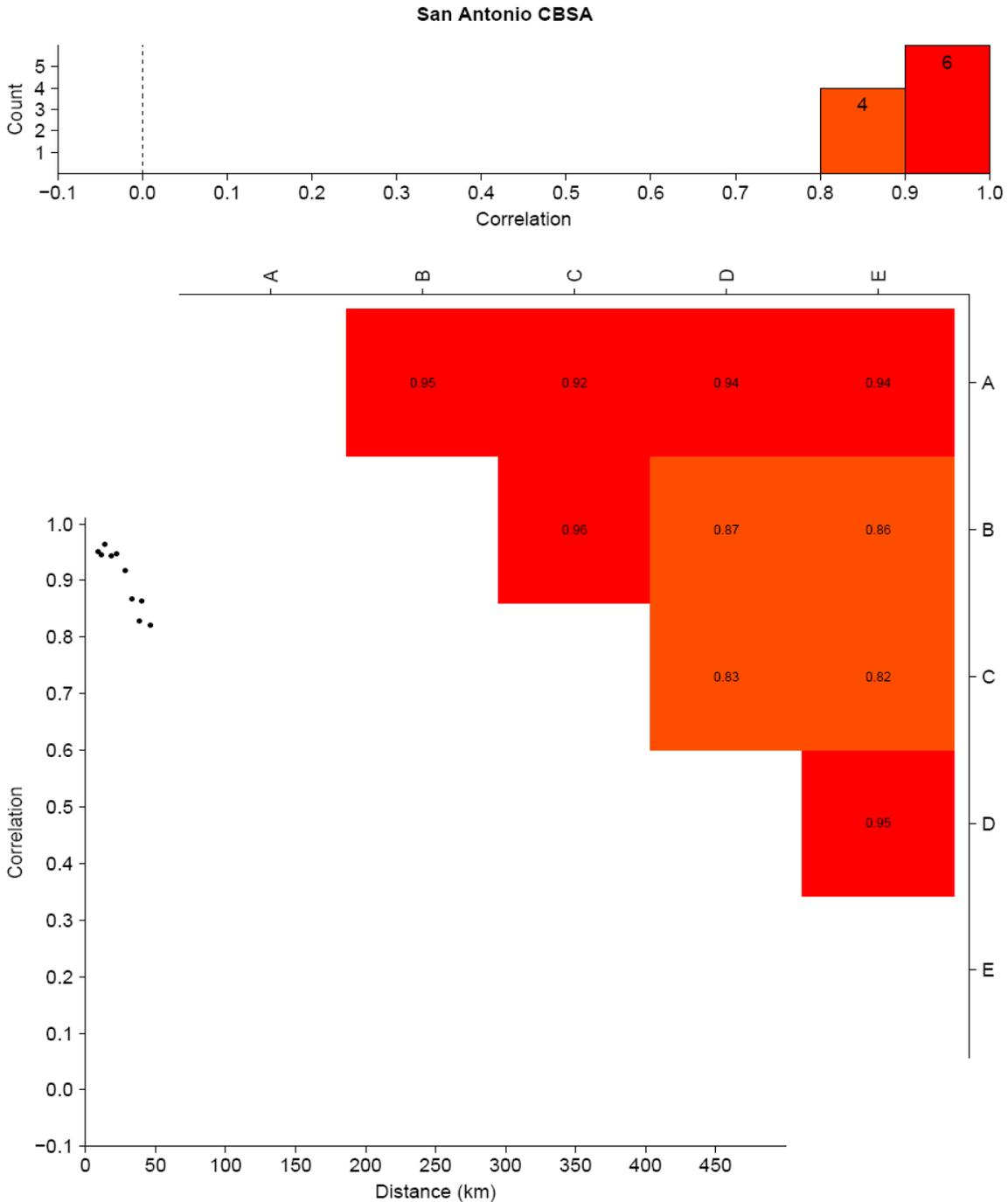
**Figure 3A-69. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Phoenix CBSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.**



**Figure 3A-70. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Pittsburgh CSA. 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 3A-71. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Salt Lake City CSA. 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 3A-72. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Antonio CBSA. 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.**

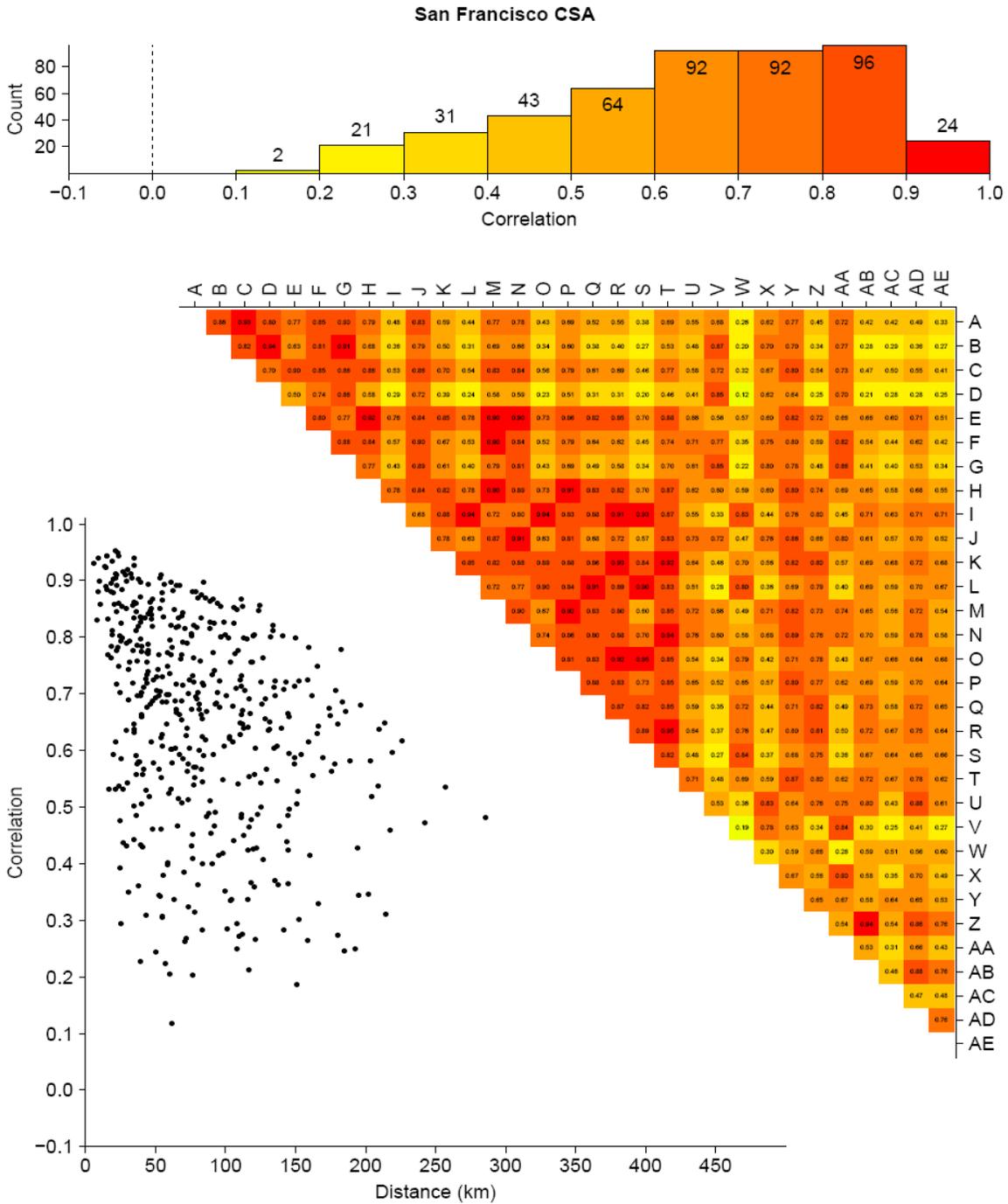
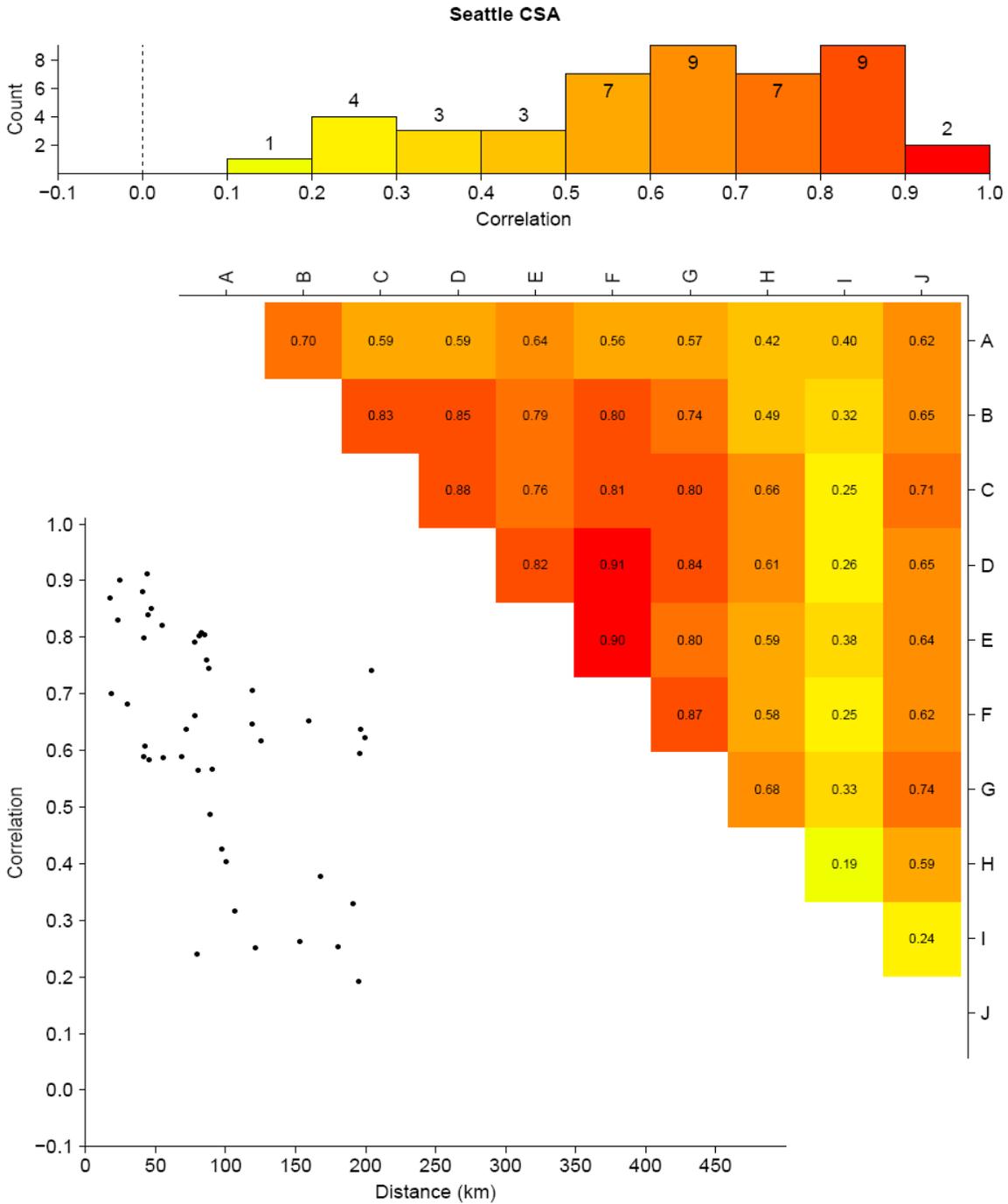
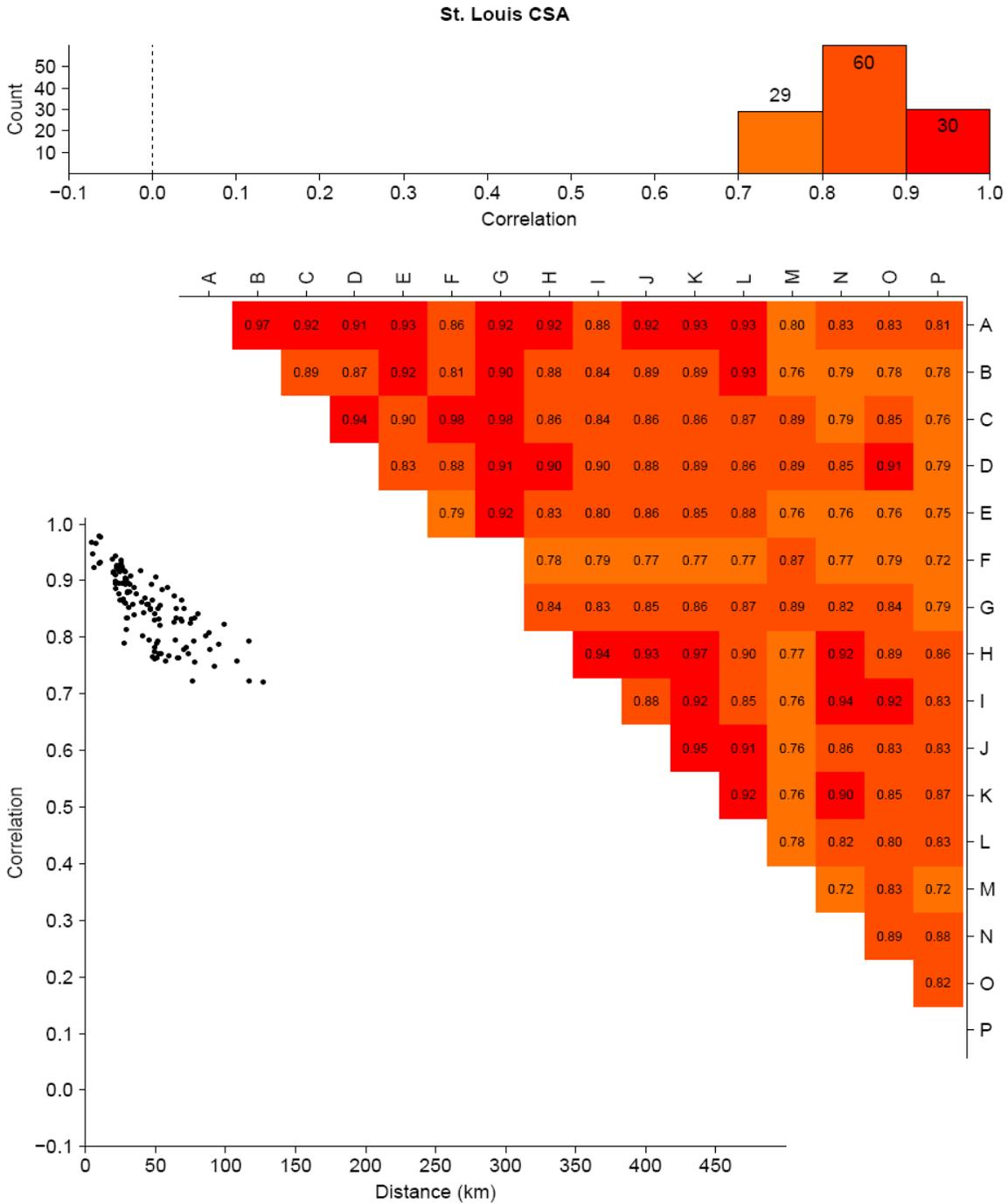


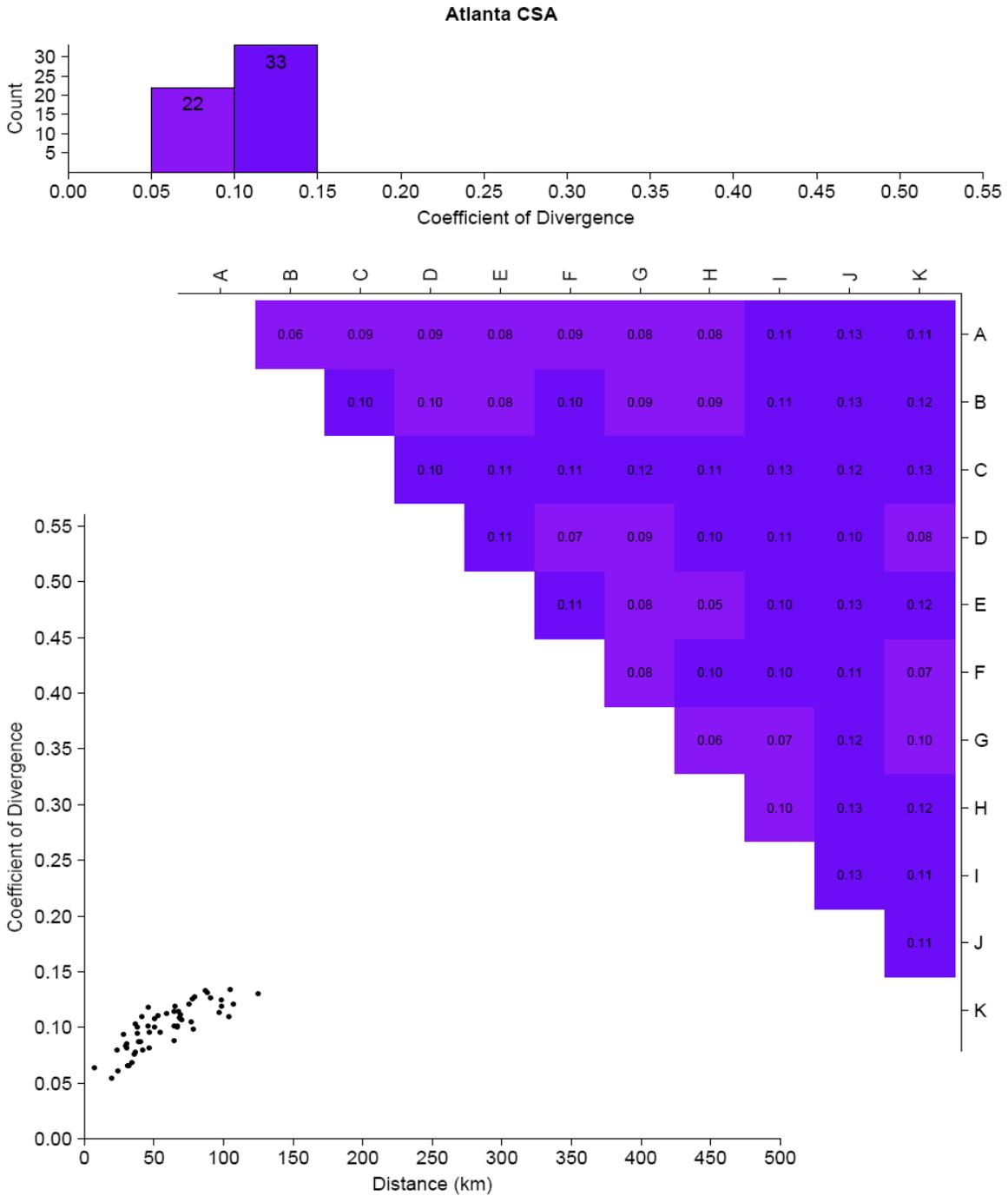
Figure 3A-73. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Francisco CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the correlations.



**Figure 3A-74. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Seattle CSA. 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 3A-75. Pair-wise monitor correlations expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the St. Louis CSA. 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 3A-76. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Atlanta CSA. □ 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.**

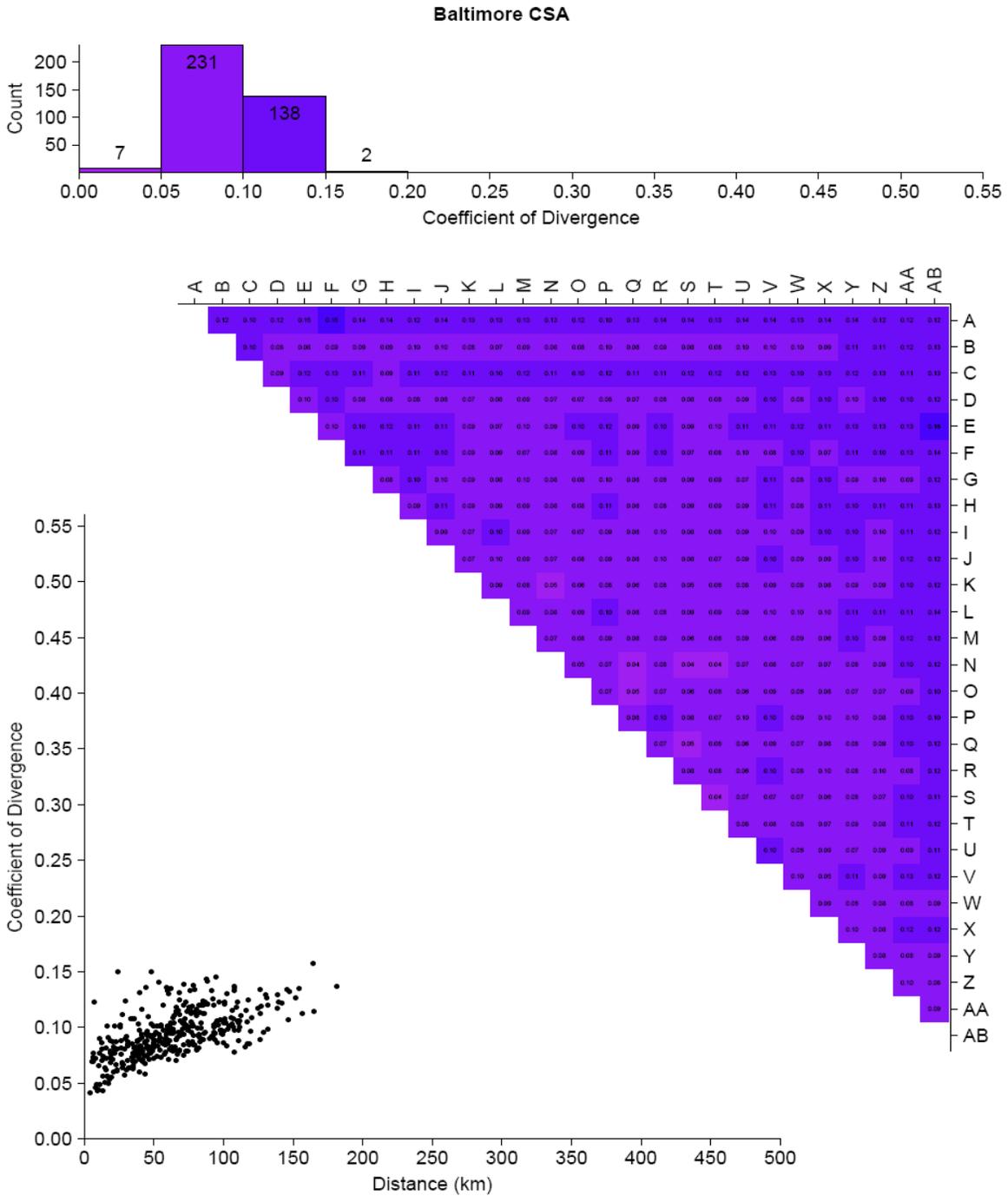
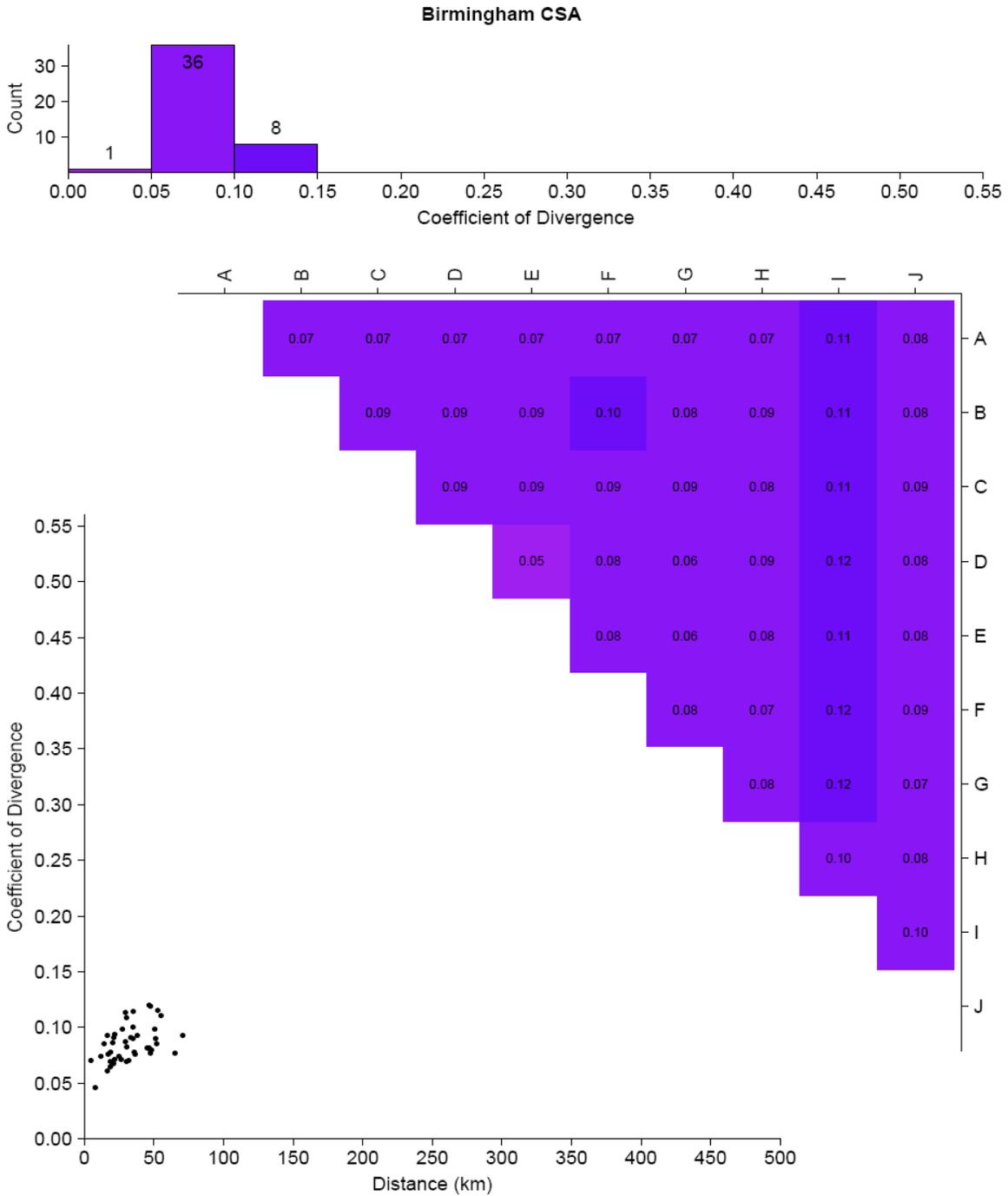
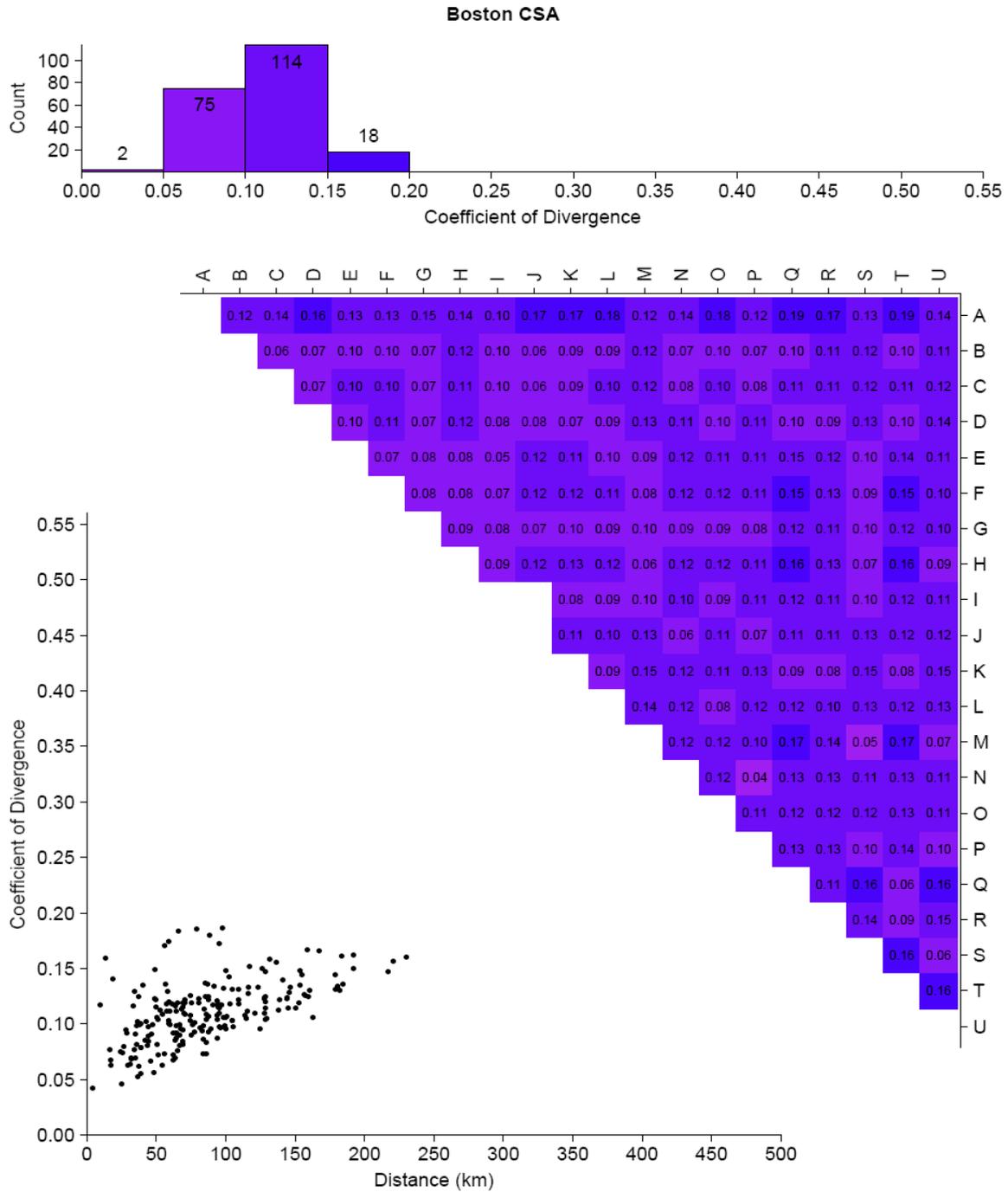


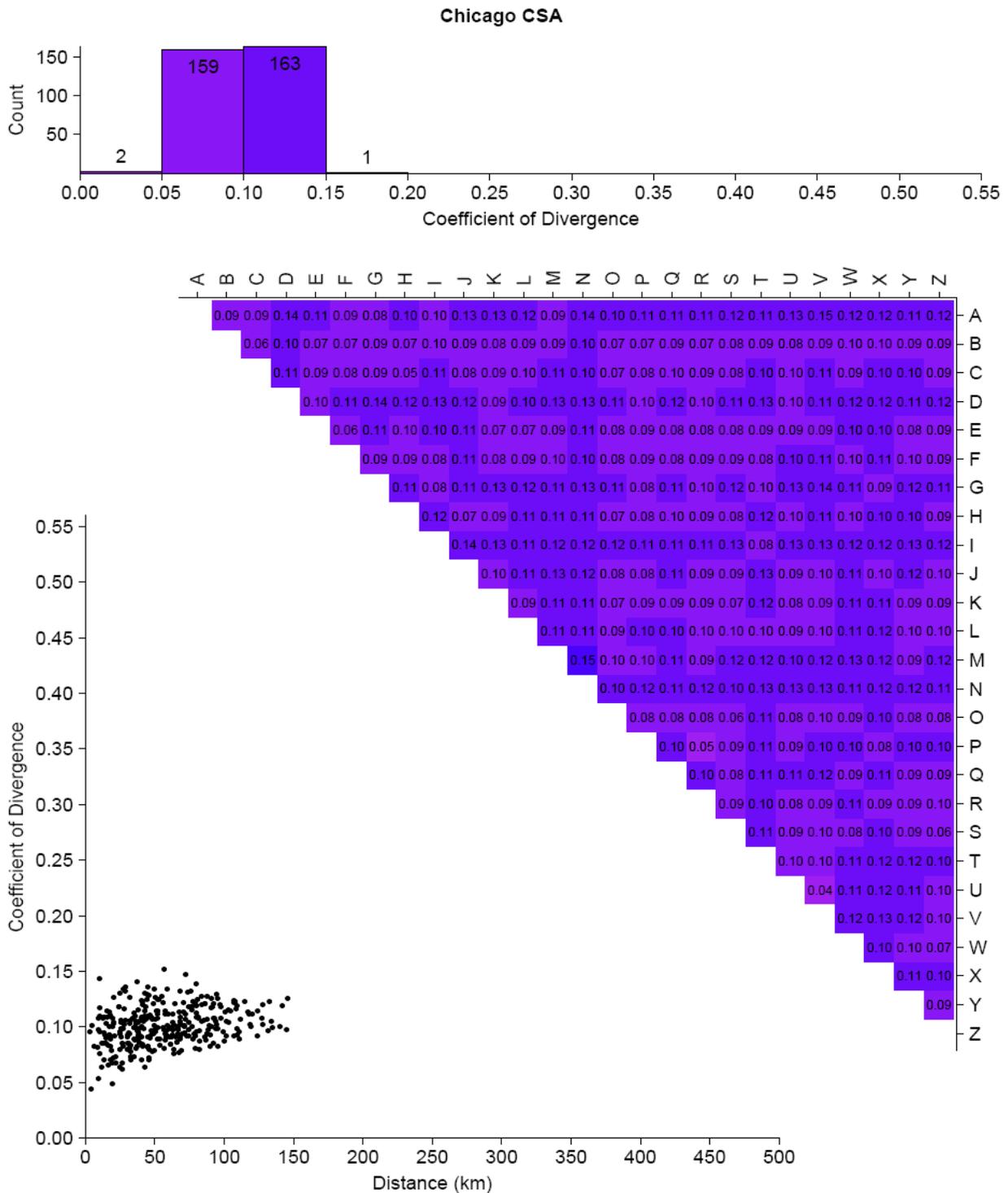
Figure 3A-77. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Baltimore CSA. □ The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.



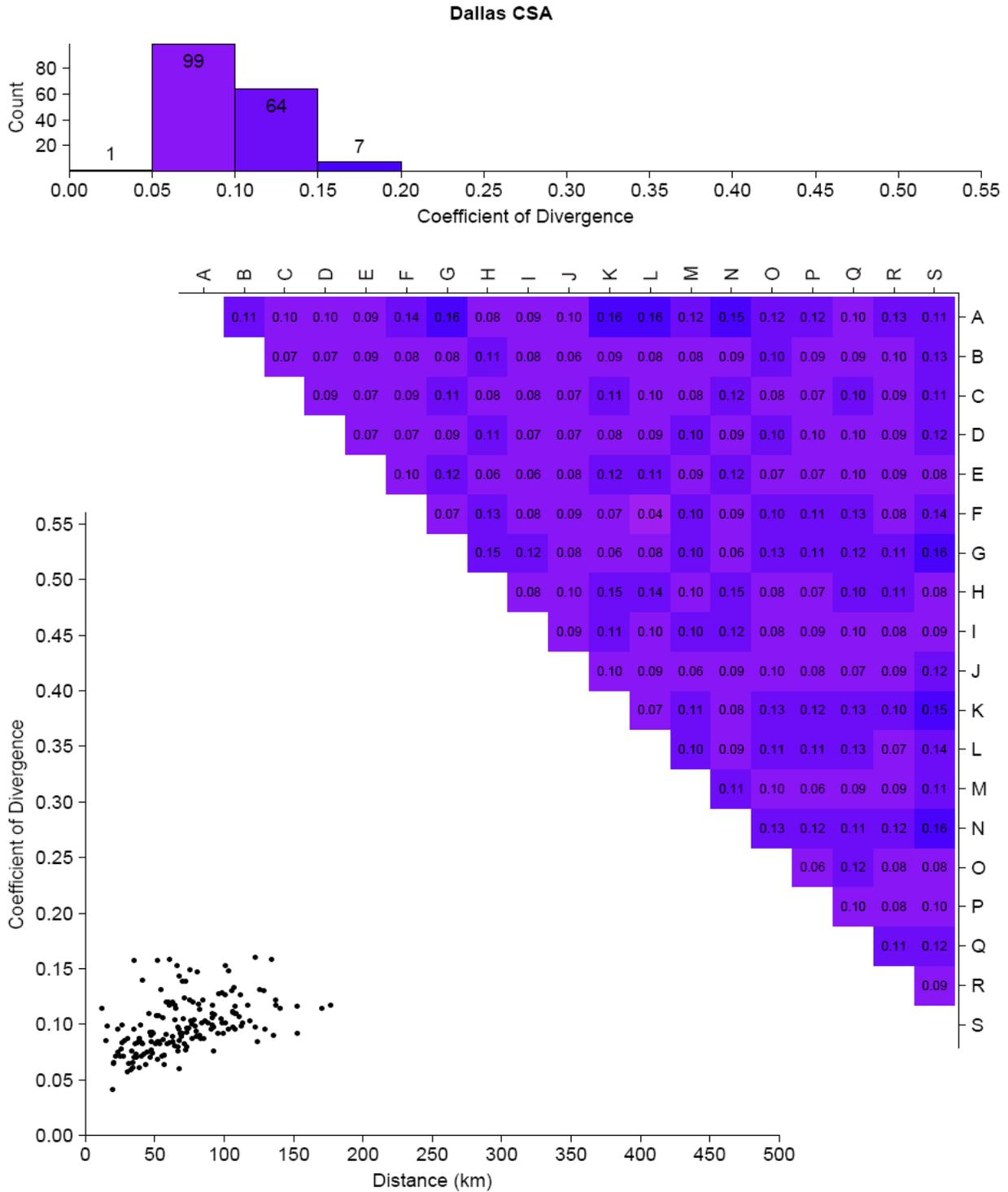
**Figure 3A-78. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Birmingham CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.**



**Figure 3A-79. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Boston CSA. □ 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 3A-80. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Chicago CSA. □ 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 3A-81. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Dallas CSA. 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.**

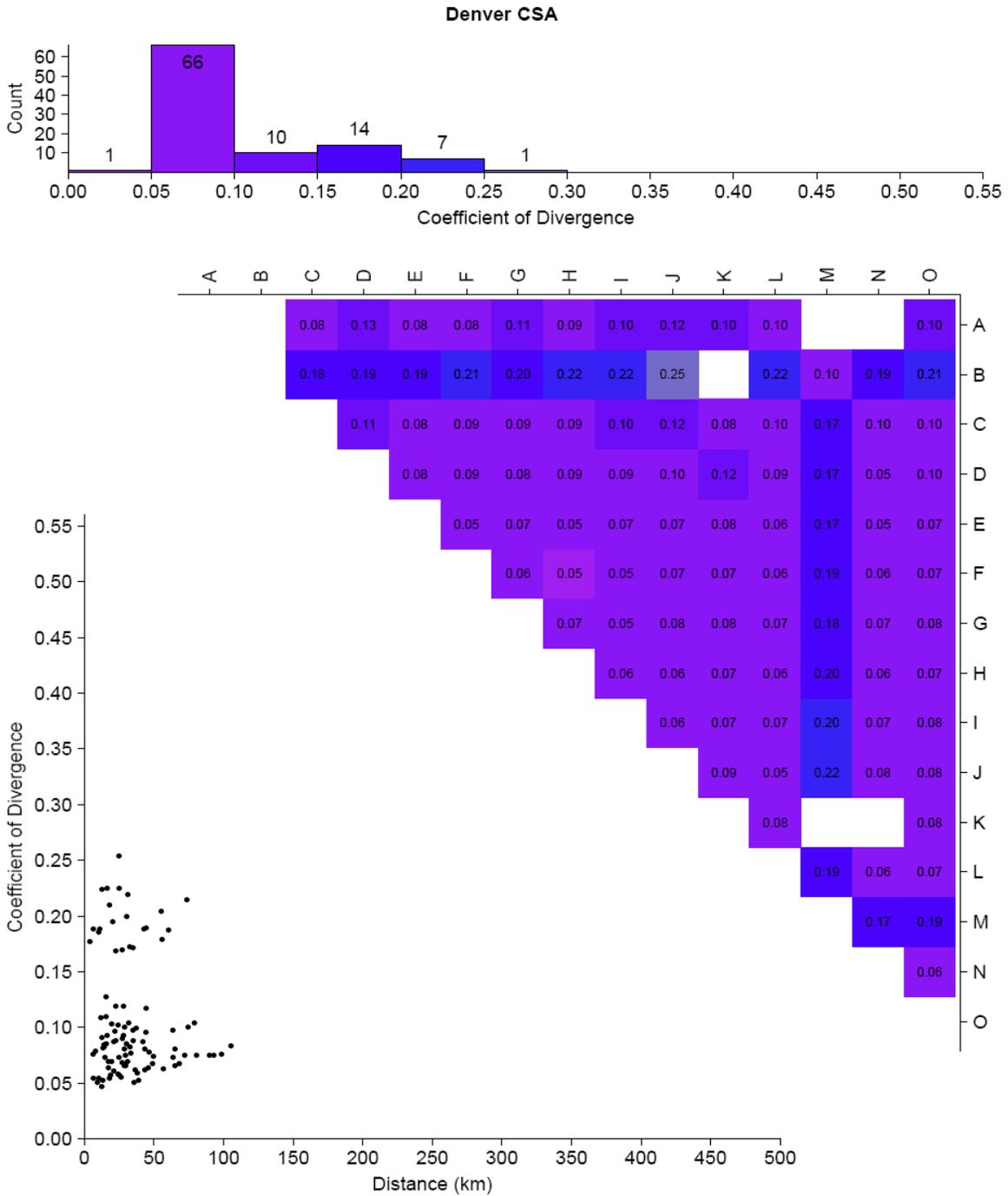
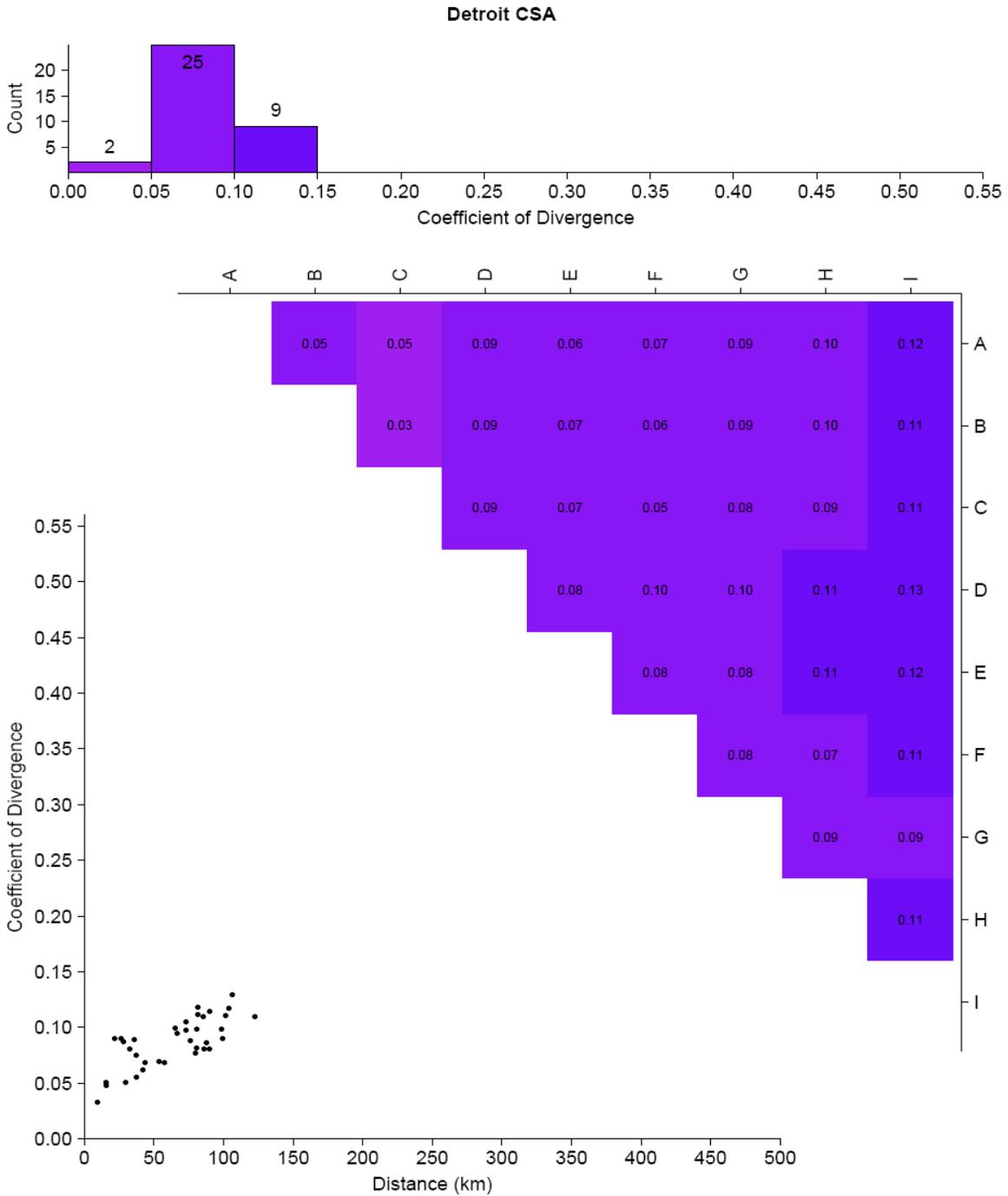
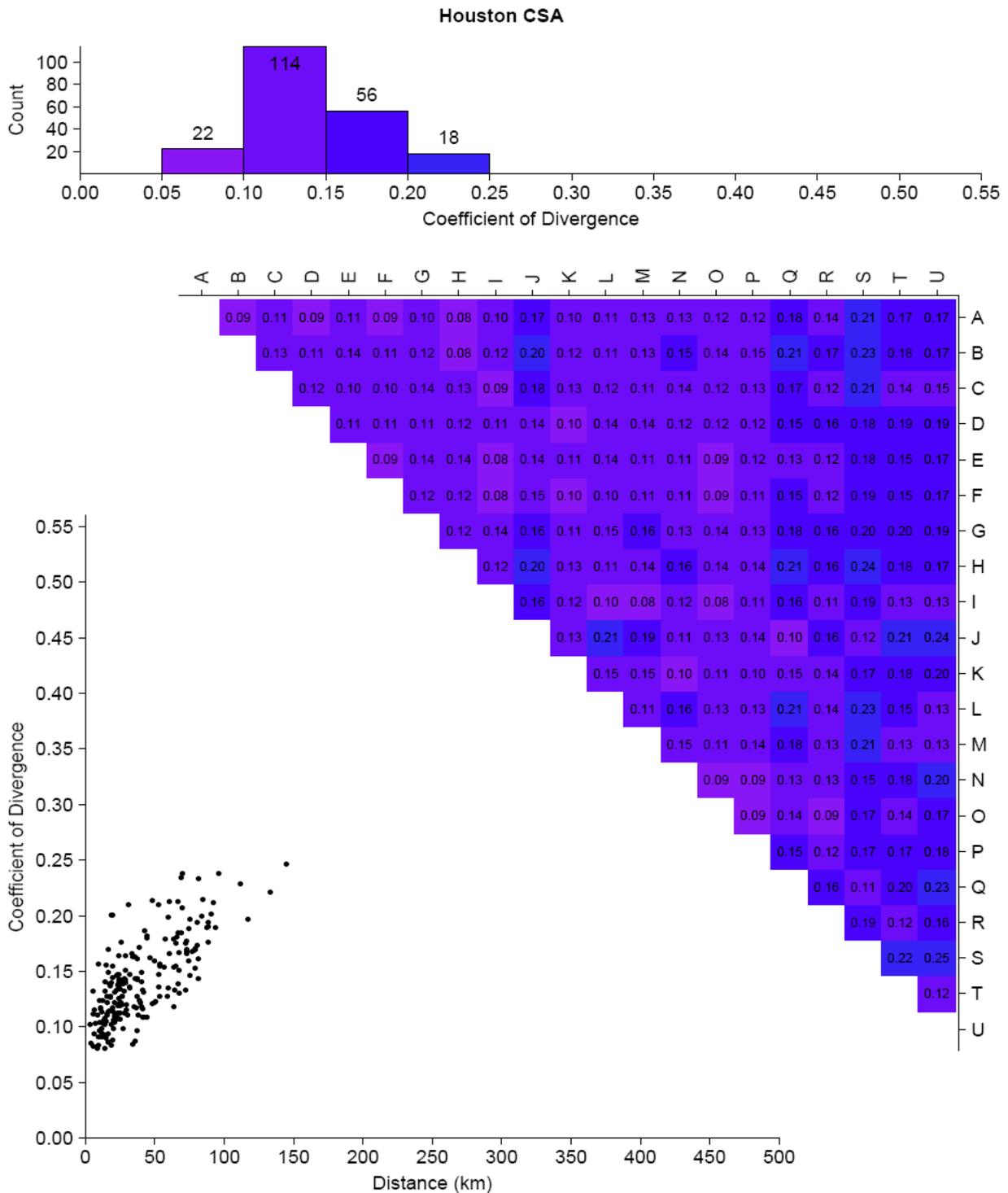


Figure 3A-82. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Denver CSA. □ The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.



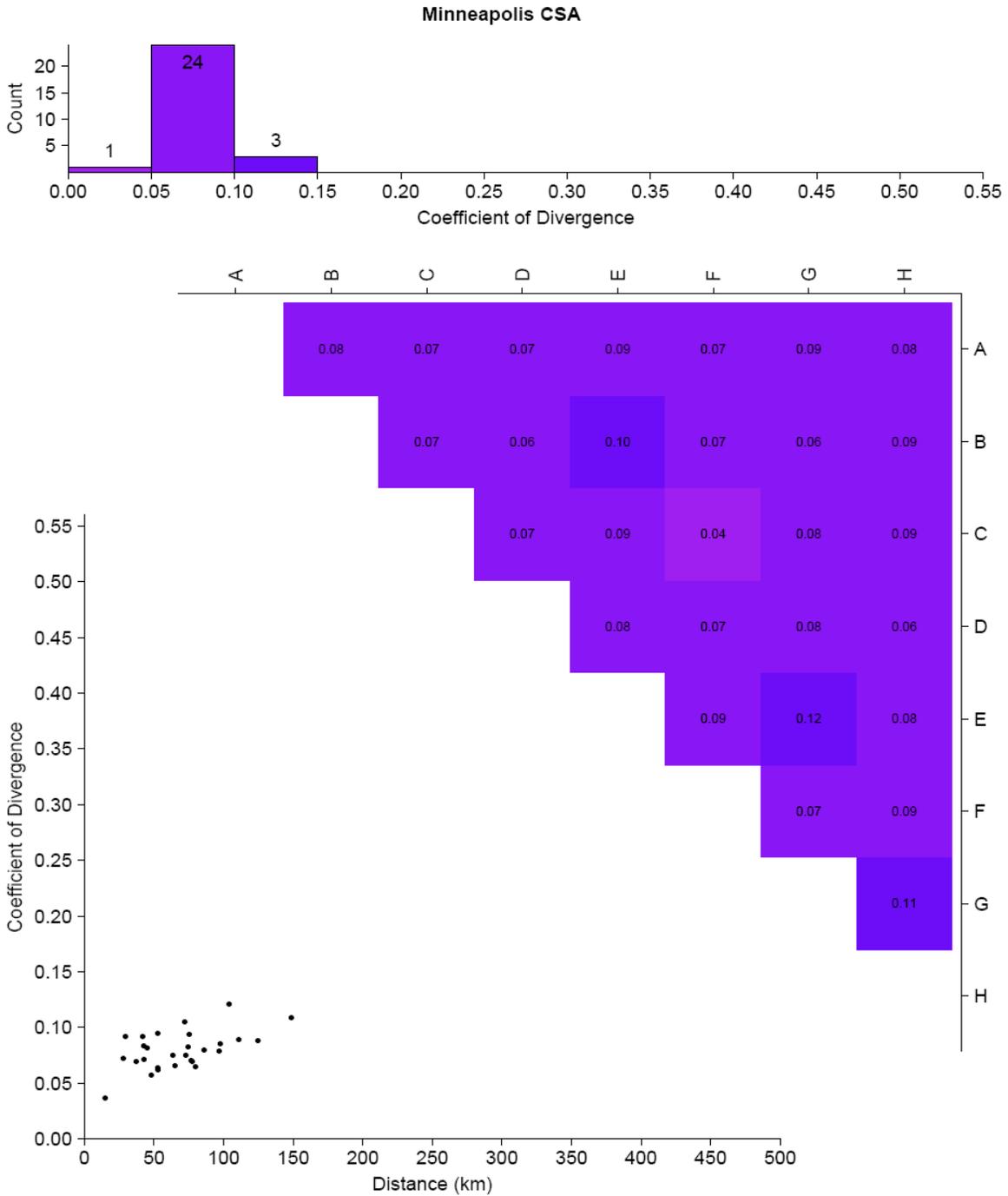
**Figure 3A-83. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Detroit CSA. □ The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.**



**Figure 3A-84. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Houston CSA. 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 3A-86. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Minneapolis CSA. 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.**

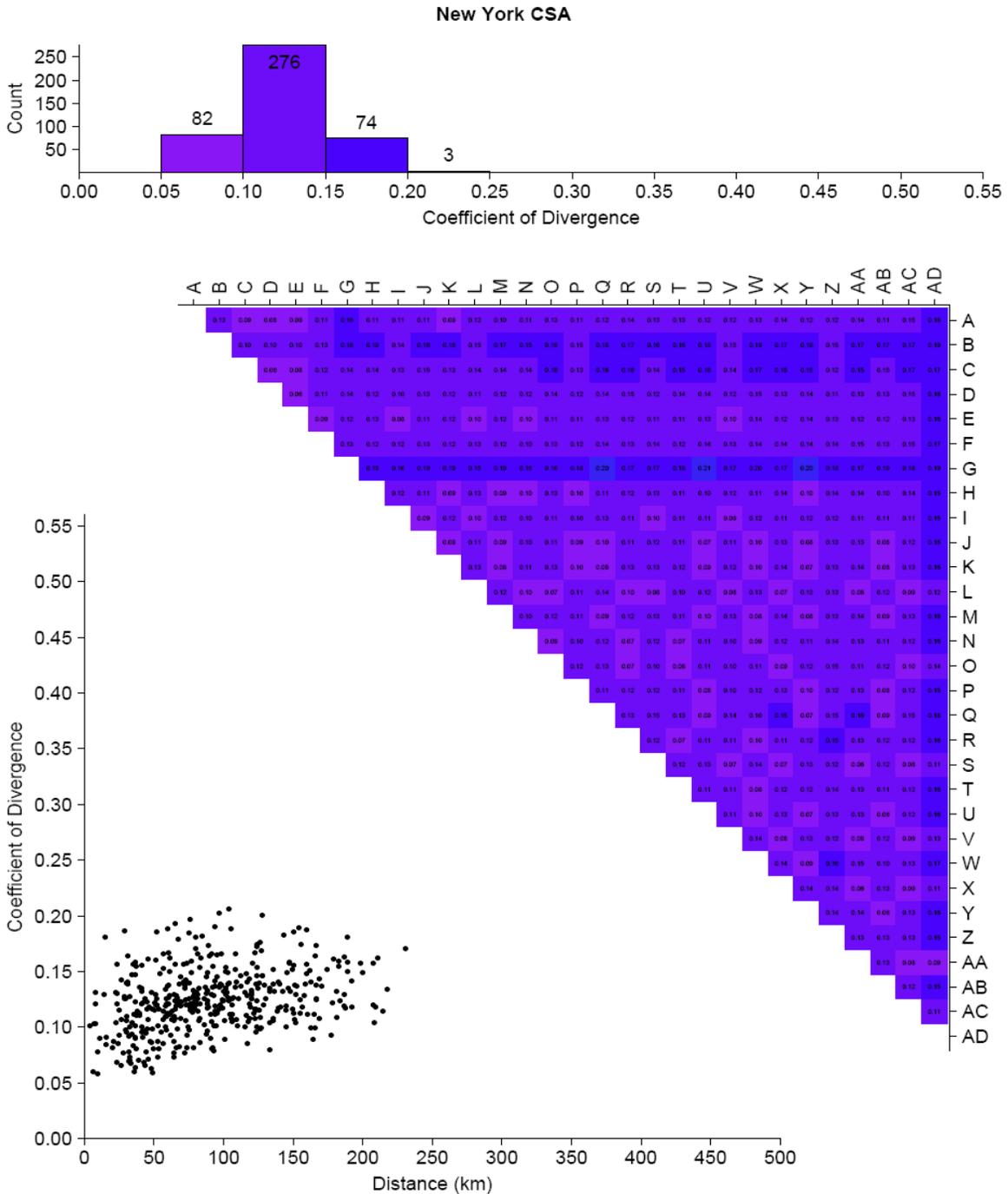
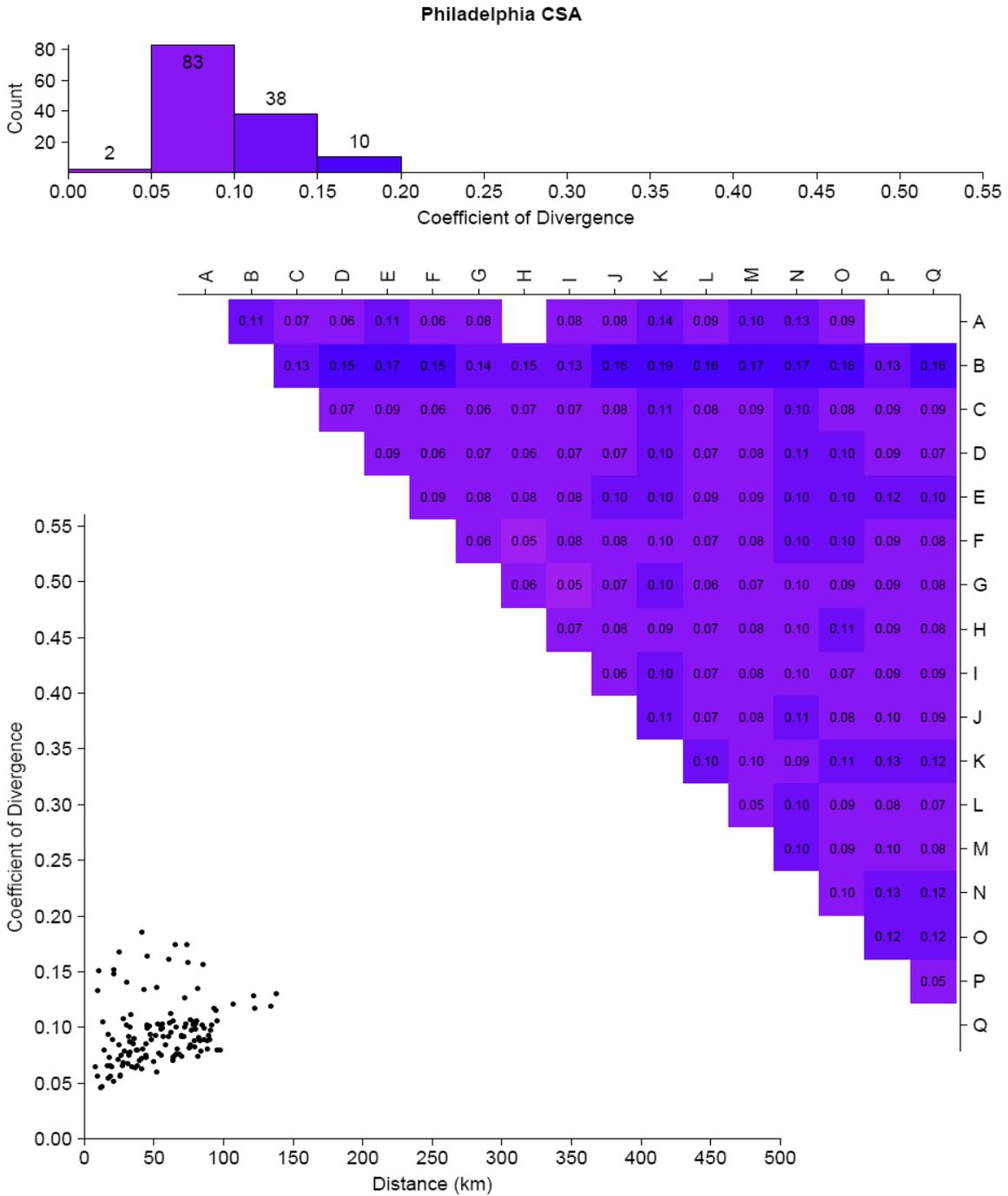


Figure 3A-87. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the New York CSA. □ The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.



**Figure 3A-88. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Philadelphia CSA. 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.**

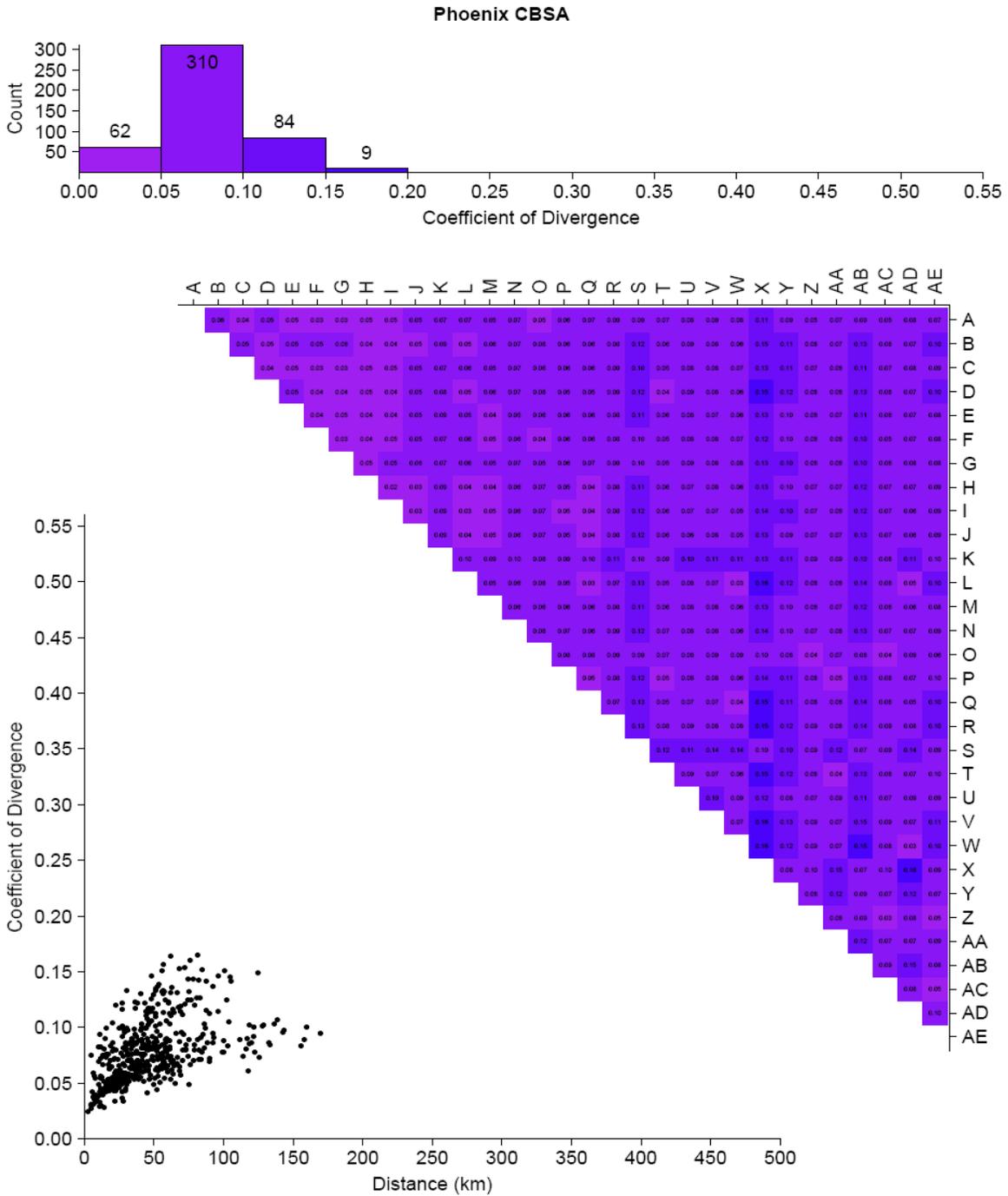
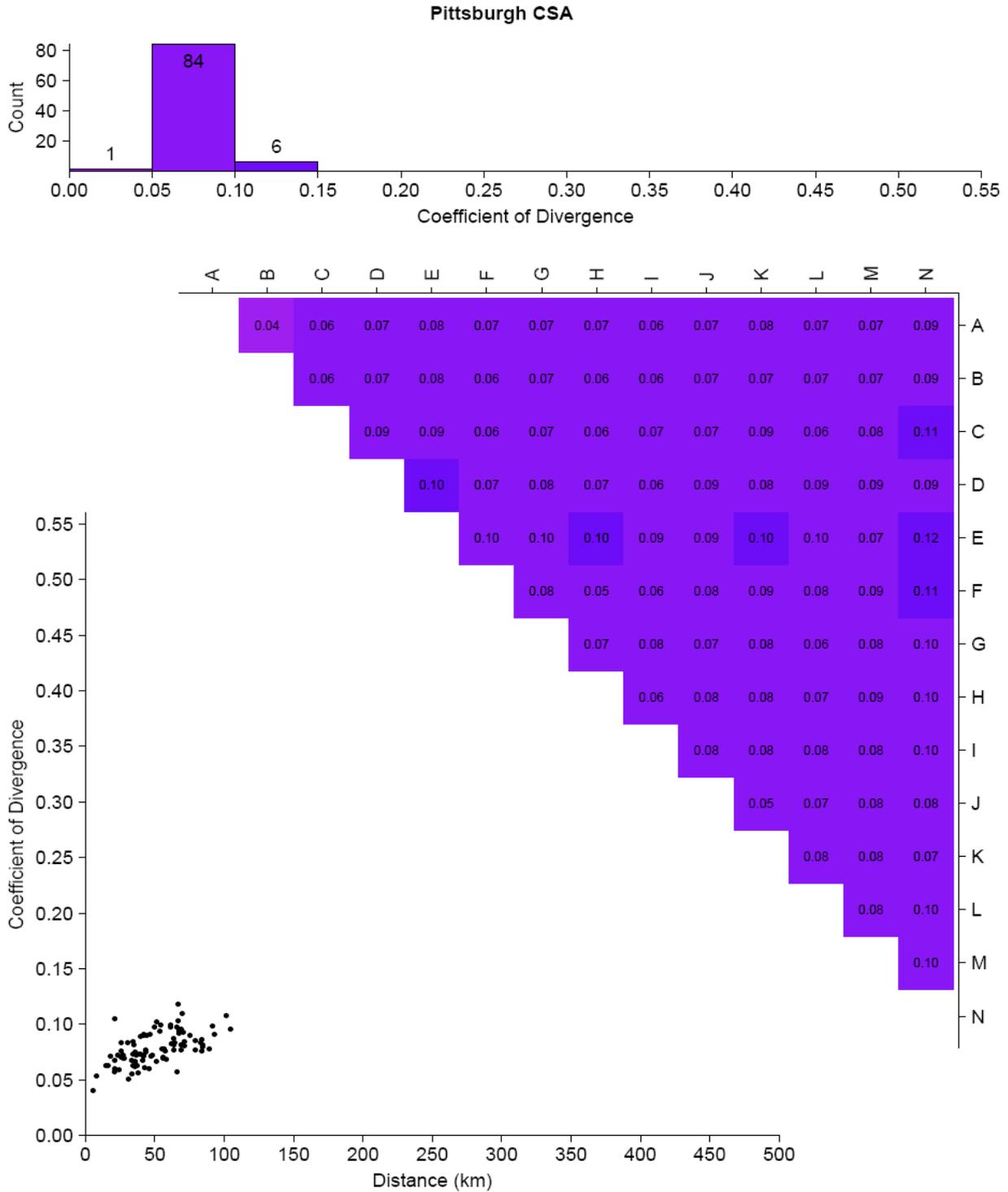
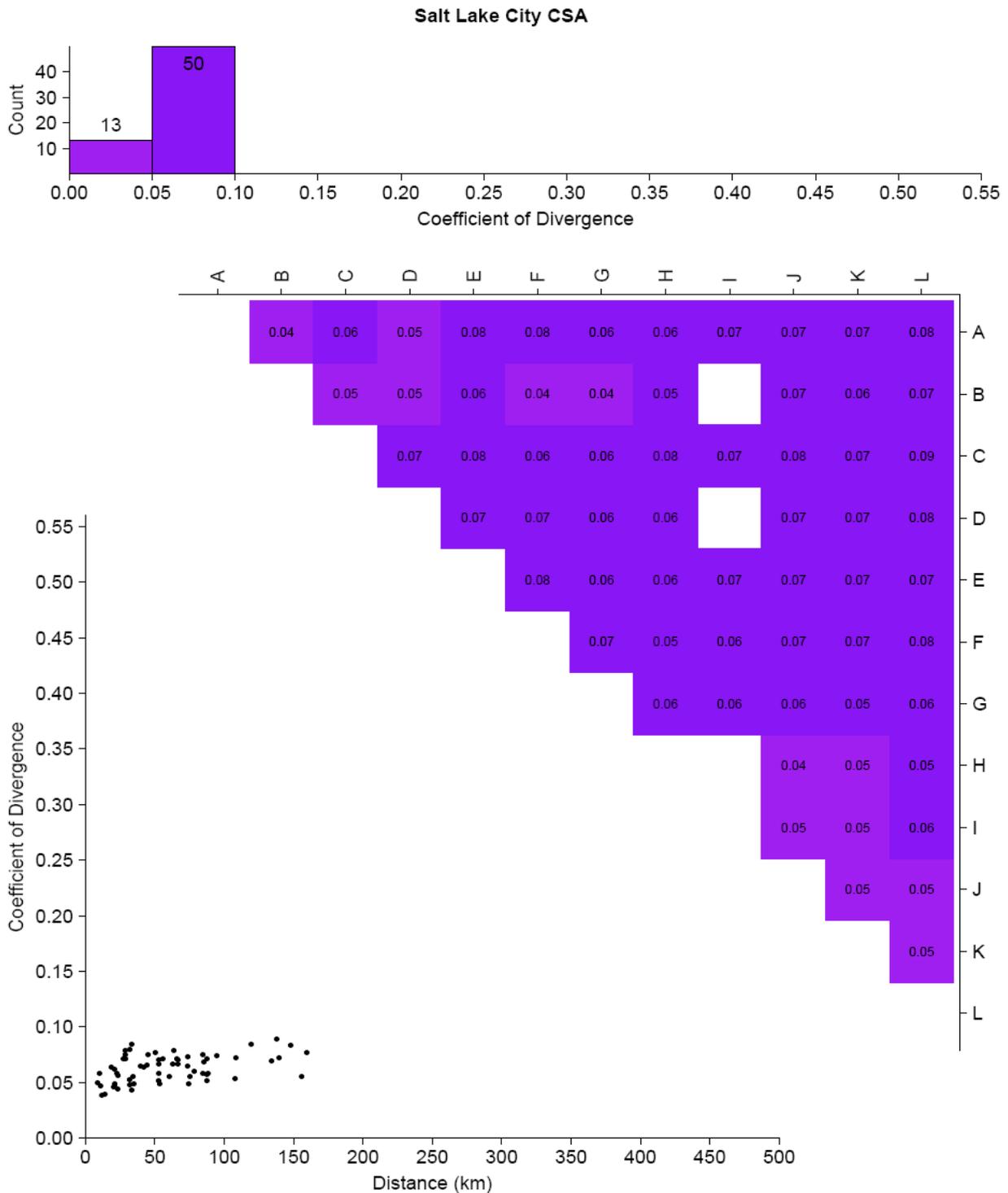


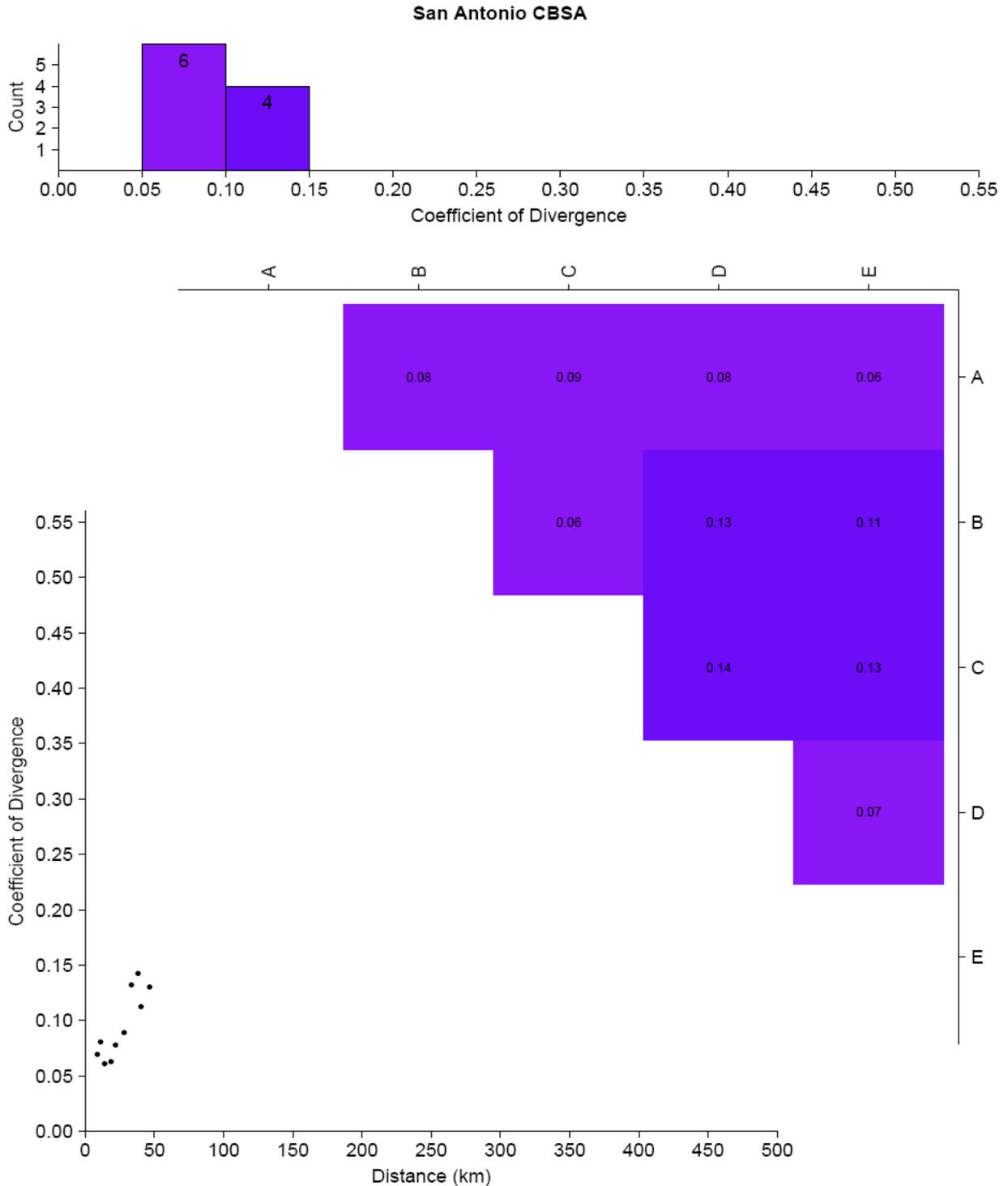
Figure 3A-89. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Phoenix CBSA. □ The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.



**Figure 3A-90. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Pittsburgh CSA. □ 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 3A-91. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Salt Lake City CSA. 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 3A-92. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Antonio CBSA. 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.**

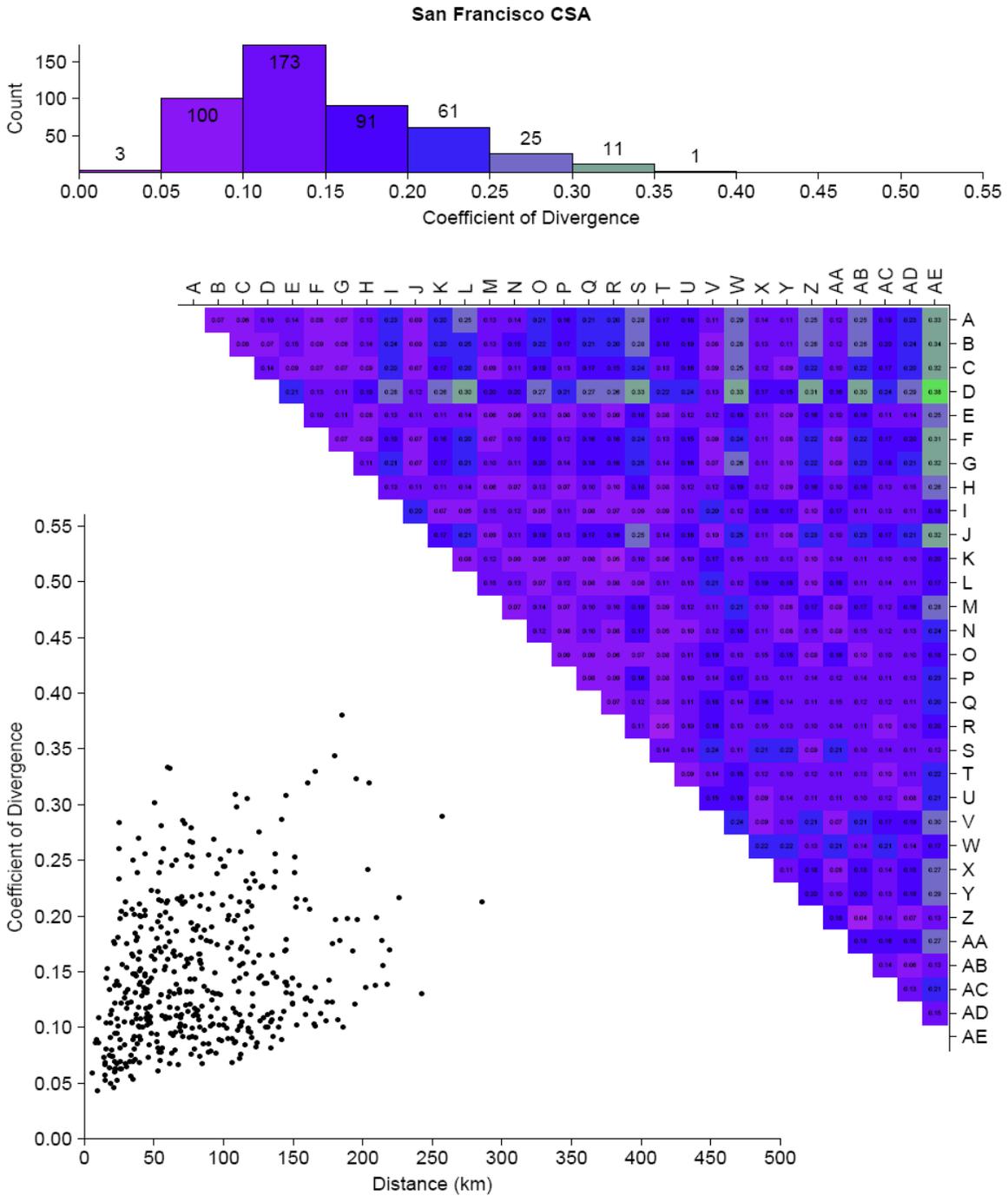
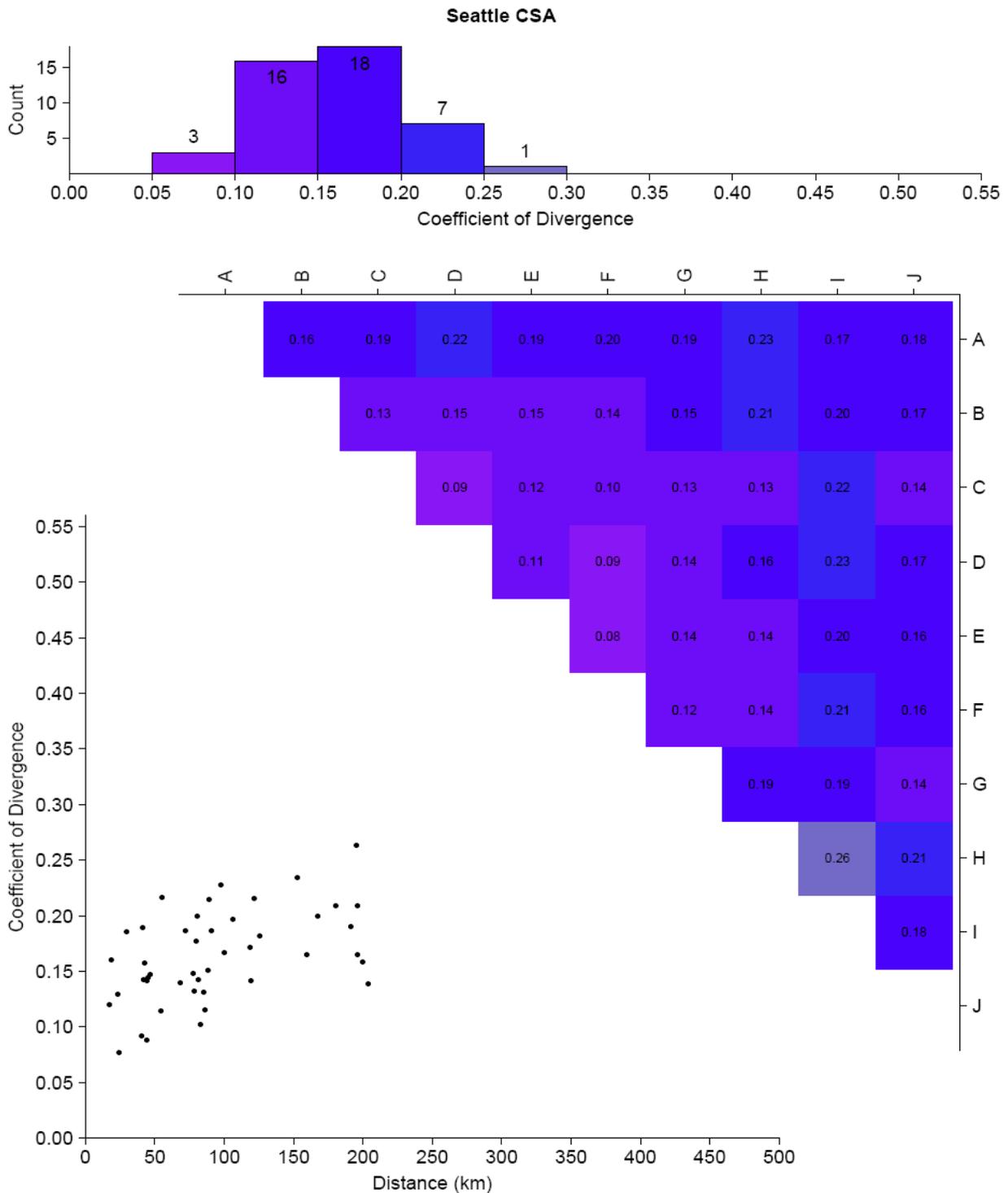
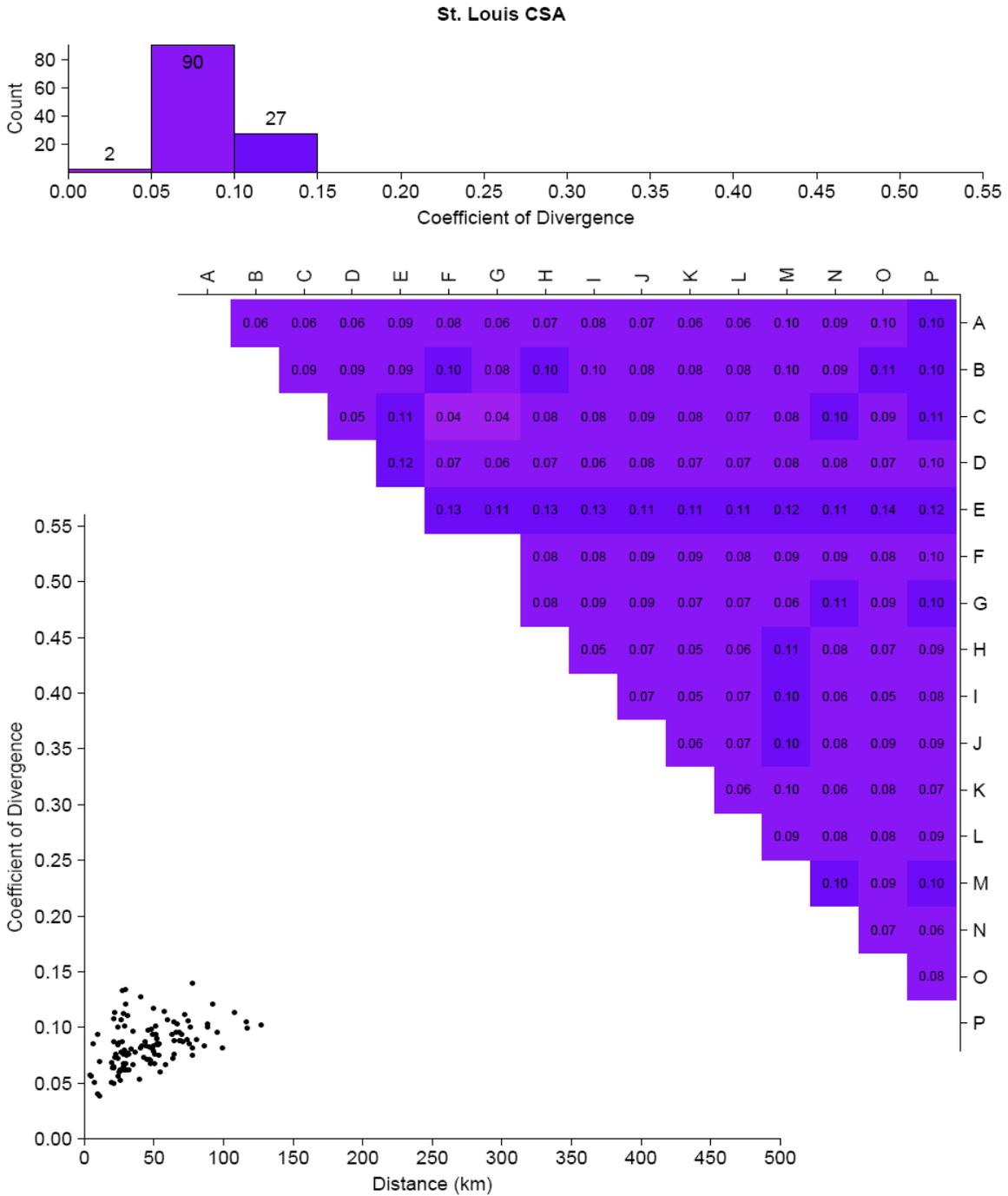


Figure 3A-93. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the San Francisco CSA. The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.



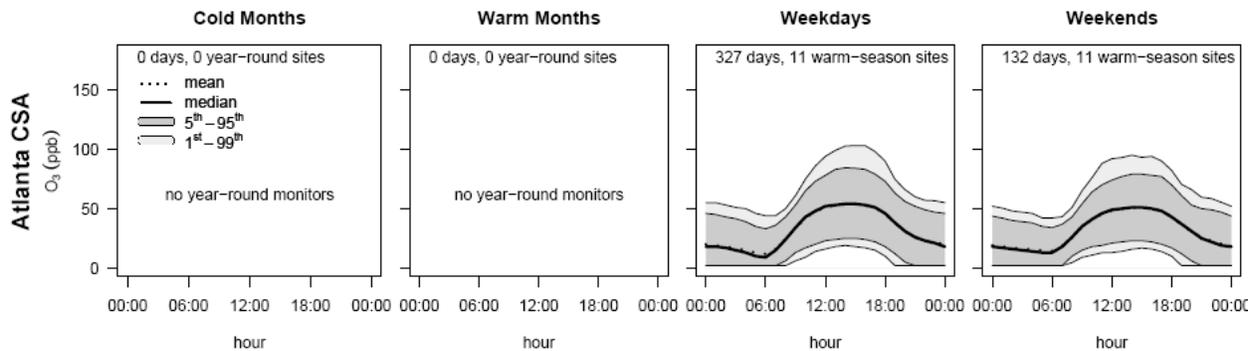
**Figure 3A-94. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the Seattle CSA. □ The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.**



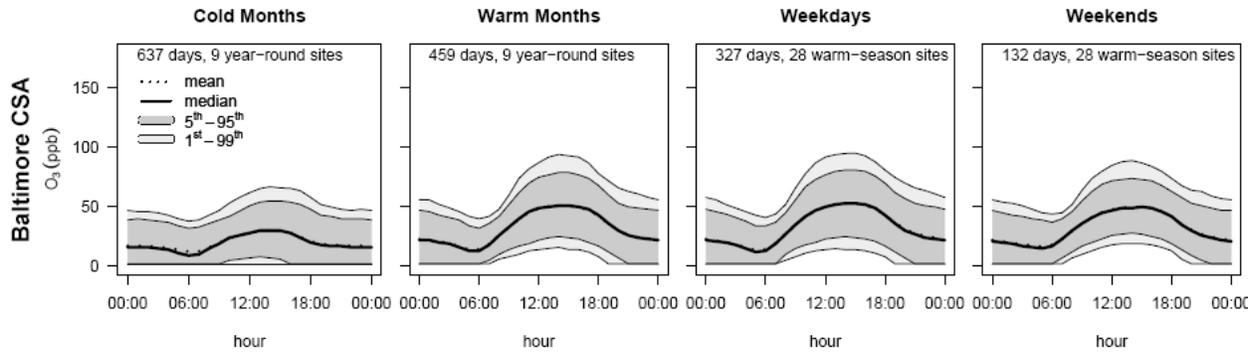
**Figure 3A-95. Pair-wise monitor COD expressed as a histogram (top), contour matrix (middle) and scatter plot versus distance between monitors (bottom) for the St. Louis CSA. □**  
**The colors in the histogram bins correspond to the levels of the contour matrix. The histogram includes the number of monitor pairs per bin and the contour matrix includes the numeric values of the CODs.**

### 3.8.5. Hourly Variations in Ozone for the Urban Focus Cities

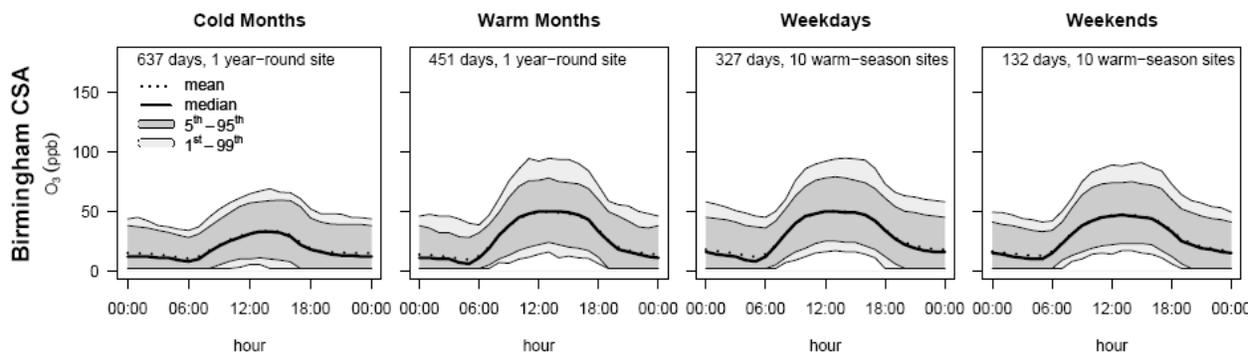
1 This section contains diel plots of 1-h avg O<sub>3</sub> data to supplement the discussion on hourly  
2 variations in O<sub>3</sub> concentrations from Section 3.6.3.2 using data from the 20 urban focus cities first  
3 introduced in Section 3.6.2.1. Comparisons are made between cold months (October - April) and  
4 warm months (May-September), using the year-round data set, and between weekdays and weekends  
5 using the warm-season data set.



**Figure 3A-96. Diel patterns in 1-h avg ozone for the Atlanta CSA 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). No year-round monitors were available for the cold month/warm month comparison in this CSA.**



**Figure 3A-97. Diel patterns in 1-h avg ozone for the Baltimore CSA 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 3A-98. Diel patterns in 1-h avg ozone for the Birmingham CSA 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).**

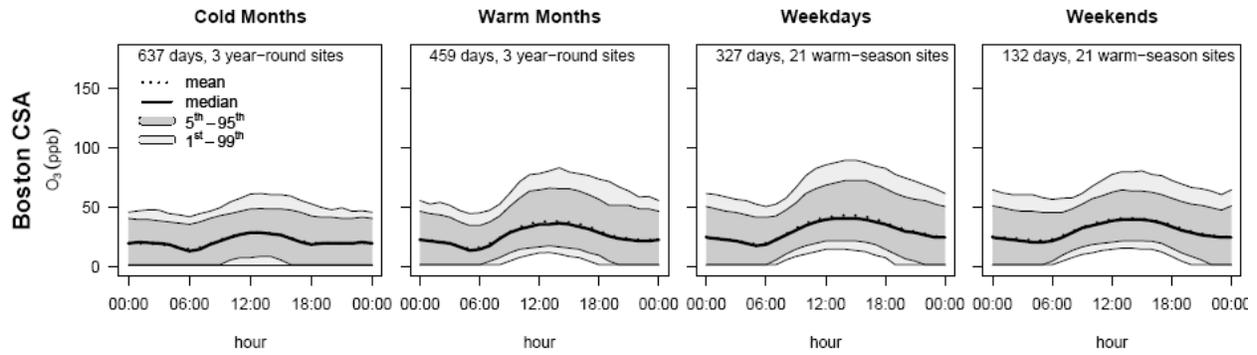


Figure 3A-99. Diel patterns in 1-h avg ozone for the Boston CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

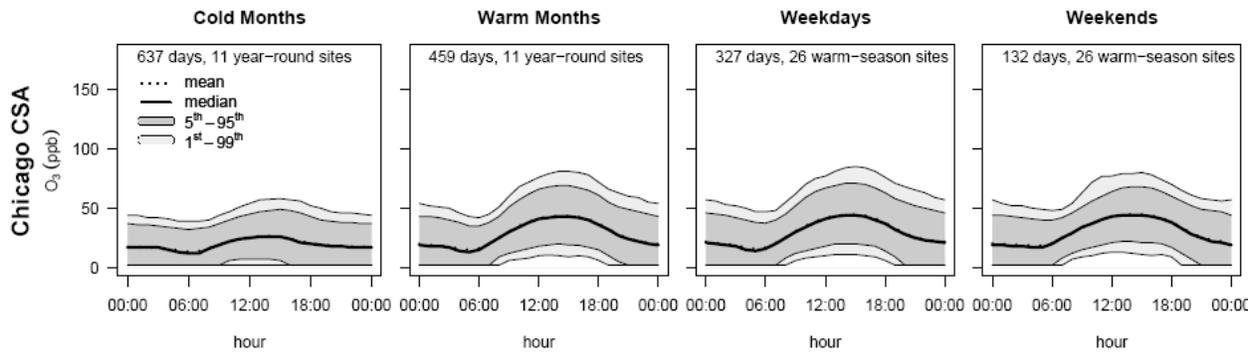
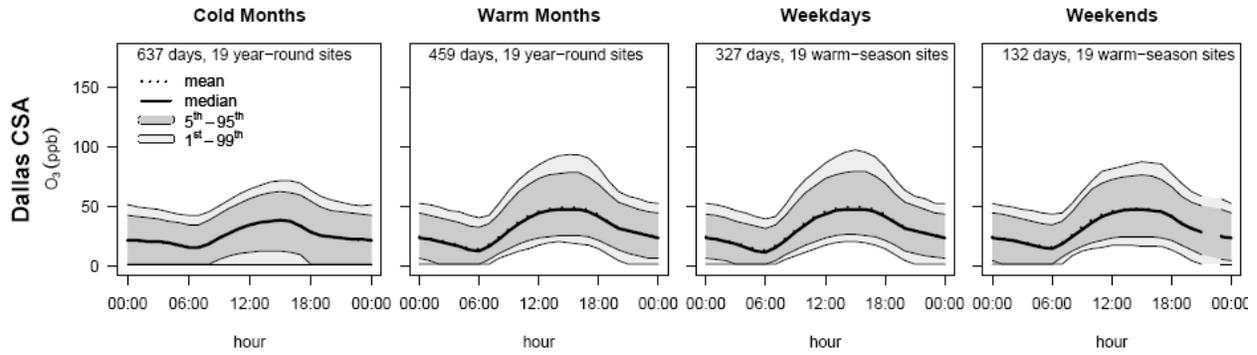
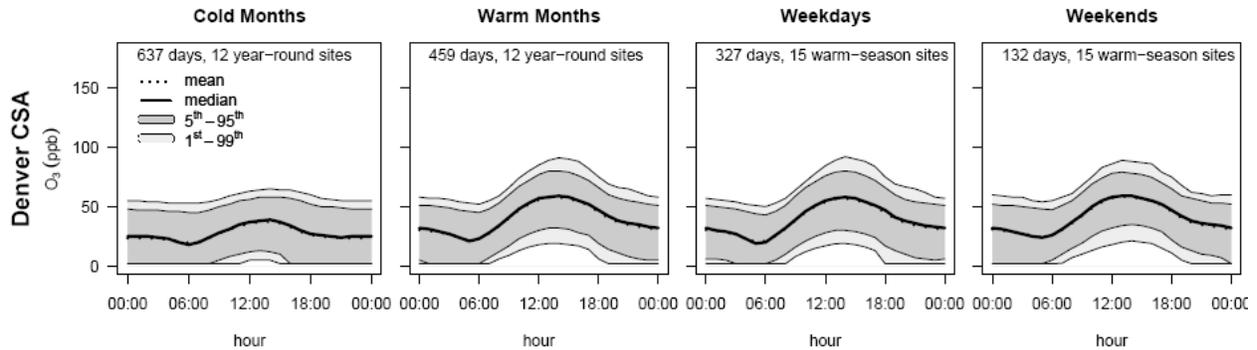


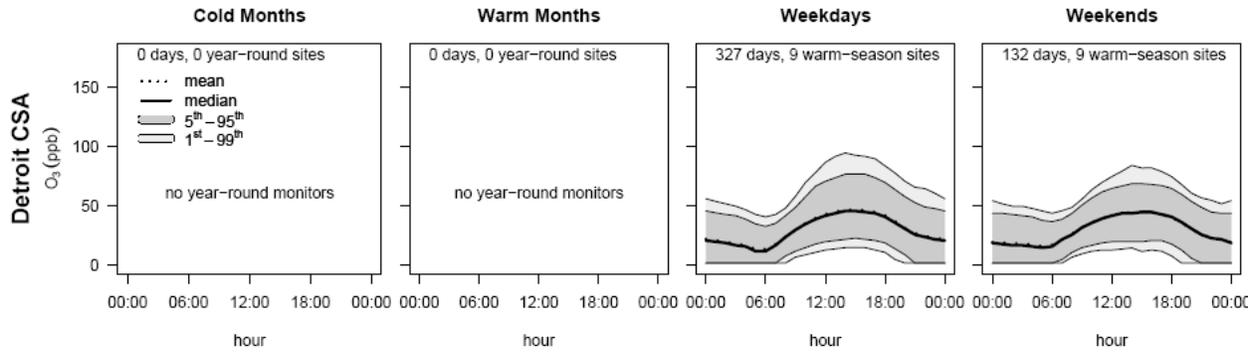
Figure 3A-100. Diel patterns in 1-h avg ozone for the Chicago CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).



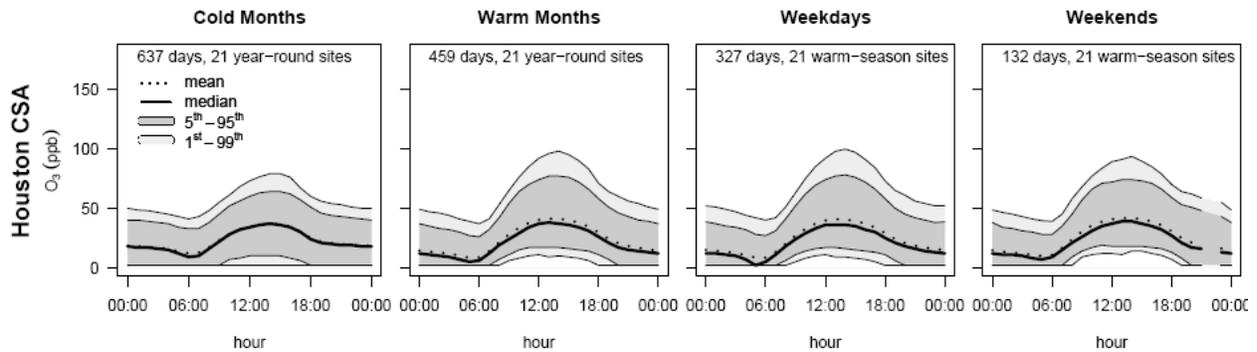
**Figure 3A-101. Diel patterns in 1-h avg ozone for the Dallas CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).**



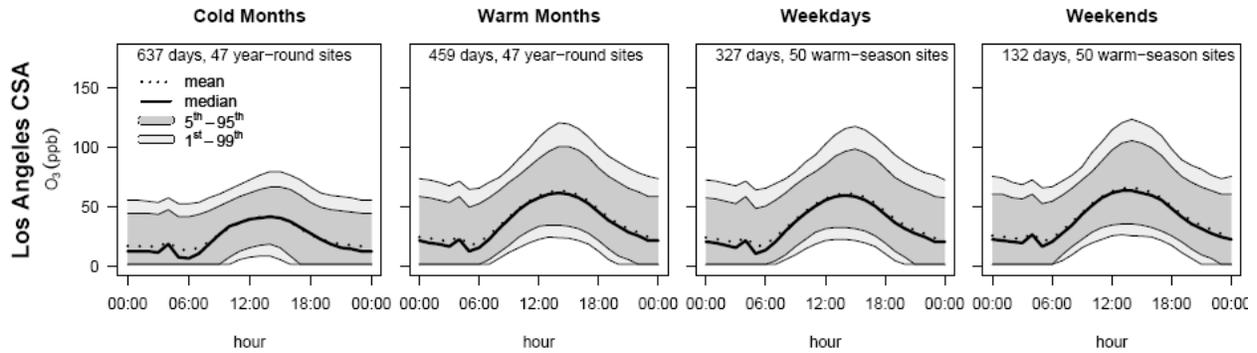
**Figure 3A-102. Diel patterns in 1-h avg ozone for the Denver CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).**



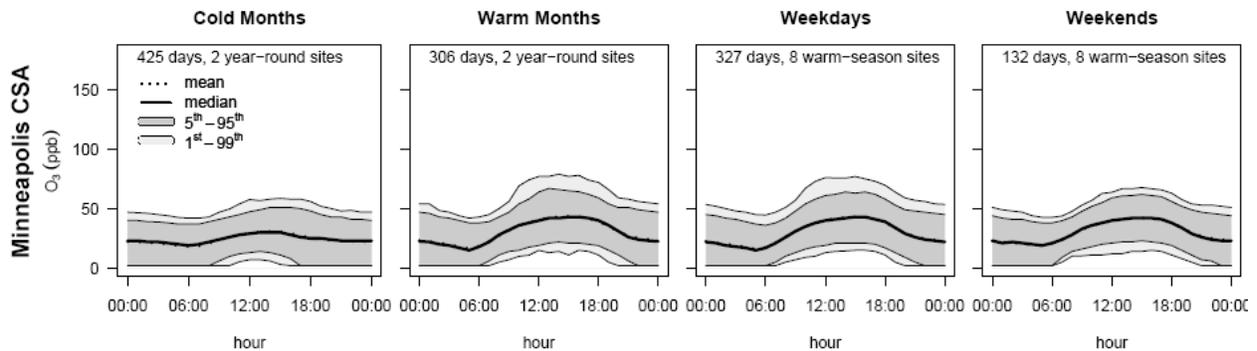
**Figure 3A-103. Diel patterns in 1-h avg ozone for the Detroit CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half). No year-round monitors were available for the cold month/warm month comparison in this CSA.**



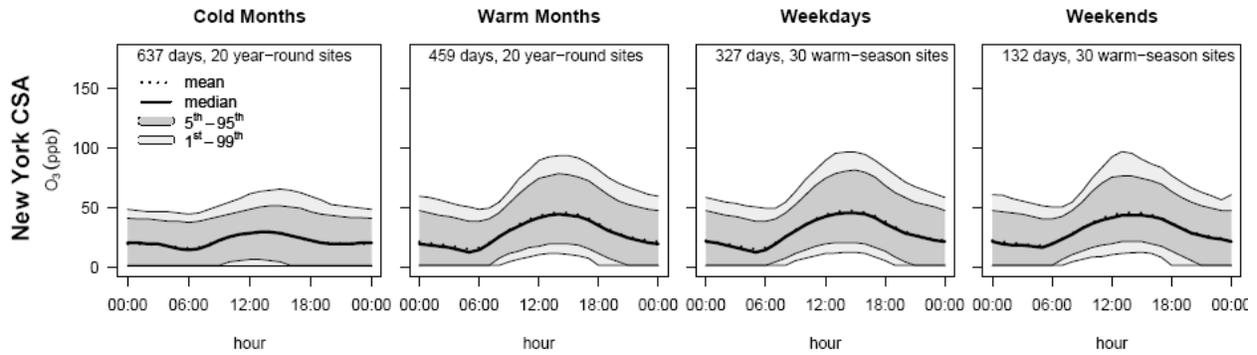
**Figure 3A-104. Diel patterns in 1-h avg ozone for the Houston CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).**



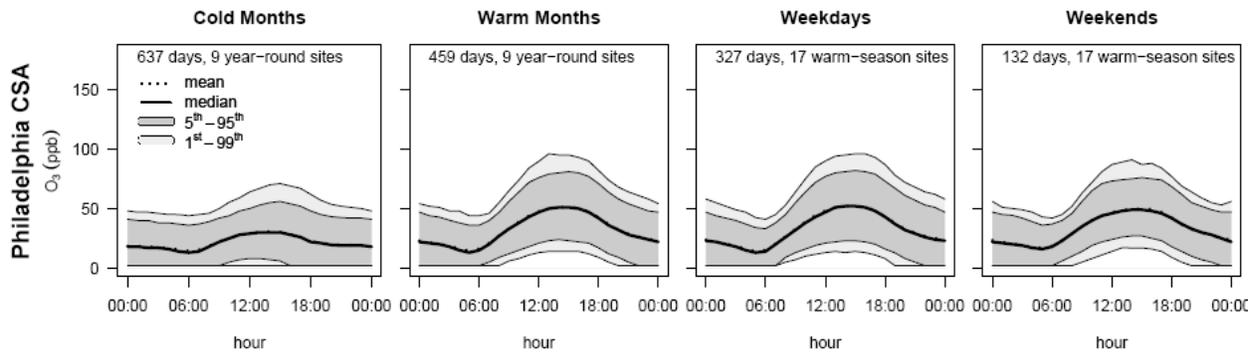
**Figure 3A-105. Diel patterns in 1-h avg ozone for the Los Angeles CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).**



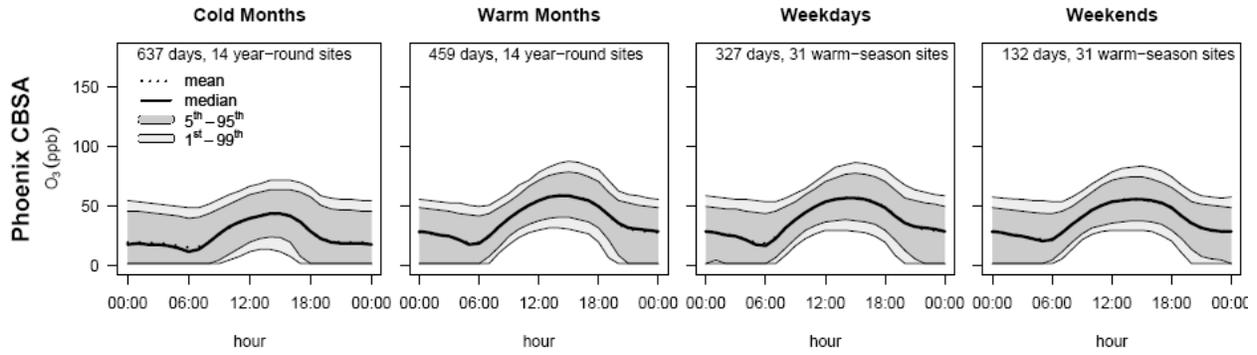
**Figure 3A-106. Diel patterns in 1-h avg ozone for the Minneapolis CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).**



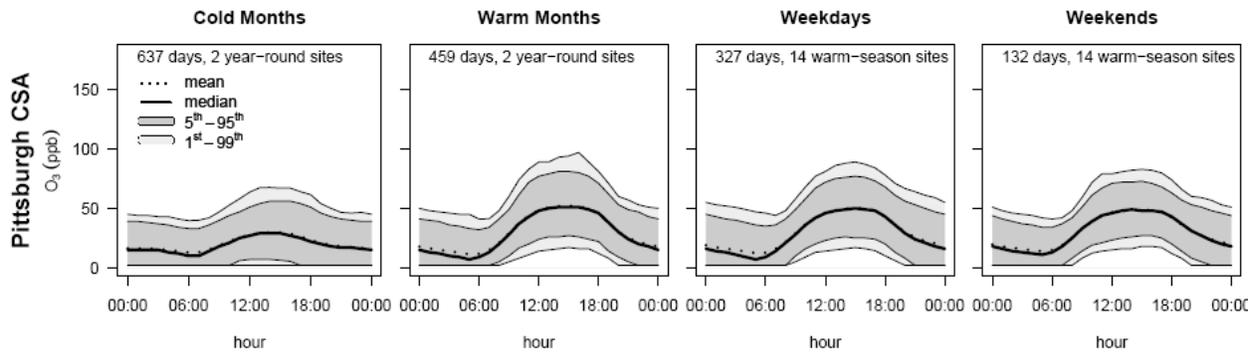
**Figure 3A-107. Diel patterns in 1-h avg ozone for the New York CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).**



**Figure 3A-108. Diel patterns in 1-h avg ozone for the Philadelphia CSA 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 3A-109. Diel patterns in 1-h avg ozone for the Phoenix CBSA 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 3A-110. Diel patterns in 1-h avg ozone for the Pittsburgh CSA 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).**

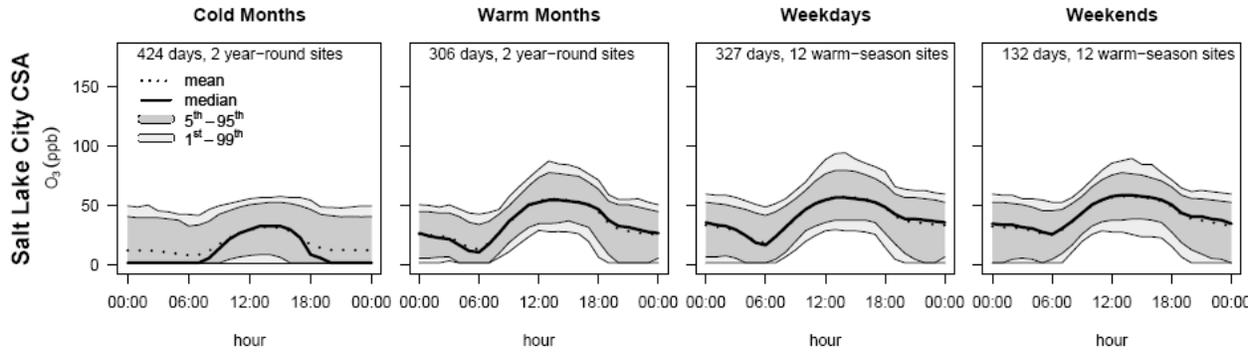


Figure 3A-111. Diel patterns in 1-h avg ozone for the Salt Lake City CSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).

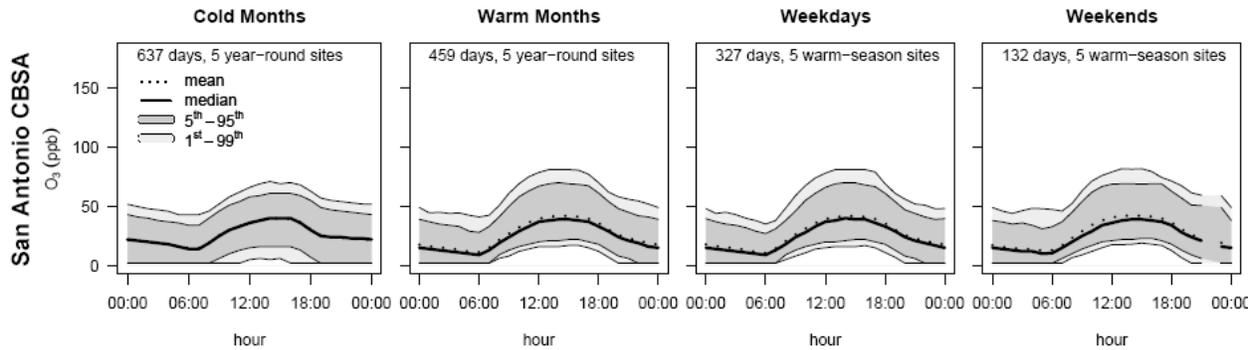
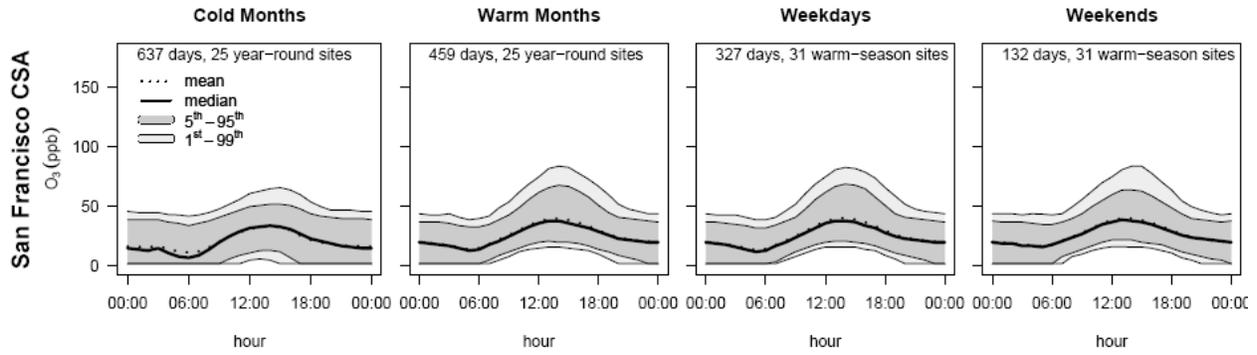
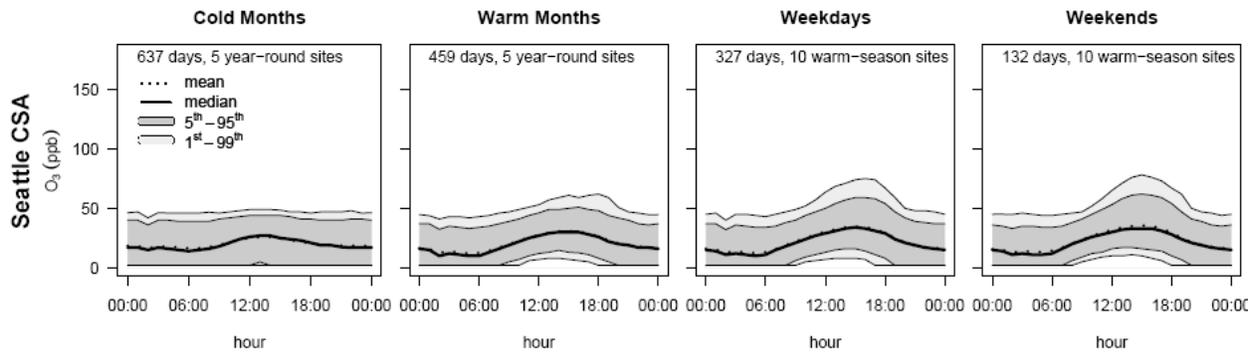


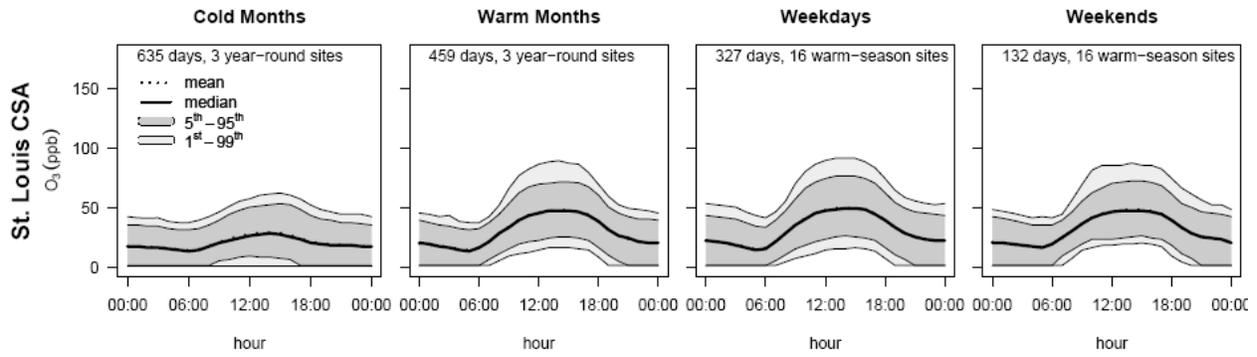
Figure 3A-112. Diel patterns in 1-h avg ozone for the San Antonio CBSA between 2007 and 2009 using the year-round data set for the cold month/warm month comparison (left half) and the warm-season data set for the weekday/weekend comparison (right half).



**Figure 3A-113. Diel patterns in 1-h avg ozone for the San Francisco CSA 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 3A-114. Diel patterns in 1-h avg ozone for the Seattle CSA 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 3A-115. Diel patterns in 1-h avg ozone for the St. Louis CSA 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).**

# Chapter 4. Exposure to Ambient Ozone

## 4.1. Introduction

1           The 2006 O<sub>3</sub> AQCD evaluated O<sub>3</sub> concentrations and exposures in multiple  
2 microenvironments, discussed methods for estimating personal and population exposure via  
3 monitoring and modeling, analyzed relationships between personal exposure and ambient  
4 concentrations, and discussed the implications of using ambient O<sub>3</sub> concentrations as an estimate of  
5 exposure in epidemiologic studies. This chapter presents new information regarding exposure to  
6 ambient O<sub>3</sub> in the context of existing relevant information summarized in the 2006 O<sub>3</sub> AQCD, which  
7 in many areas remains definitive. A brief summary of findings from the 2006 O<sub>3</sub> AQCD is presented  
8 at the beginning of each section as appropriate.

9           Section 4.2 presents general exposure concepts describing the relationship between ambient  
10 pollutant concentrations and personal exposure. Section 4.3 describes exposure measurement  
11 techniques and studies that measured personal, ambient, indoor, and outdoor concentrations of O<sub>3</sub>  
12 and related pollutants. Section 4.4 describes techniques for modeling local O<sub>3</sub> concentrations,  
13 microenvironmental concentrations, and personal and population exposure. Section 4.5 discusses the  
14 implications of using ambient O<sub>3</sub> concentrations to estimate exposure in epidemiologic studies,  
15 including several factors that contribute to exposure error.

## 4.2. General Exposure Concepts

16           A theoretical model of personal exposure is presented to highlight measurable quantities and  
17 the uncertainties that exist in this framework. An individual's time-integrated total exposure to O<sub>3</sub>  
18 can be described based on a compartmentalization of the person's activities throughout a given time  
19 period:

$$E_T = \int C_j dt$$

Equation 4-1

20           where  $E_T$  = total (T) exposure over a time-period of interest,  $C_j$  = airborne O<sub>3</sub> concentration at  
21 microenvironment  $j$ , and  $dt$  = portion of the time-period spent in microenvironment  $j$ . Equation 4-1  
22 can be decomposed into a model that accounts for exposure to O<sub>3</sub>, of ambient ( $E_a$ ) and nonambient  
23 ( $E_{na}$ ) origin of the form:

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

$$E_T = E_a + E_{na}$$

Equation 4-2

1 Ambient O<sub>3</sub> is formed through photochemical reactions involving NO<sub>x</sub>, VOCs, and other  
 2 compounds, as described in Chapter 3. Although nonambient sources of O<sub>3</sub> exist, such as O<sub>3</sub>  
 3 generators and laser printers, these sources are specific to individuals and may not represent  
 4 important sources of population exposure. Ozone concentrations generated by ambient and  
 5 nonambient sources are subject to spatial and temporal variability that can affect estimates of  
 6 exposure and influence epidemiologic effect estimates. Exposure parameters affecting interpretation  
 7 of epidemiologic studies are discussed in Section 4.5.

8 This assessment focuses on the ambient component of exposure because this is more relevant  
 9 to the NAAQS review.  $E_a$  can be expressed in terms of the fraction of time spent in various outdoor  
 10 and indoor microenvironments (Wallace et al., 2006, [089190](#); Wilson et al., 2000, [010288](#)):

$$E_a = \sum f_o C_o + \sum f_i F_{inf,i} C_{o,i}$$

Equation 4-3

11 where  $f$  = fraction of the relevant time period (equivalent to  $dt$  in Equation 4-1), subscript  $o$  = index  
 12 of outdoor microenvironments, subscript  $i$  = index of indoor microenvironments, subscript  $o,i$  =  
 13 index of outdoor microenvironments adjacent to a given indoor microenvironment  $i$ , and  $F_{inf,i}$  =  
 14 infiltration factor for indoor microenvironment ( $i$ ). Equation 4-3 is subject to the constraint  $\sum f_o +$   
 15  $\sum f_i = 1$  to reflect the total exposure over a specified time period, and each term on the right hand side  
 16 of the equation has a summation because it reflects various microenvironmental exposures. Here,  
 17 “indoors” refers to being inside any aspect of the built environment, e.g., home, office buildings,  
 18 enclosed vehicles (automobiles, trains, buses), and/or recreational facilities (movies, restaurants,  
 19 bars). “Outdoor” exposure can occur in parks or yards, on sidewalks, and on bicycles or motorcycles.  
 20  $F_{inf}$  is a function of the building air exchange characteristics. Assuming steady state ventilation  
 21 conditions, the infiltration factor is a function of the penetration ( $P$ ) of O<sub>3</sub>, the air exchange rate ( $a$ )  
 22 of the microenvironment, and the rate of O<sub>3</sub> loss ( $k$ ) in the microenvironment;  $F_{inf} = Pa/(a+k)$ .

23 In epidemiologic studies,  $C_a$  is often used in lieu of outdoor microenvironmental data to  
 24 represent these exposures based on the availability of data. Thus it is often assumed that  $C_o = C_a$  and  
 25 that the fraction of time spent outdoors can be expressed cumulatively as  $f_o$ ; the indoor terms still  
 26 retain a summation because infiltration differs among different microenvironments. If an  
 27 epidemiologic study employs only  $C_a$ , then the assumed model of an individual’s exposure to  
 28 ambient O<sub>3</sub>, first given in Equation 4-3, is re-expressed solely as a function of  $C_a$ :

$$E_a = (f_o + \sum f_i P) C_a$$

Equation 4-4

29 Meteorology, varying precursor emissions and O<sub>3</sub> formation rates, spatial variability of O<sub>3</sub>  
 30 concentration, design of the epidemiologic study, and other factors determine whether or not  
 31 Equation 4-4 is a reasonable approximation for Equation 4-3. Errors and uncertainties inherent in use

1 of Equation 4-4 in lieu of Equation 4-3 are described in Section 4.5 with respect to implications for  
2 interpreting epidemiologic studies. Epidemiologic studies often use concentration measured at a  
3 central site monitor to represent ambient concentration; thus  $\alpha$ , the ratio between personal exposure  
4 to ambient O<sub>3</sub> and the ambient concentration of O<sub>3</sub>, is defined as:

$$\alpha = \frac{E_a}{C_a}$$

Equation 4-5

5 Combination of Equation 4-4 and Equation 4-5 yields:

$$\alpha = f_o + \sum f_i P$$

Equation 4-6

6 where  $\alpha$  varies between 0 and 1. If a person's exposure occurs in a single microenvironment, the  
7 ambient component of a microenvironmental O<sub>3</sub> concentration can be represented as the product of  
8 the ambient concentration and  $P$ . Wallace et al. (2006, [089190](#)) note that time-activity data and  
9 corresponding estimates of  $P$  for each microenvironmental exposure are needed to compute an  
10 individual's  $\alpha$  with accuracy. If local sources and sinks exist and are significant but not captured by  
11 central site monitors, then the ambient component of the local outdoor concentration may be  
12 estimated using dispersion models, land use regression models, receptor models, fine scale CTMs or  
13 some combination of these techniques. These techniques are described in Section 4.4.

## 4.3. Exposure Measurement

### 4.3.1. Personal Monitoring Techniques

14 As described in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), a passive sampler has been  
15 developed and deployed to measure personal exposure to O<sub>3</sub>. This sampler uses a filter coated with  
16 nitrite, which is converted to nitrate by O<sub>3</sub> and then quantified by a technique such as ion  
17 chromatography (Koutrakis et al., 1993, [202808](#)). This method has been licensed and marketed by  
18 Ogawa, Inc., Japan (Ogawa & Company, 2007, [090937](#)). The cumulative sampling and the detection  
19 limit of the passive badges makes them suitable for monitoring periods of 24 hours or greater, which  
20 limits their ability to measure short-term daily fluctuations in personal O<sub>3</sub> exposure. Longer  
21 sampling periods give lower detection limits; use of the badges for a 6-day sampling period yields a  
22 detection limit of 1 ppb, while a 24-hour sampling period gives a detection limit of approximately 5-  
23 10 ppb. This can result in a substantial fraction of daily samples being below the detection limit  
24 (Sarnat et al., 2005, [087531](#); Sarnat et al., 2006, [089784](#)).

25 The nitrite-nitrate conversion reaction has also been used as the basis for an active sampler  
26 consisting of a nitrite-coated glass tube through which air is drawn by a pump operating at  
27 65 mL/min (Geyh et al., 1997, [086151](#); Geyh et al., 1999, [016908](#)). The reported detection limit is

1 10 ppb-h, enabling the quantification of O<sub>3</sub> concentrations measured over a few hours rather than a  
2 full day (Geyh et al., 1999, [016908](#)).

3 A portable active O<sub>3</sub> monitor based on the UV photometric technique used for stationary  
4 monitors (Chapter 3) has recently been approved as a FEM (75 FR 22126) (2010, [687659](#)). This  
5 monitor includes a Nafion tube in the inlet line to equalize humidity, reducing the effect of humidity  
6 changes in different microenvironments (Wilson and Birks, 2006, [595155](#)). Its size and weight  
7 (approximately 10×20×30 cm; 2 kg) make it suitable for use in a backpack configuration. The  
8 monitors are currently used by the U.S. National Park service as stationary monitors to measure O<sub>3</sub>  
9 in several national parks (Chapter 3).

### 4.3.2. Indoor-Outdoor Concentration Relationships

10 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) presented results from several studies on the  
11 relationship between indoor O<sub>3</sub> concentration and the O<sub>3</sub> concentration immediately outside the  
12 indoor microenvironment. These studies show that the indoor concentration is often substantially  
13 lower than the outdoor concentration unless indoor sources are present. Low indoor O<sub>3</sub>  
14 concentrations can be explained by reactions of O<sub>3</sub> with surfaces and airborne constituents. Studies  
15 have shown that O<sub>3</sub> is deposited onto indoor surfaces where reactions produce secondary pollutants  
16 such as formaldehyde (Reiss et al., 1995, [078727](#); Reiss et al., 1995, [078743](#)). However, the indoor-  
17 outdoor relationship is greatly affected by the air exchange rate; under conditions of high air  
18 exchange rate, such as open windows, the indoor O<sub>3</sub> concentration may approach the outdoor  
19 concentration. Geyh et al. (2000, [001775](#)) measured 6-day (approximately 144 hours) indoor and  
20 outdoor concentrations at 116 homes in southern California, approximately equally divided between  
21 the community of Upland and several mountain communities. The extended sampling period  
22 resulted in a relatively low detection limit (1 ppb) for the passive samplers used. The Upland homes  
23 were nearly all air-conditioned, while the mountain community homes were ventilated by opening  
24 windows. During the O<sub>3</sub> season, the indoor O<sub>3</sub> concentration averaged over all homes was  
25 approximately 24% of the overall mean outdoor concentration in Upland (11.8 versus 48.2 ppb),  
26 while in the mountain communities, the indoor concentration was 36% of the outdoor concentration  
27 (21.4 versus 60.1 ppb). This is consistent with the increased air exchange rate expected in homes  
28 using window ventilation. In the non-ozone season, when homes are likely to be more tightly closed  
29 to conserve heat, the ratios of indoor to outdoor concentration were 0.15 (3.2 versus 21.1 ppb) and  
30 0.08 (2.8 versus 35.7 ppb) in Upland and the mountain communities, respectively. Avol et al. (1998,  
31 [018270](#)) observed a mean (standard deviation) indoor-outdoor (I/O) ratio of 0.37 (0.25) for 239  
32 matched 24-h samples collected between February and December at homes in the Los Angeles area.  
33 The I/O ratio during summer was higher than the non-summer I/O ratio (0.43 versus 0.32). The  
34 authors also reported a correlation of 0.58 between the indoor concentration and the outdoor  
35 concentration, which was only slightly higher than the correlation between the indoor concentration  
36 and the concentration at the neighborhood fixed-site monitor (0.49). Romieu et al. (1998, [049834](#))  
37 reported a mean I/O ratio of 0.20 (SD = 0.18) in 145 homes in Mexico City for 14-day cumulative

1 samples, with the highest ratios observed in homes where windows were usually open during the day  
2 and where there was no carpeting or air filters. Studies conducted in Nashville, TN and Toronto,  
3 Canada both reported mean residential I/O ratios of approximately 0.1 (Lee et al., 2004, [055599](#); Liu  
4 L-JS; Koutrakis et al., 1995, [039061](#)).

5 Investigators have also measured I/O ratios for non-residential microenvironments, including  
6 schools and vehicles. Romieu et al. (1998, [049834](#)) reported that O<sub>3</sub> concentrations measured during  
7 school hours (10-day cumulative sample, 5 h/day) were 30-40% of concentrations immediately  
8 outside the schools, while overall I/O ratios (14-day cumulative sample, 24 h/day) were  
9 approximately 15%. The authors attribute this discrepancy to increased air exchange during the  
10 school day due to opening doors and windows. Air exchange was also identified as an important  
11 factor in the I/O ratios measured at eight French schools (Blondeau et al., 2005, [078044](#)). In this  
12 study, the I/O ratios based on simultaneous continuous measurements ranged from 0-0.45, increasing  
13 with decreasing building tightness. Although no indoor measurements were made, Rundell et al.  
14 (2006, [089785](#)) report a mean daytime continuous outdoor O<sub>3</sub> concentration of 106 ppb at one  
15 university and four elementary school playing fields, indicating the potential for elevated O<sub>3</sub>  
16 exposure in the school outdoor microenvironment.

17 Gradients in O<sub>3</sub> concentrations observed near roadways provide evidence of the NO-O<sub>3</sub>  
18 titration reaction that takes place in the ambient environment in which NO emitted from vehicles  
19 reacts with O<sub>3</sub> to produce NO<sub>2</sub> (Finlayson-Pitts and Pitts, 1986, [035054](#)). Ozone concentration has  
20 been observed in several studies to increase with increasing distance from the roadway, both upwind  
21 and downwind of the road (Section 3.6.2.1). Depending on wind direction, O<sub>3</sub> concentrations near  
22 the roadway have been found to be 20-80% of ambient concentrations at sites 400 m or more distant  
23 from roads. This indicates that exposures in near-road, on-road and in-vehicle microenvironments,  
24 while highly variable, may be lower than those in other microenvironments. A study on patrol cars  
25 during trooper work shifts reported in-vehicle 9-h concentrations that were approximately 51% of  
26 simultaneously measured roadside concentrations (mean of 11.7 versus 28.3 ppb) (Riediker et al.,  
27 2003, [043761](#)).

### 4.3.3. Personal-Ambient Concentration Relationships

#### 4.3.3.1. Personal-Ambient Correlations

28 The relationship between personal exposure and ambient O<sub>3</sub> concentrations has been evaluated  
29 in several research studies, many of which were conducted prior to 2005 and are discussed in the  
30 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). Some studies evaluated subject-specific, or longitudinal  
31 correlations, which describe multiple daily measurements for a single individual. These studies  
32 indicate the inter-individual variability of personal-ambient correlations. Another type of correlation  
33 is a pooled correlation, which combines data from multiple individuals over multiple monitoring  
34 periods (e.g., days), providing an overall indicator of the personal-ambient relationship for all study

1 subjects. A third type of correlation is a community-average correlation, which correlates average  
2 exposure across all study subjects with fixed-site monitor concentrations. Community-average  
3 correlations are particularly informative for interpreting time-series epidemiologic studies, in which  
4 ambient concentrations are used as a surrogate for community-average exposure.

5 The results of these studies indicate that personal exposures are moderately well correlated  
6 with ambient concentrations, and that the ratio of personal exposure to ambient concentration is  
7 higher in outdoor microenvironments and during the summer season. In situations where a lack of  
8 correlation was observed, this may be due in part to a high proportion of personal measurements  
9 below the detection limit. Chang et al. (2000, [001276](#)) measured hourly personal exposures in  
10 multiple microenvironments and found that the pooled correlation between personal exposure and  
11 ambient concentration was highest for outdoor microenvironments ( $r = 0.68-0.91$ ). Correlations in  
12 residential indoor microenvironments were very low ( $r = 0.05-0.09$ ), with moderate correlations  
13 ( $0.34-0.46$ ) in other indoor microenvironments such as restaurants and shopping malls. Liard et al.  
14 (1999, [001426](#)) evaluated community-average correlations based on 4-day mean personal O<sub>3</sub>  
15 exposure measurements for adults and children and found a relatively high correlation ( $r = 0.83$ )  
16 with ambient concentrations, even though 31-82% of the personal measurements were below the  
17 detection limit. Sarnat et al. (2000, [001852](#)) studied a population of older adults in Baltimore and  
18 found that longitudinal correlations between 24-h personal exposure and ambient concentration  
19 varied by subject and season, with somewhat higher correlations observed during summer (mean =  
20 0.20) than in winter (mean = 0.06). Some evidence was presented that subjects living in well-  
21 ventilated indoor environments have higher correlations than those living in poorly ventilated indoor  
22 environments, although exceptions to this were also observed. A moderate pooled correlation of 0.61  
23 was reported between 24-h avg personal and central-site measurements by Linn et al. (1996, [082508](#))  
24 for a population of southern California schoolchildren who spent an average of 101-136 minutes  
25 outdoors. The authors also report a correlation of 0.70 between central-site measurements and  
26 concentrations outside the children's schools. Although the average school outdoor concentration  
27 (34 ppb) was higher than the average central-site concentration (23 ppb) and the average personal  
28 exposure concentration was lower (5 ppb) than the central-site value, the similarity between the  
29 correlations indicate that central-site monitor concentrations can represent personal exposures in  
30 addition to representing local outdoor concentrations. A similar result was observed in a study in  
31 Vancouver, BC comparing three groups spending different amounts of time outdoors: health clinic  
32 workers (0-25% of time outdoors), camp counselors (7.5-45% of time outdoors), and farm workers  
33 (100% of time outdoors) (Brauer and Brook, 1997, [083339](#)). Health clinic workers and camp  
34 counselors were monitored 24 h/day, while farm workers were monitored during their work shift  
35 (6-14 hours). In this study, the pooled correlations between personal exposure and fixed-site  
36 concentration were similar among the groups, without a clear trend ( $r = 0.60, 0.42, \text{ and } 0.64$ ,  
37 respectively), although the ratios of personal exposure to fixed-site monitor concentration increased  
38 among the groups with increasing amount of time spent outdoors (0.28, 0.48, and 0.96, respectively).

1 This indicates that temporal variations in personal exposure to O<sub>3</sub> are driven by variations in ambient  
2 concentration, even for individuals that spend little time outdoors.

### 4.3.3.2. Personal-Ambient Ratios

3 Additional studies were summarized in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#))  
4 evaluating the ratio of personal O<sub>3</sub> exposure to ambient concentration or regressing personal  
5 exposure on ambient concentration. O'Neill et al. (2003, [042752](#)) studied a population of shoe  
6 cleaners working outdoors in Mexico City and presented a regression model indicating a 0.56 ppb  
7 increase in 6-h personal exposure for each 1 ppb increase in ambient concentration (95% CI: 0.43,  
8 0.69). Regression analyses by Sarnat et al. for 24-h data from mixed populations of children and  
9 older adults in Baltimore (2001, [019401](#)) and Boston (2005, [087531](#)) found differing results between  
10 the two cities, with Baltimore subjects showing a near-zero slope (0.01) during the summertime  
11 while Boston subjects showed a positive slope of 0.27 ppb personal exposure per 1 ppb ambient  
12 concentration. In both cities, the winter slope was near zero. Differences between the study areas  
13 may be due to differences in time spent outdoors, residential ventilation conditions, or other factors.  
14 Xue et al. (2005, [087532](#)) measured 6-day personal exposure of children in southern California and  
15 found that the average ratio of personal exposure to ambient concentration was relatively stable  
16 throughout the year at 0.3. These authors also regressed personal exposures on ambient  
17 concentration after adjusting for time-activity patterns and housing characteristics and found a slope  
18 of 0.54 ppb/ppb, with an R<sup>2</sup> value of 0.58. Unadjusted regression slopes were not presented.

19 A few studies have been published since the 2006 O<sub>3</sub> AQCD comparing personal exposures  
20 with ambient concentrations, and these findings generally confirm the conclusions of the 2006 O<sub>3</sub>  
21 AQCD. Sarnat et al. (2006, [089784](#)) measured 24-h personal exposures for a panel of older adults in  
22 Steubenville, OH during summer and fall 2000. Subjects were classified as high-ventilation or low-  
23 ventilation based on whether they spent time in indoor environments with open windows. Regression  
24 of personal exposures on ambient concentration found a higher slope for high-ventilation subjects  
25 compared with low-ventilation subjects in both summer (0.18 versus 0.08) and fall (0.27 versus  
26 0.20). Although no personal exposures were measured, McConnell et al. (2006, [089256](#)) found that  
27 average 24-h home outdoor O<sub>3</sub> concentrations were within 6 ppb of O<sub>3</sub> concentrations measured at  
28 central-site monitors in each of three southern California communities, with a combined average  
29 home outdoor concentration of 33 ppb compared to the central-site average of 36 ppb. Ramirez-  
30 Aguilar et al. (2008, [098930](#)) measured 48- to 72-h personal exposures of four groups of asthmatic  
31 children aged 6-14 in Mexico City during 1998-2000. A moderate pooled correlation (r = 0.35) was  
32 observed between these exposures and corresponding ambient concentrations. Regression of  
33 personal exposures on ambient concentrations yielded a slope of 0.17 ppb/ppb (95% CI: 0.13, 0.21)  
34 after adjustment for distance to the fixed-site monitor, time spent outdoors, an interaction term  
35 combining these two variables, and an interaction term representing neighborhood and study group.

36 Taken together, results from previous and recently published studies indicate that while the  
37 relationship between personal exposures and ambient concentrations varies due to a number of

1 factors, such as activity patterns, housing characteristics, and season, O<sub>3</sub> concentrations measured at  
2 central-site monitors are representative of day-to-day changes in average personal O<sub>3</sub> exposure,  
3 which is the important parameter for time-series epidemiologic studies. Another important finding is  
4 that the magnitude of personal exposures is smaller than concentrations reported at fixed-site  
5 monitors due to time spent indoors and the low indoor penetration of O<sub>3</sub>.

#### 4.3.4. Co-Exposure to Other Pollutants and Environmental Stressors

##### 4.3.4.1. Personal Exposure to Ozone and Co-pollutants

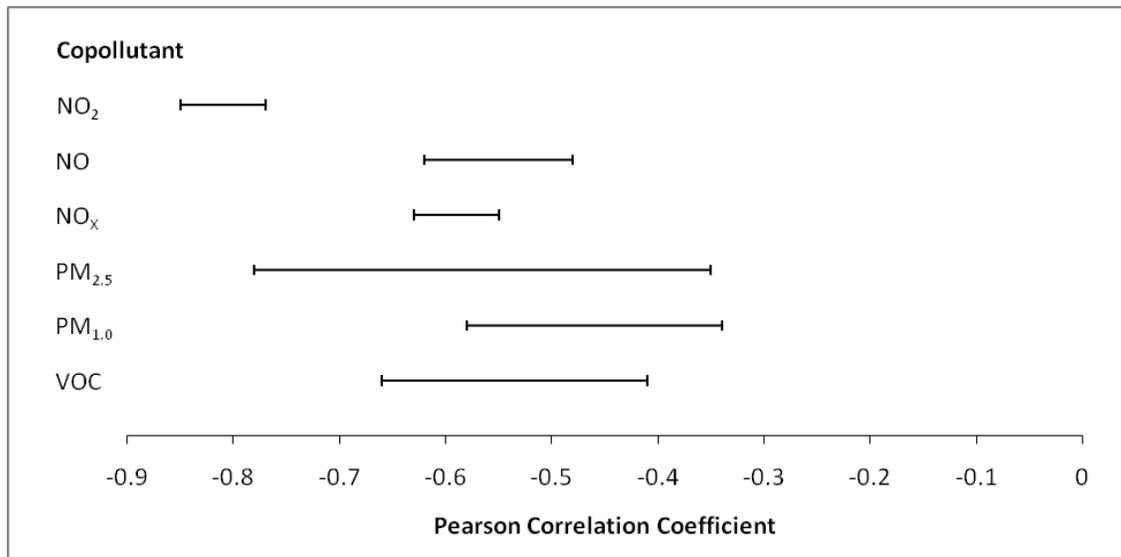
6 Personal exposure to O<sub>3</sub> shows variable correlation with personal exposure to other pollutants,  
7 with differences in correlation depending on factors such as season, city-specific characteristics, and  
8 spatial variability of the co-pollutant. Suh and Zanobetti (2010, [677202](#)) reported Spearman rank  
9 correlation coefficients during spring and fall between 24-h avg O<sub>3</sub> measurements and co-pollutants  
10 of 0.14, 0.00, and -0.03 for PM<sub>2.5</sub>, EC, and NO<sub>2</sub>, respectively. Note the higher correlation observed  
11 for PM<sub>2.5</sub>, a regional pollutant, in contrast with the extremely low correlations for the traffic-related  
12 and more spatially variable pollutants EC and NO<sub>2</sub>. Chang et al. (2000, [001276](#)) measured hourly  
13 personal exposures to PM<sub>2.5</sub> and O<sub>3</sub> in summer and winter in Baltimore, Maryland. Correlations  
14 between PM<sub>2.5</sub> and O<sub>3</sub> were 0.05 and -0.28 in summer and winter, respectively. Results indicate  
15 personal O<sub>3</sub> exposures were not significantly associated with personal PM<sub>2.5</sub> exposures in either  
16 summer or winter. These non-significant correlations may be attributed in part to the relatively low  
17 personal O<sub>3</sub> exposures observed in this study.

18 Studies conducted in Baltimore (Sarnat et al., 2001, [019401](#)) and Boston (Sarnat et al., 2005,  
19 [087531](#)) found differing results for the correlation between 24-h avg personal O<sub>3</sub> and personal PM<sub>2.5</sub>  
20 exposures, particularly during the winter season. Sarnat et al. (2001, [019401](#)) found a positive slope  
21 when regressing personal exposures of both total PM<sub>2.5</sub> (0.21) and PM<sub>2.5</sub> of ambient origin (0.22)  
22 against personal O<sub>3</sub> exposures during the summer season, but negative slopes (-0.05 and -0.18,  
23 respectively) during the winter season. The summertime slope for personal PM<sub>2.5</sub> exposure versus  
24 personal O<sub>3</sub> exposure was much higher for children (0.37) than for adults (0.07), which may be the  
25 result of different activity patterns. This team of researchers also found a positive, although higher,  
26 summer slope between 24-h avg personal O<sub>3</sub> and personal PM<sub>2.5</sub> in Boston (0.72) (Sarnat et al.,  
27 [2005, 087531](#)). However, the winter slope was positive (1.25) rather than negative, as in Baltimore.  
28 In both cities during both seasons, there was a wide range of subject-specific correlations between  
29 personal O<sub>3</sub> and personal PM<sub>2.5</sub> PM<sub>2.5</sub>, with some subjects showing relatively strong positive  
30 correlations (>0.75) and others showing strong negative correlations (<-0.50). The median  
31 correlation in both cities was slightly positive in the summer and near zero (Boston) or slightly  
32 negative (Baltimore) in the winter. These results indicate the potential effects of city-specific  
33 characteristics, such as housing stock and building ventilation patterns, on relationships between O<sub>3</sub>  
34 and co-pollutants.

### 4.3.4.2. Near-Road Exposure to Ozone and Co-pollutants

1 Beckerman et al. (2008, [096484](#)) measured both 1-week and continuous concentrations of O<sub>3</sub>,  
2 NO, NO<sub>2</sub>, NO<sub>x</sub>, PM<sub>2.5</sub>, PM<sub>1.0</sub>, and several VOCs (the BTEX compounds, MTBE, hexane, and THC)  
3 in the vicinity of heavily traveled (annual average daily traffic [AADT] >340,000) roadways in  
4 Toronto, Canada. Passive samplers were deployed for one week in August 2004. Ozone  
5 concentrations were negatively correlated with all pollutants, with the exception of VOCs at one of  
6 the monitoring sites which were suspected of being influenced by small area sources. Site specific  
7 correlations are given in Figure 4-1. Correlations were -0.77 to -0.85 for NO<sub>2</sub>, -0.48 to -0.62 for NO,  
8 and -0.55 to -0.63 for NO<sub>x</sub>. Pooled correlations using data from both sites were somewhat lower in  
9 magnitude. PM<sub>2.5</sub> and PM<sub>1.0</sub> correlations were -0.35 to -0.78 and -0.34 to -0.58, respectively. At the  
10 monitoring site not influenced by small area sources, O<sub>3</sub>-VOC correlations ranged from -0.41 to  
11 -0.66.

12 Beckerman et al. (2008, [096484](#)) also made on-road measurements of multiple pollutants with  
13 a instrumented vehicle. Concentrations were not reported, but correlations between O<sub>3</sub> and other  
14 pollutants were negative and somewhat greater in magnitude (i.e., more negative) than the near-road  
15 correlations. SO<sub>2</sub>, CO, and BC were measured in the mobile laboratory, although not at the roadside,  
16 and they all showed negative correlations with O<sub>3</sub> when the data were controlled for site.  
17 Correlations for continuous concentrations between O<sub>3</sub> and co-pollutants were somewhat lower than  
18 the 1-week correlations, except for O<sub>3</sub>-PM<sub>2.5</sub> correlations. Correlations were -0.90, -0.66, -0.77, and -  
19 0.89 for NO<sub>2</sub>, NO, NO<sub>x</sub>, and PM<sub>1.0</sub> respectively. The continuous O<sub>3</sub>-PM<sub>2.5</sub> correlation was -0.62,  
20 which is in the range of the 1-week correlation.



Source: Beckerman et al. (2008, [096484](#))

**Figure 4-1. Correlations between 1-week ozone concentrations and co-pollutants.**

### 4.3.4.3. Indoor Exposure to Ozone and Co-pollutants

1 Ambient O<sub>3</sub> that infiltrates indoors reacts with organic compounds and other chemicals to  
2 form oxidized products, as described in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). It is  
3 anticipated that individuals are exposed to these reaction products, although little evidence is  
4 available on personal exposures. The reactions are similar to those occurring in the ambient air, as  
5 summarized in Chapter 3. For example, O<sub>3</sub> can react with terpenes and other compounds from  
6 cleaning products, air fresheners, and wood products to form particulate and gaseous species, such as  
7 formaldehyde (Aoki and Tanabe, 2007, [449034](#); Reiss et al., 1995, [078743](#)). Ozone has also been  
8 shown to react with material trapped on HVAC filters and generate airborne products (Bekö et al.,  
9 2007, [601190](#); Hyttinen et al., 2006, [134392](#)). It is possible that these reaction products may have  
10 health effects in addition to, or greater than, those from O<sub>3</sub> itself (Anderson et al., 2007, [600123](#);  
11 Weschler and Shields, 1997, [084530](#)). Ozone may also react to form other oxidants, which then go  
12 on to participate in additional reactions. White et al. (2010, [633874](#)) found evidence that HONO or  
13 other oxidants may have been present during experiments to estimate indoor OH concentrations,  
14 indicating complex indoor oxidant chemistry. Rates of these reactions are dependent on indoor O<sub>3</sub>  
15 concentration, temperature, and air exchange rate, making estimation of exposures to reaction  
16 products difficult.

### 4.3.5. Population Proximity to Fixed-Site Ozone Monitors

17 The distribution of O<sub>3</sub> monitors across urban areas varies between cities (Section 3.6.2.1), and  
18 the population living near each monitor varies as well. It is not necessarily true that proximity to a  
19 monitor determines the degree to which that monitor represents an individual's ambient exposure,  
20 but proximity is one indicator. One way to calculate monitor representativeness is to calculate the  
21 fraction of the urban population living within a certain radius of a monitor. Table 4-1 presents the  
22 fraction of the population in selected cities living within 1, 5, 10, and 20 km of an O<sub>3</sub> monitor. Values  
23 are presented for both total population and for those under 18 years of age, a potentially susceptible  
24 population to the effects of O<sub>3</sub>. The data indicate that relatively few people live within 1 km of an O<sub>3</sub>  
25 monitor, while nearly all of the population in most cities lives within 20 km of a monitor. Many O<sub>3</sub>  
26 monitors are sited at “neighborhood scale,” intended to represent an area of the city with dimensions  
27 in the 0.5-4 km range (Section 3.5.6.1). Looking at the results for a 5-km radius, generally 20-30%  
28 of the population lives within this distance from an O<sub>3</sub> monitor. Some cities have a greater  
29 population in this buffer, such as Salt Lake City, while others have a lower percentage, such as  
30 Minneapolis and Seattle. Percentages for children are generally similar to the total population, with  
31 no clear trend.

**Table 4-1. 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 Another approach is to divide the metropolitan area into sectors surrounding each monitor  
2 such that every person in the sector lives closer to that monitor than any other. This facilitates  
3 calculation of the fraction of the city's population represented (according to proximity) by each  
4 monitor. In Atlanta, for example, the population fraction represented by each of the 11 monitors in  
5 the city ranged from 2.9-22%. The two monitors closest to the city center (sites A and B on  
6 Figure 3-24) accounted for 16% and 8% of the population, respectively. Site B has two listed  
7 monitoring objectives, highest concentration and population exposure. The other monitor in Atlanta  
8 with a listed objective of highest concentration is Site C, which represents the largest fraction of the  
9 population (22%). The eight monitors with a primary monitoring objective of population exposure  
10 account for 2.9-17% of the population per monitor.

11 Atlanta population fractions for children (<18 years of age) are similar to those for the general  
12 population, but other populations show a different pattern of monitor representativeness. Older adults  
13 (age 65 and up) were somewhat differently distributed with respect to the monitors, with most  
14 monitors showing a difference of more than a percentage point compared to the general population.  
15 Based on 2000 population data, the fraction of older adults closest to the two city center monitors (A  
16 and B) was 4% higher and 2% lower, respectively, than the fraction for the population as a whole.  
17 Site C showed the highest differential, with 21% of the total population but only 15% of the older

1 adult population. This indicates the potential for monitors to differentially represent potentially  
2 susceptible populations.

## 4.4. Exposure Modeling

### 4.4.1. Concentration Surface Modeling

3 One approach to improve exposure estimates in urban areas involves construction of a  
4 concentration surface over a geographic area, with concentration at locations between monitors  
5 estimated using a model to compensate for missing data. The calculated O<sub>3</sub> concentration surface can  
6 then be used to estimate exposures outside residences, schools, workplaces, roadways, or other  
7 locations of interest. This technique does not estimate exposure directly because it does not account  
8 for activity patterns or concentrations in different microenvironments. There are three main types of  
9 approaches: spatial interpolation of measured concentrations; statistical models using meteorological  
10 variables, pollutant concentrations, and other predictors to estimate concentrations at receptors in the  
11 domain; and rigorous first-principle models, such as chemistry-transport models or dispersion  
12 models incorporating O<sub>3</sub> chemistry. Some researchers have developed models that combine these  
13 techniques. The models may be applied over urban, regional, or national spatial scales, and can be  
14 used to estimate daily concentrations or longer-term averages. This discussion will focus on short-  
15 term concentrations estimated across urban areas.

16 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) discussed concentration surface models,  
17 focusing on chemistry-transport models as well as geospatial and spatiotemporal interpolation  
18 techniques (Christakos and Vyas, 1998, [029728](#); Christakos and Vyas, 1998, [011987](#); e.g.,  
19 Georgopoulos et al., 1997, [083591](#)). Recent research has continued to refine and extend the modeling  
20 approaches. A few recent papers have compared different approaches for the same urban area.

21 Marshall et al. (2008, [193983](#)) compared four spatial interpolation techniques for estimation of  
22 O<sub>3</sub> concentrations in Vancouver, BC. The investigators assigned a daily average O<sub>3</sub> concentration to  
23 each of the 51,560 postal-code centroids using one of the following techniques: (1) the concentration  
24 from the nearest monitor within 10 km; (2) the average of all monitors within 10 km; (3) the inverse-  
25 distance-weighted (IDW) average of all monitors in the area; and (4) the IDW average of the 3  
26 closest monitors within 50 km. Method 1 (the nearest-monitor approach) and Method 4 (IDW-50  
27 km) had similar mean and median estimated annual- and monthly-average concentrations, although  
28 the 10th-90th percentile range was smaller for IDW-50. This is consistent with the averaging of  
29 extreme values inherent in IDW methods. The Pearson correlation coefficient between the two  
30 methods was 0.93 for monthly-average concentrations and 0.78 for annual-average concentrations.  
31 Methods 2 and 3 were considered sub-optimal and were excluded from further analysis. In the case  
32 of Method 2, a single downtown high-concentration monitor skewed the results in the vicinity,  
33 partially as a result of the asymmetric layout of the coastal city of Vancouver. Method 3 was too  
34 spatially homogenous because it assigned most locations a concentration near the regional average,

1 except for locations immediately adjacent to a monitoring site. CMAQ concentration estimates using  
2 a 4 km×4 km grid were also compared to the interpolation techniques in this study. Mean and  
3 median concentrations from CMAQ were approximately 50% higher than Method 1 and Method 4  
4 estimates for both annual and monthly average concentrations. This may be due in part to the CMAQ  
5 grid size, which was too coarse to reveal near-roadway decrements in O<sub>3</sub> concentration due to  
6 titration by NO. The IQR for the annual average was similar between CMAQ and the interpolation  
7 techniques, but the monthly average CMAQ IQR was approximately twice as large, indicating a  
8 seasonal effect. Bell (2006, [194358](#)) compared CMAQ estimates for northern Georgia with  
9 nearest-monitor and spatial interpolation techniques, including IDW and kriging. The area-weighted  
10 concentration estimates from CMAQ indicated areas of spatial heterogeneity that were not captured  
11 by approaches based on the monitoring network. The author concluded that some techniques, such as  
12 spatial interpolation, were not suitable for estimation of exposure in certain situations, such as for  
13 rural areas. Using the concentration from the nearest monitor resulted in an overestimation of  
14 exposure relative to model estimates.

15 Land use regression (LUR) models have been developed to estimate levels of air pollutants,  
16 predominantly NO<sub>2</sub>, as a function of several land use factors, such as land use designation, traffic  
17 counts, home heating usage, point source strength, and population density (Briggs et al., 1997,  
18 [025950](#); Gilliland et al., 2005, [098820](#); Ryan and LeMasters, 2007, [156063](#)). LUR, initially termed  
19 regression mapping (Briggs et al., 1997, [025950](#)), is a regression derived from monitored  
20 concentrations as a function of data from a combination of the land use factors. The regression is  
21 then used for predicting concentrations at multiple locations based on the independent variables at  
22 those particular locations without monitors. Hoek et al. (2008, [195851](#)) warn of several limitations of  
23 LUR, including distinguishing real associations between pollutants and covariates from those of  
24 correlated co-pollutants, limitations in spatial resolution from monitor data, applicability of the LUR  
25 model under changing temporal conditions, and introduction of confounding factors when LUR is  
26 used in epidemiologic studies. These limitations may partially explain the lack of LUR models that  
27 have been developed for O<sub>3</sub> at the urban scale. Brauer et al. (2008, [156292](#)) evaluated the use of  
28 LUR and IDW-based spatial-interpolation models in epidemiologic analyses for Vancouver, BC and  
29 suggested that LUR is appropriate for directly-emitted pollutants with high spatial variability, such  
30 as NO and BC, while IDW is appropriate for secondary pollutants such as NO<sub>2</sub> and PM<sub>2.5</sub> with less  
31 spatial variability. Although this study did not evaluate an LUR model for O<sub>3</sub>, possibly due to the  
32 lack of the required dedicated sampling campaign, the IDW approach would be expected to be  
33 favored since O<sub>3</sub> is a secondary pollutant. At a much larger spatial scale, EU-wide, Beelen et al.  
34 (2009, [601157](#)) compared a LUR model for O<sub>3</sub> with ordinary kriging and universal kriging, which  
35 incorporated meteorological, topographical, and land use variables to characterize the underlying  
36 trend. The LUR model performed reasonably well at rural locations (5-km resolution), explaining a  
37 higher percentage of the variability ( $R^2 = 0.62$ ) than for other pollutants. However, at the urban scale  
38 (1-km resolution), only one variable was selected into the O<sub>3</sub> LUR model (high-density residential  
39 land use), and the  $R^2$  value was very low (0.06). Universal kriging was the best method for the large-

1 scale composite EU concentration map, for O<sub>3</sub> as well as for NO<sub>2</sub> and PM<sub>10</sub>, with an R<sup>2</sup> value for O<sub>3</sub>  
2 of 0.70. The authors noted that these methods were not designed to capture spatial variation in  
3 concentrations that are known to occur within tens of meters of roadways (Section 3.6.2.1), which  
4 could partially explain poor model performance at the urban scale.

5 Titration of O<sub>3</sub> with NO emitted by motor vehicles tends to reduce O<sub>3</sub> concentrations near  
6 roadways. McConnell et al. (2006, [089256](#)) developed a regression model to predict residential O<sub>3</sub>  
7 concentrations in southern California using estimates of residential NO<sub>x</sub> calculated from traffic data  
8 with the CALINE4 line source dispersion model. The authors estimated that local traffic contributes  
9 18% of NO<sub>x</sub> concentrations measured in the study communities, with the remainder coming from  
10 regional background. Their regression model indicates that residential NO<sub>x</sub> reduces residential O<sub>3</sub>  
11 concentrations by 0.51 ppb O<sub>3</sub> per 1 ppb NO<sub>x</sub>, and that a 10th-90th percentile increase in local NO<sub>x</sub>  
12 results in a 7.5 ppb decrease in local O<sub>3</sub> concentrations. This intra-urban traffic-related variability in  
13 O<sub>3</sub> concentrations suggests that traffic patterns are an important factor in the relationship between  
14 central site monitor and residential O<sub>3</sub>, and that differences in traffic density between the central site  
15 monitor and individual homes could result in either an overestimate or underestimate of residential  
16 O<sub>3</sub>.

17 A substantial number of researchers have used geostatistical methods and chemistry-transport  
18 models to estimate O<sub>3</sub> concentrations at urban, regional, national, and continental scales, both in the  
19 U.S. and in other countries (Hooyberghs et al., 2006, [608180](#); e.g., Pakalapati et al., 2009, [615781](#)).  
20 In addition to short-term exposure assessment for epidemiologic studies, such models may also be  
21 used for long-term exposure assessment, O<sub>3</sub> forecasts (Sahu et al., 2009, [618189](#)), or evaluating  
22 emission control strategies (Gabusi and Volta, 2005, [606112](#)). It is difficult to determine the utility of  
23 these methods for exposure assessment; while improved local-scale estimates of outdoor  
24 concentrations may contribute to better assignment of exposures, information on activity patterns is  
25 needed to produce estimates of personal exposure.

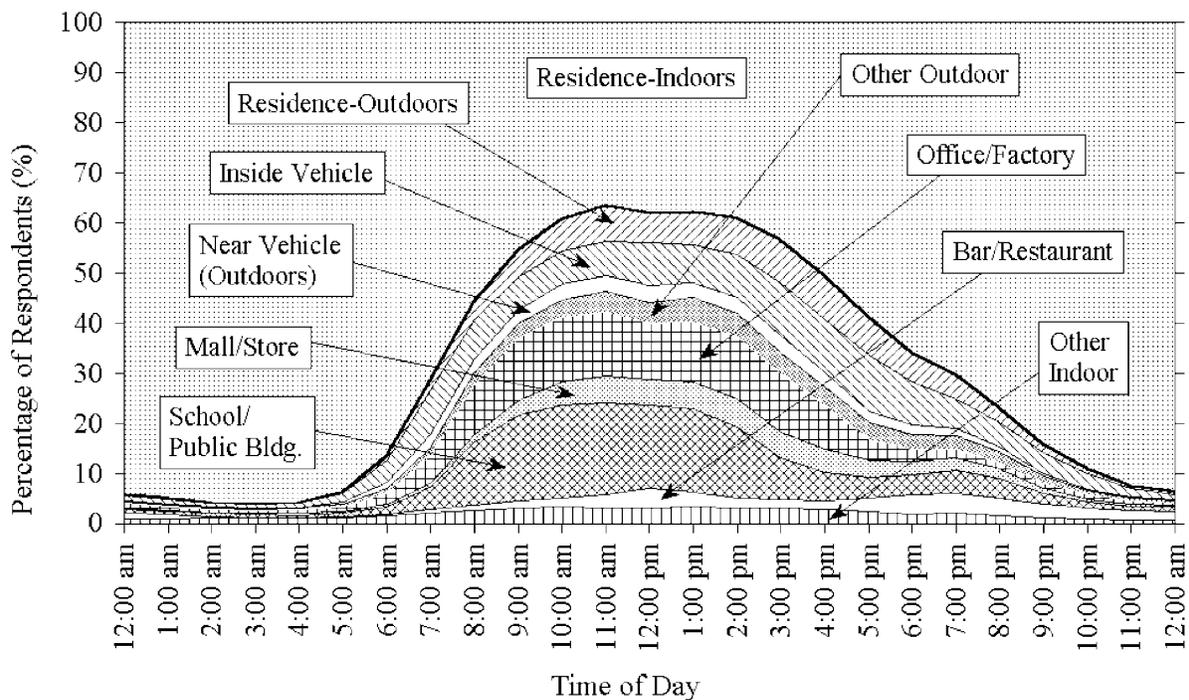
#### 4.4.2. Microenvironmental Models

26 Population-based methods, such as the Air Pollution Exposure (APEX) and Stochastic Human  
27 Exposure and Dose Simulation (SHEDS) models, involve stochastic treatment of the model inputs  
28 (Burke et al., 2001, [014050](#); U.S. EPA, 2009, [194009](#)). These are described in detail in the 2008 NO<sub>x</sub>  
29 ISA (U.S. EPA, 2008, [157073](#)), in AX3.6.1. Stochastic models utilize distributions of pollutant-  
30 related and individual-level variables, such as ambient and local O<sub>3</sub> concentration contributions and  
31 breathing rate respectively, to compute the distribution of individual exposures across the modeled  
32 population. The models also have the capability to estimate received dose through a dosimetry  
33 model. Using distributions of input parameters in the model framework rather than point estimates  
34 allows the models to incorporate uncertainty and variability explicitly into exposure estimates (Zidek  
35 et al., 2007, [190076](#)). These models estimate time-weighted exposure for modeled individuals by  
36 summing exposure in each microenvironment visited during the exposure period.

1           The initial set of input data for population exposure models is ambient air quality data, which  
2 may come from a monitoring network or model estimates. Estimates of concentrations in a set of  
3 microenvironments are generated either by mass balance methods or microenvironmental factors.  
4 Microenvironments modeled include indoor residences; other indoor locations, such as schools,  
5 offices, and public buildings; and vehicles. The sequence of microenvironments and exertion levels  
6 during the exposure period is determined from characteristics of each modeled individual. The  
7 APEX model does this by generating a profile for each simulated individual by sampling from  
8 distributions of demographic variables such as age, gender, and employment; physiological variables  
9 such as height and weight; and situational variables such as living in a house with a gas stove or air  
10 conditioning. Activity patterns from a database such as Consolidated Human Activity Database  
11 (CHAD) are assigned to the simulated individual using age, gender, and biometric characteristics  
12 (U.S. EPA, 2009, [194010](#)). Breathing rates are calculated for each activity based on exertion level,  
13 and the corresponding received dose may then be computed. Summaries of individual- and  
14 population-level metrics are produced, such as maximum exposure or dose, number of individuals  
15 exceeding a specified exposure/dose threshold, and number of person-days at or above benchmark  
16 exposure levels. The models also consider the nonambient contribution to total exposure.  
17 Nonambient source terms are added to the infiltration of ambient pollutants to calculate the total  
18 concentration in the microenvironment. Output from model runs with and without nonambient  
19 sources can be compared to estimate the ambient contribution to total exposure and dose.

20           An analysis has been conducted for the APEX model to evaluate the contribution of  
21 uncertainty in input parameters and databases to the uncertainty in model outputs (Langstaff, 2007,  
22 [090315](#)). The Monte Carlo analysis indicates that the uncertainty in model exposure estimates for  
23 asthmatic children during moderate exercise is small to moderate, with 95% confidence intervals of  
24 at most  $\pm 6$  percentage points at exposures above 60, 70, and 80 ppb (8-h avg) However, APEX  
25 appears to substantially underestimate the frequency of multiple high-exposure events for a single  
26 individual. The two main sources of uncertainty identified were related to the activity pattern  
27 database and the spatial interpolation of fixed-site monitor concentrations to other locations. One  
28 area of potential improvement in the activity pattern database is additional information on children's  
29 activities. Improved information on spatial variation of O<sub>3</sub> concentrations, including in near-roadway  
30 and indoor microenvironments, would also contribute to reduced uncertainty. Another area of need is  
31 for improved personal exposure monitors with shorter averaging times to capture peak exposures and  
32 lower detection limits to capture low indoor concentrations. A similar modeling approach has  
33 recently been developed which is suitable for panel epidemiologic studies or for controlled human  
34 exposure studies, in which activity pattern data specific to the individuals in the study can be  
35 collected. Time-activity data is combined with questionnaire data on housing characteristics,  
36 presence of indoor or personal sources, and other information to develop a personalized set of model  
37 input parameters for each individual. This model, the Exposure Model for Individuals, is being  
38 developed by EPA's National Exposure Research Laboratory.

1           Recent larger-scale human activity databases, such as those developed for the CHAD or the  
 2 National Human Activity Pattern Survey (NHAPS), have been designed to characterize exposure  
 3 patterns among much larger population subsets than can be examined during individual panel studies  
 4 (Klepeis et al., 2001, [002437](#); McCurdy et al., 2000, [000782](#)). CHAD consists of a consolidation of  
 5 human activity data obtained during several panel studies in which diary or retrospective activity  
 6 data were obtained, while NHAPS acquired sample population time-activity data through surveys  
 7 about human activity (Klepeis et al., 2001, [002437](#)). The complex human activity patterns across the  
 8 population (all ages) are illustrated in Figure 4--2 (Klepeis et al., 2001, [002437](#)), which is presented  
 9 to illustrate the diversity of daily activities among the entire population as well as the proportion of  
 10 time spent in each microenvironment. For example, about 25% of the individuals reported being  
 11 outdoors or in a vehicle between 2:00 and 3:00 pm, when daily O<sub>3</sub> levels are peaking, although about  
 12 half of this time was spent in or near a vehicle, where O<sub>3</sub> concentrations are likely to be lower than  
 13 ambient concentrations. Different patterns would be anticipated when breaking down activity  
 14 patterns only for subgroups such as children or the elderly. Population exposures can be estimated  
 15 using O<sub>3</sub> concentration data in each microenvironment.



Source: Reprinted with permission from Nature Publishing Group, Klepeis et al. (2001, [002437](#)).

**Figure 4-2. Distribution of time that NHAPS respondents spent in ten microenvironments based on smoothed 1-min diary data.**

### 4.4.3. Hybrid Model Approaches

1 Georgopoulos et al. (2005, [080269](#)) used the MENTOR/SHEDS modeling framework to  
2 estimate O<sub>3</sub> exposure in Philadelphia over a 2-week period in July 1999. They found that both the  
3 50th and 95th percentile O<sub>3</sub> concentrations were correlated with census-tract level outdoor  
4 concentrations estimated by photochemical modeling combined with spatiotemporal interpolation,  
5 and attributed this correlation to the lack of indoor sources of O<sub>3</sub>. Relationships between exposure  
6 and concentrations at fixed-site monitors were not reported.

## 4.5. Implications for Epidemiologic Studies

### 4.5.1. Exposure Measurement Error

7 Exposure error can be an important contributor to variability in epidemiologic study results.  
8 Community-level time-series studies may involve a population of thousands or millions of people  
9 across an urban area whose exposure and health status is estimated over the course of a few years  
10 using a short monitoring interval (hours to days). Community-averaged concentration is typically  
11 used as a surrogate for ambient exposure in community time-series studies. Exposures and health  
12 effects are spatially aggregated over the time intervals of interest because community time-series  
13 studies are designed to examine health effects and their potential causes at the community level. A  
14 longitudinal cohort epidemiology study, such as the ACS cohort study, typically involves hundreds  
15 or thousands of subjects followed over several years or decades (e.g., Jerrett et al., 2009, [194160](#)).  
16 Concentrations are generally aggregated over time and by community to estimate exposures. In  
17 addition, panel studies, which consist of a relatively small sample (typically tens) of study  
18 participants followed over a period of days to months, have been used to examine the health effects  
19 associated with exposure to ambient concentrations of air pollutants (e.g., Delfino et al., 1996,  
20 [080788](#)). Panel studies may also apply a microenvironmental model to represent exposure to an air  
21 pollutant.

22 Exposure error can mask epidemiologic associations between pollutants and health outcomes,  
23 although this may be less of an issue for O<sub>3</sub> because it is a regional pollutant with relatively low  
24 spatial variability. For example, a study in Atlanta observed associations between HRV parameters  
25 and two traffic-related pollutants (EC and NO<sub>2</sub>), but the associations were only statistically  
26 significant when personal exposures to the pollutants were used in the regression model (Suh and  
27 Zanobetti, 2010, [677202](#)). No association was observed with ambient concentrations of these two  
28 pollutants. In contrast, associations were similar for ambient concentrations and personal exposures  
29 of O<sub>3</sub> and PM<sub>2.5</sub>, another regional pollutant. Further discussion of the effect of spatial variability is  
30 provided in Section 4.5.3.

31 The importance of exposure misclassification varies with study design and is dependent on the  
32 spatial and temporal aspects of the design. For example, the use of a community-averaged O<sub>3</sub>

1 concentration in a community time-series epidemiologic study may not allow for adequate  
2 examination of the role of spatial variability. Other factors that could influence exposure estimates  
3 include nonambient exposure; spatial and temporal variability, topography of the natural and built  
4 environment, and meteorology; measurement errors; use of ambient O<sub>3</sub> concentration as a surrogate  
5 for ambient O<sub>3</sub> exposure; and the presence of O<sub>3</sub> in a mixture of pollutants. The following sections  
6 will consider various sources of error and how they affect the interpretation of results from  
7 epidemiologic studies of different designs.

## 4.5.2. Nonambient Ozone Exposure

8 For other criteria pollutants, nonambient sources can be an important contributor to total  
9 personal exposure. There are relatively few indoor sources of O<sub>3</sub>, so personal O<sub>3</sub> exposure is  
10 expected to be dominated by ambient O<sub>3</sub> in outdoor microenvironments and in indoor  
11 microenvironments with high air exchange rates (e.g., with open windows). Even in  
12 microenvironments where nonambient exposure is substantial, such as in a room with an O<sub>3</sub>  
13 generator, this nonambient exposure is unlikely to be temporally correlated with ambient O<sub>3</sub>  
14 exposure (Wilson and Suh, 1997, [077408](#)), and therefore would not affect epidemiologic associations  
15 between O<sub>3</sub> and the health effect (Sheppard et al., 2005, [079176](#)). In simulations of a nonreactive  
16 pollutant, Sheppard et al. (2005, [079176](#)) concluded that nonambient exposure does not influence the  
17 health outcome effect estimate if ambient and nonambient concentrations are independent. It should  
18 be noted that the effect estimate calculated from using personal exposure to ambient O<sub>3</sub> rather than  
19 ambient concentration will be increased in inverse proportion to the ratio of ambient exposure to  
20 ambient concentration, and daily fluctuations in this ratio can widen the confidence intervals in the  
21 ambient concentration effect estimate, but uncorrelated nonambient exposure will not bias the effect  
22 estimate.

## 4.5.3. Spatiotemporal Variability

### 4.5.3.1. Spatial Variability

23 Compared with directly emitted pollutants such as CO and NO<sub>x</sub>, O<sub>3</sub> exhibits relatively low  
24 spatial variability across urban areas, as discussed in Chapter 3. Spatial variability contributes to  
25 exposure error if the ambient O<sub>3</sub> concentration measured at the central site monitor is used as an  
26 ambient exposure surrogate and differs from the actual ambient O<sub>3</sub> concentration outside a subject's  
27 residence and/or worksite (in the absence of indoor O<sub>3</sub> sources). Averaging data from a large number  
28 of samplers will dampen intersampler variability, and use of multiple monitors over smaller land  
29 areas may allow for more variability to be incorporated into an epidemiologic analysis.

30 Community exposure may not be well represented when monitors cover large areas with  
31 several subcommunities having different sources and topographies, such as the Los Angeles CSA  
32 (Chapter 3). Ozone monitors in Los Angeles had a much wider range of intermonitor correlations

1 (-0.06 to 0.97) than Atlanta (0.61 to 0.96) or Boston (0.56 to 0.97) using 2007-2009 data. Although  
2 the negative and near-zero correlations in Los Angeles were observed for monitors located some  
3 distance apart (>150 km), some closer monitor pairs had low positive correlations, likely due to  
4 changes in topography and airflow patterns over short distances. The spatial variability in O<sub>3</sub>  
5 concentration in 24 MSAs across the U.S. was examined in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006,  
6 [088089](#)). Spatial variability was examined by using Pearson correlation coefficients, values of the  
7 90th percentile of the absolute difference in O<sub>3</sub> concentrations, and CODs. No clear discernible  
8 regional differences across the U.S. were found in the ranges of parameters analyzed.

9 However, spatial variation in atmospheric constituents that participate in O<sub>3</sub> formation and  
10 titration reactions contribute to spatial variability in some areas, particularly near roadways (Section  
11 3.6.2.1). Liu et al. (1995, [039061](#)) conducted a O<sub>3</sub> exposure assessment study in Toronto, Canada  
12 during the winter and summer of 1992. Results indicated that outdoor O<sub>3</sub> concentrations exhibited  
13 spatial variation over the study area. The spatial variation is believed to result from population and  
14 traffic density. The results are consistent with a smaller-scale study by McKendry (1993, [677201](#)) in  
15 Montreal, Canada, in which the investigator examined spatial variation using measurements from  
16 nine ambient monitoring sites and found the spatial pattern of O<sub>3</sub> concentration to be more distinct in  
17 the winter than in the summer.

18 Sarnat et al. (2010, [385852](#)) studied the spatial variability of O<sub>3</sub>, along with PM<sub>2.5</sub>, NO<sub>2</sub>, and  
19 CO, in the Atlanta, GA, metropolitan area and evaluated how spatial variability affects interpretation  
20 of epidemiologic results, using time-series data for circulatory disease ED visits. The authors found  
21 that associations with ambient O<sub>3</sub> concentration were similar among all sites tested, including  
22 multiple urban sites and a rural site some 38 miles from the city center. This result was also observed  
23 for PM<sub>2.5</sub>, another regional pollutant. In contrast, the more spatially variable pollutants CO and NO<sub>2</sub>  
24 showed different associations for the rural site than the urban sites, although the urban site  
25 associations were similar to one another for CO. This suggests that choice of monitor may have little  
26 impact on the results of O<sub>3</sub> epidemiologic studies.

### 4.5.3.2. Seasonality

27 The relationship between personal exposure and ambient concentration has been found to vary  
28 by season, with at least three factors potentially contributing to this variation: differences in building  
29 ventilation (e.g., air conditioning or heater use versus open window ventilation), higher O<sub>3</sub>  
30 concentrations during the O<sub>3</sub> season contributing to increased exposure and improved detection by  
31 personal monitors; and changes in activity pattern resulting in more time spent outside. Evidence has  
32 been presented in studies conducted in several cities regarding the effect of ventilation on personal-  
33 ambient and indoor-outdoor O<sub>3</sub> relationships (see Sections 4.3.3 and 4.3.4). More limited evidence is  
34 available regarding the specific effects of O<sub>3</sub> detection limits and activity pattern changes on O<sub>3</sub>  
35 relationships.

36 Several studies have found increased summertime correlations or ratios between personal  
37 exposure and ambient concentration (Sarnat et al., 2000, [001852](#); Sarnat et al., 2005, [087531](#)) or

1 between indoor and outdoor O<sub>3</sub> concentrations (Avol et al., 1998, [018270](#); Geyh et al., 2000,  
2 [001775](#)). However, others have found higher ratios in fall than in summer (Sarnat et al., 2006,  
3 [089784](#)) or equivalent, near-zero ratios in winter and summer (Sarnat et al., 2001, [019401](#)), possibly  
4 because summertime use of air conditioners decreases building air exchange rates. It should be noted  
5 that O<sub>3</sub> concentrations during winter are generally much lower than summertime concentrations,  
6 possibly obscuring wintertime relationships due to detection limit issues. Studies specifically  
7 evaluating the effect of ventilation conditions on O<sub>3</sub> relationships have found increased correlations  
8 or ratios for individuals or buildings experiencing higher air exchange rates (Geyh et al., 2000,  
9 [001775](#); Romieu et al., 1998, [049834](#); Sarnat et al., 2000, [001852](#); Sarnat et al., 2006, [089784](#)).

10 Increased correlations or ratios between personal exposure and ambient concentration, or  
11 between indoor and outdoor concentration, are likely to reduce error in exposure estimates used in  
12 epidemiologic studies. This suggests that studies conducted during the O<sub>3</sub> season or in periods when  
13 communities are likely to have high air exchange rates (e.g., during mild weather) may be less prone  
14 to exposure error than studies conducted only during winter. Year-round studies that include both the  
15 O<sub>3</sub> and non-O<sub>3</sub> seasons may have an intermediate level of exposure error.

#### 4.5.4. Exposure to Co-pollutants and Ozone Reaction Products

16 Although indoor O<sub>3</sub> concentrations are usually well below ambient concentrations, the same  
17 reactions that consume O<sub>3</sub> indoors form particulate and gaseous species, including other oxidants, as  
18 summarized in Section 4.3.4.3. Exposures to these reaction products would therefore be expected to  
19 be correlated with ambient O<sub>3</sub> concentrations, and could potentially contribute to health effects  
20 observed in epidemiologic studies. Current evidence regarding personal exposures to these reaction  
21 products is extremely limited.

#### 4.5.5. Exposure Estimation Methods in Epidemiologic Studies

22 The use of O<sub>3</sub> measurements from central ambient monitoring sites is the most common  
23 method for assigning exposure in epidemiologic studies. However, fixed-site measurements do not  
24 account for the effects of spatial variation in O<sub>3</sub> concentration, ambient and non-ambient  
25 concentration differences, and varying activity patterns on personal exposures (Brown et al., 2009,  
26 [190895](#); Chang et al., 2000, [001276](#); Zeger et al., 2000, [001949](#)). The use of fixed-site  
27 concentrations results in minimal exposure error when: (1) O<sub>3</sub> concentrations are uniform across the  
28 region; (2) personal activity patterns are similar across the population; and (3) housing  
29 characteristics, such as air exchange rate and indoor reaction rate, are constant over the study area.  
30 Since these factors vary by location and population, there will be errors in the magnitude of total  
31 exposure based solely on ambient monitoring data.

32 As described in Section 4.3.4, results from previous and recently published studies indicate  
33 that while the relationship between personal exposures and ambient concentrations varies due to a  
34 number of factors, such as activity patterns, housing characteristics, and season, O<sub>3</sub> concentrations

1 measured at central-site monitors are representative of day-to-day changes in average personal O<sub>3</sub>  
2 exposure, which is the important parameter for time-series epidemiologic studies. Another important  
3 finding is that the magnitude of personal exposures is smaller than concentrations reported at fixed-  
4 site monitors due to time spent indoors and the low indoor penetration of O<sub>3</sub>. This tends to support the  
5 use of fixed-site concentrations as exposure estimates in epidemiologic studies.

6 Modeling approaches can also be used to estimate exposures for epidemiologic studies, as  
7 discussed in Section 4.4. Geostatistical spatial interpolation techniques can provide finer-scale  
8 estimates of local concentration over urban areas. A microenvironmental modeling approach  
9 simulates exposure using empirical distributions of concentrations in specific microenvironments  
10 together with human activity pattern data. The main advantage of the modeling approach is that it  
11 can be used to estimate exposures over a wide range of population and scenarios. A main  
12 disadvantage of the modeling approach is that the results of modeling exposure assessment must be  
13 compared to an independent set of measured exposure levels (Klepeis, 1999, [001697](#)). In addition,  
14 resource-intensive development of validated and representative model inputs is required, such as  
15 human activity patterns, distributions of air exchange rate, and deposition rate. Therefore, modeled  
16 exposures are used much less frequently in epidemiologic studies.

## 4.6. Summary and Conclusions

### 4.6.1. Exposure Measurement

#### 4.6.1.1. Measurement of Ozone Exposure

17 Passive badge samplers are the most widely used technique for measuring personal O<sub>3</sub>  
18 exposure. They operate on the nitrite-nitrate conversion principle, and are convenient since they  
19 require no pumps or wet chemistry in the field. They represent a cumulative (rather than continuous)  
20 sample, and their detection limit makes them suitable for monitoring periods of 24 hours or greater.  
21 This limits their applicability in measuring short-term daily fluctuations in personal exposure. Over a  
22 24-h period, the detection limit of the badges is approximately 5-10 ppb, which may result in an  
23 appreciable fraction of the samples being below the detection limit. An active sampler based on the  
24 nitrite-nitrate conversion reaction is also available, with a reported detection limit of 10 ppb-h,  
25 enabling measurement of sub-daily O<sub>3</sub> concentrations. A portable continuous O<sub>3</sub> monitor based on a  
26 different principle, UV absorption, has recently become available. Its size and weight make it  
27 suitable for use in a backpack configuration, although its use for personal exposure measurements  
28 has been limited.

29 Several studies described in the 2006 O<sub>3</sub> AQCD, along with a few new studies published since,  
30 describe the relationship between indoor O<sub>3</sub> concentration and the O<sub>3</sub> concentration immediately  
31 outside the indoor microenvironment. These studies show that the indoor concentration is often  
32 substantially lower than the outdoor concentration unless indoor sources are present. Low indoor O<sub>3</sub>

1 concentrations can be explained by reaction of O<sub>3</sub> with surfaces and airborne constituents. However,  
2 the indoor-outdoor relationship is greatly affected by the air exchange rate; under conditions of high  
3 air exchange rate, such as open windows, the indoor O<sub>3</sub> concentration may approach the outdoor  
4 concentration. In residential microenvironments, studies report indoor-outdoor ratios ranging from  
5 approximately 0.1-0.4, with the highest ratios observed in the summer O<sub>3</sub> season and for homes with  
6 increased window ventilation. A correlation of 0.58 was reported between indoor and outdoor O<sub>3</sub>  
7 concentrations, indicating that variations in outdoor concentration may be reflected indoors, though  
8 the magnitude of the concentration is lower. Indoor-outdoor ratios at schools were similar, with  
9 higher ratios observed during the school day when opening doors and windows may lead to  
10 increased air exchange rates. In vehicles, high air exchange rates that would normally lead to high  
11 interior-exterior concentration ratios are offset by O<sub>3</sub> scavenging through vehicle-emitted NO,  
12 resulting in reported in-vehicle concentrations that were approximately 50% of those measured at the  
13 roadside.

14 The relationship between personal exposure and ambient O<sub>3</sub> concentrations has been evaluated  
15 in several research studies, many of which were conducted prior to 2005 and are discussed in the  
16 2006 O<sub>3</sub> AQCD. The results of these studies indicate that personal exposures are moderately well  
17 correlated with ambient concentrations, and that the ratio of personal exposure to ambient  
18 concentration is higher in outdoor microenvironments and during the summer season. In situations  
19 where a lack of correlation was observed, this may be due in part to a high proportion of personal  
20 measurements below the detection limit. Correlations reported for daily or multi-day measurements  
21 range from approximately 0.3-0.8, with the upper end of the range reflecting longer-duration (4-day)  
22 community average measurements that may limit the influence of inter-individual variability in  
23 exposure. Hourly measurements in specific microenvironments show greater variability in  
24 correlations between personal exposure and ambient concentration, with residential indoor  
25 correlations <0.1 and outdoor correlations of 0.7-0.9. Slopes from regression analyses of personal  
26 exposure on ambient concentration generally ranged from approximately 0.1-0.3. Higher slopes were  
27 observed in studies that either adjusted for activity pattern and air exchange rate (0.54) or focused on  
28 outdoor shoe cleaners (0.56), who may have increased exposure due to spending a substantial  
29 fraction of the day outdoors. Ratios of personal exposure to ambient concentration showed similar  
30 results, with a ratio of 0.3 reported for a year-round study in southern California, while ratios ranged  
31 from 0.28-0.96 for outdoor workers, increasing with time spent outdoors.

32 Taken together, results from previous and recently published studies indicate that while the  
33 relationship between personal exposures and ambient concentrations varies due to a number of  
34 factors, such as activity patterns, housing characteristics, and season, O<sub>3</sub> concentrations measured at  
35 central-site monitors are representative of day-to-day changes in average personal O<sub>3</sub> exposure,  
36 which is the important parameter for time-series epidemiologic studies. Another important finding is  
37 that the magnitude of personal exposures is smaller than concentrations reported at fixed-site  
38 monitors due to time spent indoors and the low indoor penetration of O<sub>3</sub>.

### 4.6.1.2. Co-Exposure to Ozone and Other Pollutants

1 Individuals may be exposed to other pollutants in conjunction with exposure to O<sub>3</sub>. Personal  
2 exposure to O<sub>3</sub> shows variable association with personal exposure to other pollutants, with  
3 differences in association depending on factors such as season, city-specific characteristics, and  
4 spatial variability of the co-pollutant. For PM<sub>2.5</sub>, a rank correlation of 0.14 was reported between  
5 daily O<sub>3</sub> and PM<sub>2.5</sub> exposures during spring and fall in Atlanta. Positive slopes were reported during  
6 summer in both Baltimore and Boston, although the slopes were somewhat different (0.21 and 0.72,  
7 respectively). The summertime slope in Baltimore was higher for children (0.37) than for adults  
8 (0.07), which may be the result of different activity patterns and time spent outdoors. Additional  
9 evidence of variation by season and city is provided by the differing signs of the wintertime slopes,  
10 with Baltimore showing a negative slope and Boston showing a positive slope. Interindividual  
11 variability likely played a role as well, since both cities showed a wide range (including both  
12 negative and positive values) for individual-specific personal O<sub>3</sub>- PM<sub>2.5</sub> slopes. For EC and NO<sub>2</sub>,  
13 near-zero correlations were reported with O<sub>3</sub> during spring and fall in Atlanta. These extremely low  
14 correlations for the traffic-related and spatially variable pollutants EC and NO<sub>2</sub> contrast with the  
15 higher correlation observed for PM<sub>2.5</sub>, a regional pollutant.

16 In near-road and on-road microenvironments, correlations between O<sub>3</sub> and traffic-related  
17 pollutants are moderately to strongly negative, with the most strongly negative correlations observed  
18 for NO<sub>2</sub> (-0.8 to -0.9). This is consistent with the chemistry of NO oxidation, in which O<sub>3</sub> is  
19 consumed to form NO<sub>2</sub>. The more moderate negative correlations observed for PM<sub>2.5</sub>, PM<sub>1.0</sub>, and  
20 VOC may reflect reduced concentrations of O<sub>3</sub> in more polluted environments due to other  
21 scavenging reactions. A similar process occurs indoors, where infiltrated O<sub>3</sub> reacts with airborne or  
22 surface-associated materials to form secondary compounds, such as formaldehyde. Although such  
23 reactions decrease indoor O<sub>3</sub> exposure, they result in increasing exposure to other species which may  
24 themselves have health effects.

### 4.6.2. Exposure Modeling

25 Exposures estimates in urban areas may be improved by constructing a concentration surface  
26 over a geographic domain using a model to compensate for missing data. The calculated  
27 concentration surface can then be used to estimate exposures outside residences, schools,  
28 workplaces, roadways, or other locations of interest. This technique does not estimate exposure  
29 directly because it does not account for activity patterns or concentrations in different  
30 microenvironments. Most such modeling efforts have focused on the less-reactive pollutants PM or  
31 NO<sub>2</sub>. In a study that extended CALINE4 NO<sub>x</sub> modeling results to evaluate the impact on residential  
32 O<sub>3</sub> concentrations (see Section 4.4.1), O<sub>3</sub> concentrations were reduced by 0.51 ppb O<sub>3</sub> per 1 ppb  
33 NO<sub>x</sub>. This intra-urban traffic-related variability in O<sub>3</sub> concentrations suggests that differences in  
34 traffic density between the central site monitor and individual homes could result in either an  
35 overestimate or underestimate of residential O<sub>3</sub>.

1 A separate class of models, known as microenvironmental models, estimate time-weighted  
2 exposure for modeled individuals by summing exposure in each microenvironment visited during the  
3 exposure period. Stochastic microenvironmental models, such as APEX and SHEDS, utilize  
4 distributions of pollutant-related and individual-level variables, such as ambient and local O<sub>3</sub>  
5 concentration contributions and breathing rate respectively, to compute the distribution of individual  
6 exposures across the modeled population. The models also have the capability to estimate received  
7 dose through a dosimetry model. Using distributions of input parameters in the model framework  
8 rather than point estimates allows the models to incorporate uncertainty and variability explicitly into  
9 exposure estimates. For the APEX model, an analysis has been conducted indicating that the  
10 uncertainty in model exposure estimates for asthmatic children during moderate exercise is small to  
11 moderate; however, APEX appears to substantially underestimate the frequency of multiple high-  
12 exposure events for a single individual. Microenvironmental models, such as EMI, are also being  
13 developed to use individual-specific information derived from measurements or questionnaires,  
14 rather than population distributions, to estimate exposures. This approach is particularly suitable for  
15 panel health studies where information is available for each participant, and may reduce uncertainty  
16 in health effect estimates by improving exposure estimates.

#### 4.6.3. Implications for Epidemiologic Studies

17 Exposure error can be an important contributor to variability in epidemiologic study results,  
18 although this may be less of an issue for O<sub>3</sub> because it is a secondary pollutant with relatively low  
19 spatial variability across an urban area. For example, an epidemiologic study in Atlanta observed  
20 similar associations between HRV parameters and either ambient concentrations or personal  
21 exposures of O<sub>3</sub> and PM<sub>2.5</sub>, another regional pollutant. The importance of exposure error varies with  
22 study design and is dependent on the spatial and temporal aspects of the design. Several factors that  
23 could influence exposure estimates include nonambient exposure, spatial and temporal variability,  
24 and the presence of O<sub>3</sub> in a mixture of pollutants. Nonambient exposure is unlikely to influence  
25 health effect estimates because of the lack of indoor O<sub>3</sub> sources and because indoor-generated O<sub>3</sub>  
26 exposures are unlikely to be correlated with ambient O<sub>3</sub> exposure. Compared with directly emitted  
27 pollutants such as CO and NO<sub>x</sub>, O<sub>3</sub> exhibits relatively low spatial variability across urban areas, as  
28 discussed in Chapter 3. Averaging data from a large number of samplers will dampen intersampler  
29 variability, and use of multiple monitors over smaller land areas may allow for more variability to be  
30 incorporated into an epidemiologic analysis. Evidence from a study comparing the effect of spatial  
31 variability on effect estimates for O<sub>3</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, and CO suggests that choice of monitor for more  
32 spatially homogenous pollutants such as O<sub>3</sub> may have little impact on the results of epidemiologic  
33 studies. Season, however, may have a substantial effect due to much lower O<sub>3</sub> concentrations during  
34 the winter, along with the higher correlations between ambient concentrations and personal  
35 exposures observed during the summer. Studies conducted during the O<sub>3</sub> season or in periods when  
36 communities are likely to have high air exchange rates (e.g., during mild weather) may be less prone  
37 to exposure error than studies conducted only during winter. Year-round studies that include both the

1 O<sub>3</sub> and non-O<sub>3</sub> seasons may have an intermediate level of exposure error. Exposure to mixtures of  
2 pollutants containing O<sub>3</sub> also complicates interpretation of epidemiologic results. Moderate to strong  
3 negative correlations between O<sub>3</sub> and traffic-related pollutants, particularly NO<sub>2</sub>, make it difficult to  
4 determine to what extent O<sub>3</sub>-based effect estimates quantitatively reflect the independent effect of O<sub>3</sub>  
5 itself, or the effect of another pollutant or pollutants in the mixture. Interpretation of O<sub>3</sub> effects in the  
6 presence of PM is additionally complicated by the highly variable correlations observed, which  
7 differ by city, season, and population characteristics (e.g., children versus adults). Although these  
8 sources of exposure error should be considered in evaluating epidemiologic results, previous and  
9 recently published exposure research indicate that O<sub>3</sub> concentrations measured at central-site  
10 monitors are indicative of day-to-day changes in average personal O<sub>3</sub> exposure, making ambient  
11 concentrations a useful parameter for epidemiologic studies.

# References

A list of all references considered for inclusion in this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=475](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=475)

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# Chapter 5. Dosimetry and Mode of Action

## 5.1. Human and Animal Ozone Dosimetry

### 5.1.1. 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. The measurement of  
3 the dose of reactive gases such as O<sub>3</sub> can range in refinement from their concentration in the ambient  
4 exposure atmosphere to the “effective” dose of the chemical or its reaction products that actively  
5 participate in toxic reactions (Dahl, 1990, [094536](#)). Thus, the units for the expression of the dose of  
6 O<sub>3</sub> might range from the concentration of gas in the air (units of ppm or mg/m<sup>3</sup>), to the quantity of  
7 gas inhaled as the product of gas concentration × minute ventilation × time (units of ppm × L × h), to  
8 the quantity of gas retained by the whole body, to the concentration of gas molecules that have been  
9 absorbed or reacted with the tissue (moles/g tissue weight). In modeling studies, the dose rate is  
10 often expressed as a flux per unit of surface area of a region of respiratory epithelium.

11 Ozone is a highly reactive though poorly water soluble gas. The latter feature is believed to be  
12 the reason why it is able to penetrate into targets in the lower respiratory tract. The fact that it is so  
13 chemically reactive has suggested to some that its effective dose at the target sites exists in the form  
14 of secondary oxidation products such as aldehydes and peroxides. Reaction products are formed  
15 when O<sub>3</sub> interacts with components of the extracellular lining fluid (ELF) such as lipids and  
16 antioxidants. Ozone toxicity is observed to some extent in the nasal cavity, however further toxicity  
17 exists in the deep lung where the ELF thickness narrows allowing O<sub>3</sub> to react directly with cells  
18 protruding from the ELF and surface macrophages. Ozone uptake relates directly to these ELF  
19 substrate reactions and is termed “reactive absorption.” Thus the uptake of O<sub>3</sub> is related to both the  
20 concentration of O<sub>3</sub> as well as the availability of substrates within the ELF.

21 Two types of measurement have been used to arrive at the O<sub>3</sub> dose to target sites during  
22 breathing: (1) measurement of removal of O<sub>3</sub> from the air stream (termed “uptake”); and (2)  
23 measurement of chemical reactions or the product of those reactions with tissues or with  
24 biomolecules known to be present in tissues (termed “reactions”). The results of the above

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

1 measurements have been incorporated into mathematical models for the purpose of explaining,  
2 predicting, and extrapolating O<sub>3</sub> dose in different exposure scenarios of interest.

3 This chapter is intended as an update of the past O<sub>3</sub> AQCDs (U.S. EPA, 1996, [017831](#);  
4 U.S. EPA, 2006, [088089](#)) and restates the basic concepts derived from O<sub>3</sub> dosimetry literature  
5 presented in previous documents as well as introduces the recent relevant literature. Particular  
6 attention is given to dosimetric factors influencing individual susceptibility to adverse effects from  
7 O<sub>3</sub> and factors that affect the ability to extrapolate between species (e.g., experimental animal to  
8 human). As there have been few O<sub>3</sub> dosimetry studies since the last AQCD, the reader is referred to  
9 previous documents (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)) for more detailed  
10 discussion of the literature. Evaluation of the progress in the interpretation of past dosimetry studies,  
11 as well as studies published since 2005, in the areas of reactions, uptake, and models for O<sub>3</sub>  
12 dosimetry, is discussed in the following sections.

## 5.1.2. Ozone Reactions and Reaction Products

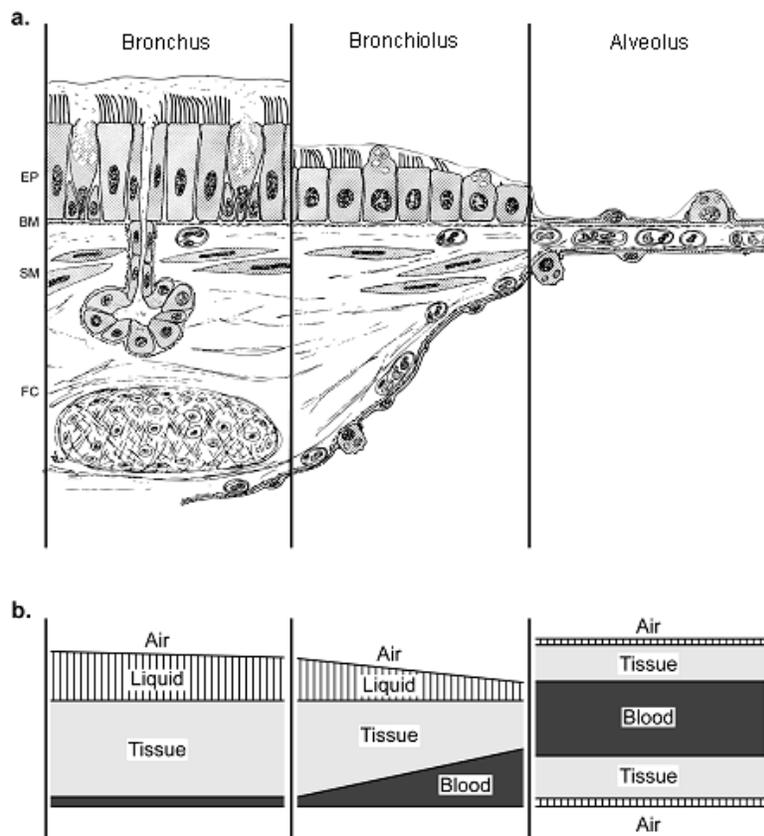
### 5.1.2.1. Summary of Findings from 2006 Ozone AQCD

13 Ozone dose can be examined by the chemical reactions or the products of these reactions that  
14 result from O<sub>3</sub> exposure. Since O<sub>3</sub> is chemically reactive with a wide spectrum of biomolecules, it is  
15 not feasible to delineate its many reaction products. Measurements of reaction formation have  
16 included either the loss of a specific molecule and appearance of plausible products, or the addition  
17 of O<sub>3</sub>-derived oxygen to biomolecules through the use of oxygen-18 labeling. In vitro exposure of  
18 ELF shows that O<sub>3</sub> disappearance from the gas phase depends on the characteristics of the ELF  
19 substrates (Hu et al., 1994, [041323](#); Postlethwait et al., 1998, [086754](#)).

20 To gain access to the underlying cellular compartments, O<sub>3</sub> must dissolve at the air-liquid  
21 interface of the airway surface and travel through the ELF layer. The ELF is comprised of the airway  
22 surface lining that includes the periciliary layer and overlying mucus layer, and the alveolar surface  
23 lining that includes the subphase of liquid and vesicular surfactant and the surfactant monolayer.  
24 There is a progressive decrease in ELF thickness and increase in interfacial surface with progression  
25 from the large airways to the alveolus, with the mucus coating becoming patchy in the distal  
26 conducting airways (Figure 5-1). Some cells, such as macrophages, may protrude into the gas phase,  
27 allowing for direct contact between O<sub>3</sub> and cell membranes. The progressive thinning in the ELF  
28 decreases the distance O<sub>3</sub> must travel to reach the cellular tissue layer. A computational fluid  
29 dynamics (CFD) model was able to predict experimentally measured O<sub>3</sub> uptake, but only with nasal  
30 mucus layer thickness considered (Cohen-Hubal et al., 1996, [043785](#)), reaffirming the importance of  
31 the resistance imparted by the ELF layer in dose and lesion patterns in the nasal passage.

32 Taking into account the high reactivity and low water solubility of O<sub>3</sub>, calculations suggest  
33 that O<sub>3</sub> will not penetrate ELF layers greater than 0.1 μm without being transformed to other more  
34 long-lived reactive species, thus initiating a reaction cascade (Pryor, 1992, [042725](#)). It follows that

1 the ELF should be considered an important target for O<sub>3</sub> toxicity in the airways. Experimental  
 2 support for this concept comes from several studies which measure the total oxygen-addition product  
 3 of O<sub>3</sub> reactions in the airways through the use of oxygen-18 labeled O<sub>3</sub>. High concentrations of O<sub>3</sub>  
 4 reaction products are found in the nasal lavage cells, bronchoalveolar lavage (BAL), mucus,  
 5 surfactant, and cells, and in the epithelial cells of the lower airways, providing evidence that O<sub>3</sub>  
 6 reacts at the air-liquid interface. Model calculations of the nasal cavity based on diffusion equations  
 7 and reaction rates of O<sub>3</sub> with model substrates predict an O<sub>3</sub> penetration distance (0.5 μm) less than  
 8 the thickness of the mucus layer (10 μm) (Santiago et al., 2001, [019841](#)). Thus, O<sub>3</sub> may cause injury  
 9 both by direct reaction with constituents of the lining layer and cells protruding from it, and by  
 10 initiating a reaction cascade that carries the oxidative burden deeper into the tissues.

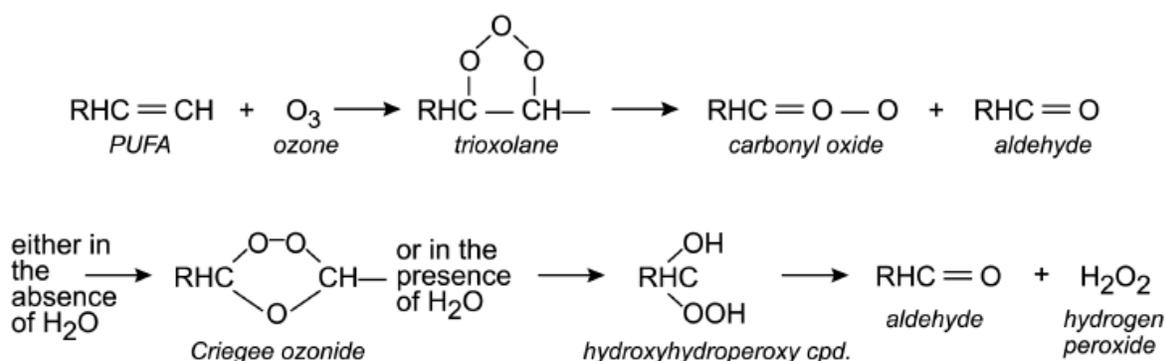


Source: Panel (a) reproduced with permission from McGraw-Hill (Weibel, 1980, [079848](#)).

**Figure 5-1. Structure of lower airways with progression from the large airways to the alveolus. □**  
**Panel (a) illustrates basic airway anatomy. Structures are epithelial cells, EP; basement membrane, BM; smooth muscle cells, SM; and fibrocartilaginous coat, FC. Panel (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.**

1 Ozone may interact with many of the components that make up the ELF including  
2 phospholipids, neutral lipids, free fatty acids, proteins, and low molecular weight antioxidants  
3 (Perez-Gil, 2008, [198890](#); Uppu et al., 1995, [076212](#)). The composition of ELF will vary as a  
4 function of anatomic location, species, strain, and likely exposure due to substrate depletion.  
5 Reduced substrates enter the ELF from the cellular layer or are transported across the cell layer from  
6 blood plasma, or can be regenerated from previously oxidized moieties that are reduced by other  
7 reduction reactions.

8 Ozone reacts with the double bond of lipids such as unsaturated fatty acids, a large component  
9 of ELF, to form stable and less reactive ozonide, aldehyde, and hydroperoxide reaction products via  
10 chemical reactions such as the Criegee ozonolysis mechanism (Figure 5-2) (Pryor et al., 1991,  
11 [042482](#)). Lipid ozonation products, such as the aldehydes hexanal, heptanal, and nonanal, have been  
12 recovered after O<sub>3</sub> exposure in human bronchial alveolar lavage fluid (BALF), rat BALF, isolated rat  
13 lung, and in vitro systems (Frampton et al., 1999, [040757](#); Postlethwait et al., 1998, [086754](#); Pryor et  
14 al., 1996, [082697](#)). It was estimated that 88% of the O<sub>3</sub> that does not come in contact with  
15 antioxidants will react with unsaturated fatty acids including phospholipids or neutral lipids in the  
16 ELF (Uppu et al., 1995, [076212](#)). Nonanal has been suggested as a relatively specific biomarker for  
17 O<sub>3</sub> exposure since the monounsaturated fatty acid parent compound, oleic acid, does not undergo  
18 autoxidation (Pryor et al., 1996, [082697](#)). Adducts of the aldehyde 4-hydroxynonenal were found in  
19 human alveolar macrophages after O<sub>3</sub> exposure (Hamilton et al., 1998, [086157](#)). Polyunsaturated  
20 fatty acid (PUFA) reactions are limited by the availability of O<sub>3</sub> since lipids are so abundant in the  
21 ELF. Yields of O<sub>3</sub>-induced aldehydes were increased by the decrease in other substrates such as  
22 ascorbic acid (AH<sub>2</sub>) (Postlethwait et al., 1998, [086754](#)). PUFA reactions may not generate sufficient  
23 bioactive materials to account for acute cell injury, however only modest amounts of products may  
24 be necessary to induce cytotoxicity (Postlethwait and Ultman, 2001, [196805](#); Postlethwait et al.,  
25 1998, [086754](#)).



Source: (U.S. EPA, 2006, [088089](#))

**Figure 5-2. Schematic overview of ozone interaction with PUFA in ELF and lung cells. It should be noted that not all secondary reaction products are shown.**

1 Cholesterol is the most abundant neutral lipid in human ELF. Reaction of cholesterol with O<sub>3</sub>  
 2 results in biologically active cholesterol products such as the oxysterols, β-epoxide and 6-oxo-3,5-  
 3 diol (Murphy and Johnson, 2008, [197792](#); Pulfer and Murphy, 2004, [076673](#); Pulfer et al., 2005,  
 4 [076663](#)). Product yields will depend on ozonolysis conditions, however cholesterol ozonolysis  
 5 products were formed in similar abundance to phospholipid-derived ozonolysis products in rat ELF  
 6 (Pulfer and Murphy, 2004, [076673](#)).

7 Antioxidant substances appear to be an important cellular defense against O<sub>3</sub>. The level and  
 8 type of antioxidant present in ELF varies between species, regions of the respiratory tract, and can be  
 9 altered by O<sub>3</sub> exposure. Endogenous antioxidants such as urate (UA), ascorbate (AH<sub>2</sub>), and reduced  
 10 glutathione (GSH) display high intrinsic reactivities toward O<sub>3</sub>, but do not possess equal O<sub>3</sub>  
 11 reactivity. In individual and in limited composite mixtures, UA was the most reactive antioxidant  
 12 tested, followed by AH<sub>2</sub> (Mudway and Kelly, 1998, [000273](#)). In human BALF samples, the mean  
 13 consumption of AH<sub>2</sub> was greater than UA (Mudway et al., 1996, [080730](#)). GSH was consistently less  
 14 reactive than UA or AH<sub>2</sub> (Kanofsky and Sima, 1995, [075973](#); Mudway and Kelly, 1998, [000273](#);  
 15 Mudway et al., 1996, [080730](#)). In a red cell based system, AH<sub>2</sub> augmented the in vitro uptake of O<sub>3</sub>  
 16 by sixfold as computed by the mass balance across the exposure chamber (Ballinger et al., 2005,  
 17 [076649](#)). In addition, O<sub>3</sub>-induced cell membrane oxidation required interactions with AH<sub>2</sub> and GSH,  
 18 but not UA or the vitamin E analog Trolox, however UA could block reactions of O<sub>3</sub> with AH<sub>2</sub>  
 19 (Ballinger et al., 2005, [076649](#)). The consumption of antioxidants by O<sub>3</sub> was linear with time and  
 20 positively correlated with initial substrate concentration and chamber O<sub>3</sub> concentration (Mudway and  
 21 Kelly, 1998, [000273](#); Mudway et al., 1996, [080730](#)). However, estimated in vitro O<sub>3</sub> uptake was not  
 22 proportional to the production of O<sub>3</sub>-derived aldehydes from red cell membrane exposure (Ballinger  
 23 et al., 2005, [076649](#)). Studies with rats exposed to O<sub>3</sub> show consumption of ascorbate that correlates

1 with O<sub>3</sub> exposure (Gunnison and Hatch, 1999, [087204](#); Gunnison et al., 1996, [080803](#); Vincent et al.,  
2 1996, [080778](#)).

3 ELF also contains proteins present in blood plasma as well as proteins secreted by surface  
4 epithelial cells. Ozone reactions with proteins have been studied by their in vitro reactions as well as  
5 reactions of their constituent amino acids (the most reactive of which are cysteine, histidine,  
6 methionine, tyrosine, and tryptophan). Ozone reaction with S-containing biomolecules has been  
7 shown to follow the following order: thiosulfate > ascorbate > cysteine > methionine > glutathione  
8 (Kanofsky and Sima, 1995, [075973](#)). Rate constants for the reaction of amino acids with O<sub>3</sub> vary  
9 between investigations due to differing reaction conditions and assumptions; however aliphatic  
10 amino acids consistently are very slow to react with O<sub>3</sub> (e.g., alanine: 25-100 moles/L/sec) (Hoigné  
11 and Bader, 1983, [625266](#); Ignatenko and Cherenkevich, 1985, [625265](#); Kanofsky and Sima, 1995,  
12 [075973](#); Pryor et al., 1984, [595130](#)). Uppu et al. (1995, [076212](#)) predicted that 12% of inhaled O<sub>3</sub>  
13 that does not react with antioxidants will react with proteins in the ELF, whereas 88% will react with  
14 PUFAs.

15 ELF exists as a complex mixture, thus it is important to look at O<sub>3</sub> reactivity in substrate  
16 mixtures. Individual antioxidant consumption rates decreased as the substrate mixture complexity  
17 increased (e.g., antioxidant mixtures and albumin addition) (Mudway and Kelly, 1998, [000273](#)).  
18 However, O<sub>3</sub> reactions with AH<sub>2</sub> predominated over the reaction with lipids, when exposed to  
19 substrate solution mixtures (Postlethwait et al., 1998, [086754](#)). It was suggested that O<sub>3</sub> may react  
20 with other substrates once AH<sub>2</sub> concentrations within the reaction plane fall sufficiently.  
21 Additionally, once AH<sub>2</sub> was consumed, the absorption efficiency diminished, allowing inhaled O<sub>3</sub> to  
22 be distributed to more distal airways (Postlethwait et al., 1998, [086754](#)). Multiple studies have  
23 concluded O<sub>3</sub> is more reactive with AH<sub>2</sub> and UA than with the weakly reacting GSH (or cysteine or  
24 methionine) or with amino acid residues and protein thiols (Cross et al., 1992, [625299](#); Kanofsky  
25 and Sima, 1995, [075973](#)).

### 5.1.2.2. Recent Publications

26 Further experiments on the reaction kinetics between O<sub>3</sub> and the antioxidants present in the  
27 ELF have been conducted since the last review. To quantify these reactions, Kermani, et al. (2006,  
28 [195643](#)) evaluated the interfacial exposure of aqueous solutions of UA, AH<sub>2</sub>, and GSH (50-200 μM)  
29 with O<sub>3</sub> (1-5 ppm). Similar to the results of Mudway and Kelly (1998, [000273](#)), this study found the  
30 hierarchy in reactivity between O<sub>3</sub> and these antioxidants to be UA>AH<sub>2</sub>>>GSH. UA and AH<sub>2</sub>  
31 shared a 1:1 stoichiometry with O<sub>3</sub>, whereas 2.5 moles of GSH were consumed per mole of O<sub>3</sub>.  
32 Using these stoichiometries, reaction rate constants were derived (5.8×10<sup>4</sup> moles/L/sec,  
33 5.5×10<sup>4</sup> moles/L/sec, and 57.5/M<sup>0.75</sup>/sec for the reaction of O<sub>3</sub> with UA, AH<sub>2</sub>, and GSH,  
34 respectively). These values are similar to those derived from data presented in Mudway and Kelly  
35 (1998, [000273](#)). Other studies reported reactive rate constants that are two to three orders of  
36 magnitude larger, however these studies used higher concentrations of O<sub>3</sub> and antioxidants under less

1 physiologically relevant experimental conditions (Giamalva et al., 1985, [595129](#); Kanofsky and  
2 Sima, 1995, [075973](#); Pryor et al., 1984, [595130](#)).

3 A series of studies used new techniques to investigate the reaction products resulting from  
4 initial air-liquid interface interactions of O<sub>3</sub> with ELF components (e.g., antioxidants and proteins) in  
5 ~1 millisecond (Enami et al., 2008, [195834](#); Enami et al., 2008, [195833](#); Enami et al., 2009, [197791](#);  
6 Enami et al., 2009, [195835](#); Enami et al., 2009, [195621](#)). Solutions of aqueous UA, AH<sub>2</sub>, GSH,  
7 α-tocopherol (α-TOH), and protein cysteines (CyS) were sprayed as microdroplets in O<sub>3</sub>(g)/N<sub>2</sub>  
8 mixtures at atmospheric pressure and analyzed by electrospray mass spectrometry. These recent  
9 studies demonstrated different reactivity toward AH<sub>2</sub>, UA, and GSH by O<sub>3</sub> in the gas phase  
10 compared to the liquid phase thus supporting the relevance of reactions between gas phase O<sub>3</sub> and  
11 ELF.

12 As was seen in previous studies (Kanofsky and Sima, 1995, [075973](#); Kermani et al., 2006,  
13 [195643](#)), the hierarchy of reactivity of these ELF components with O<sub>3</sub>(g) was determined to be AH<sub>2</sub>  
14 ≈ UA > CyS > GSH. There was some variance between the reaction rates and product formation of  
15 UA, AH<sub>2</sub>, and GSH with O<sub>3</sub>(g) as investigated by Enami et al. versus O<sub>3</sub>(aq) as described previously.  
16 UA was more reactive than AH<sub>2</sub> toward O<sub>3</sub>(aq), but in reactions with O<sub>3</sub>(g), these antioxidants have  
17 equivalent reactivity (Enami et al., 2008, [195834](#)). As O<sub>3</sub> is a kinetically slow one-electron acceptor  
18 but very reactive O-atom donor, products of the interaction of O<sub>3</sub> with UA, AH<sub>2</sub>, GSH, CyS, and α-  
19 TOH result from addition of *n* O-atoms (*n* = 1-4). These products included epoxides (e.g., U-O<sup>•</sup>),  
20 peroxides (e.g. U-O<sub>2</sub><sup>•</sup>), and ozonides (e.g., U-O<sub>3</sub><sup>•</sup>). For instance, GSH was oxidized to sulfonates  
21 (GSO<sub>3</sub><sup>-</sup>/GSO<sub>3</sub><sup>2-</sup>), not glutathione disulfide (GSSG) by O<sub>3</sub>(g) (Enami et al., 2009, [197791](#)). However,  
22 it is possible that other oxidative species are oxidizing GSH in vivo, since sulfonates are not detected  
23 in O<sub>3</sub> exposed ELF whereas GSSG is. This is also supported by the fact that O<sub>3</sub> is much less reactive  
24 with GSH than other antioxidants, such that < 3% of O<sub>3</sub> will be scavenged by GSH when in  
25 equimolar amounts with AH<sub>2</sub> (Enami et al., 2009, [197791](#)).

26 Ozonolysis product yields and formation were affected by pH. Acidified conditions (pH ≈  
27 3-4), such as those that may result from acidic particulate exposure or pathological conditions like  
28 asthma (pH ≈ 6), decreased the scavenging ability of UA and GSH for O<sub>3</sub>; such that at low pH, the  
29 scavenging of O<sub>3</sub> must be taken over by other antioxidants, such as AH<sub>2</sub> (Enami et al., 2008, [195834](#);  
30 Enami et al., 2009, [197791](#)). Also, under acidic conditions (pH ≈ 5), the ozonolysis products of AH<sub>2</sub>  
31 shifted from the innocuous dehydroascorbic acid to the more persistent products, ascorbate ozonide  
32 and threonic acid (Enami et al., 2008, [195833](#)). It is possible that the acidification of the ELF by  
33 acidic co-pollutant exposure will increase the toxicity of O<sub>3</sub> by preventing some antioxidant  
34 reactions and shifting the reaction products to more persistent compounds.

35 The ELF is a complex mixture of lipids, proteins, and antioxidants that serve as the first  
36 barrier and target for inhaled O<sub>3</sub>. The thickness of the lining fluid and mucus layer is an important  
37 determinant of the dose of O<sub>3</sub> to the tissues. The antioxidant substances present in the ELF appear in  
38 most cases to limit interaction of O<sub>3</sub> with underlying tissues and to prevent penetration of O<sub>3</sub> deeper

1 into the lung. However, new findings indicate that in some cases, the antioxidants might themselves  
 2 be participating in harmful reactions. The formation of toxic reaction products is likely related to the  
 3 concentration of antioxidants present and the quenching ability of the lining fluid. New findings also  
 4 emphasize the importance of gaseous O<sub>3</sub> acting at the air-liquid interface in initiating a reaction  
 5 cascade, and point out important distinctions in the reaction rates and product formation between  
 6 gaseous and aqueous O<sub>3</sub> reactivity toward airway antioxidants. In addition to the highly reactive O<sub>3</sub>,  
 7 secondary oxidation products formed in the aqueous phase might penetrate into the cells and cause  
 8 injury (Section 5.2).

### 5.1.3. Ozone Uptake

#### 5.1.3.1. Summary of Findings from the 2006 Ozone AQCD

9 Past AQCDs (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)) provide information on the  
 10 majority of literature relevant to understanding the state of the science in O<sub>3</sub> dosimetry. One method  
 11 of addressing the question of O<sub>3</sub> dosimetry is to measure the amount of O<sub>3</sub> removed from the air  
 12 stream during breathing (termed “uptake”). The percentage of the O<sub>3</sub> in the air stream that is  
 13 removed is termed “uptake efficiency.” Uptake studies have utilized both bolus and continuous O<sub>3</sub>  
 14 exposure techniques as well as dosimetry modeling to investigate uptake efficiency and distribution  
 15 of O<sub>3</sub> uptake between upper and lower respiratory tract regions. A number of studies that have  
 16 measured the fractional O<sub>3</sub> uptake efficiency of the human respiratory tract (F<sub>RT</sub>), upper airways  
 17 (F<sub>UA</sub>), and lower respiratory tract (F<sub>LRT</sub>) are presented in Table 5-1 as a review.

**Table 5-1. Human respiratory tract uptake efficiency data**

Reference	Mouth/Nose <sup>a</sup>	Inspiratory Flow (mL/s)	V <sub>T</sub> (mL)	f <sub>B</sub> (bpm) <sup>b</sup>	F <sub>RT</sub>	F <sub>UA</sub>	F <sub>LRT</sub>
<b>CONTINUOUS EXPOSURE</b>							
Gerrity et al. (1988, <a href="#">040899</a> )	M	509	832	18		0.40	0.91
	N	456	754	18		0.36	0.91
	M/N	350	832	12		0.41	0.93
	M/N	634	778	24		0.38	0.89
Gerrity et al. (1994, <a href="#">041314</a> ) <sup>c</sup>	M	1,360	1,650	25	0.81	0.37	0.43
	M	1,360	1,239	35	0.78	0.41	0.36
Gerrity et al. (1995, <a href="#">042785</a> )	Mouthpiece	330	825	12	0.91	0.27	0.95
Wiester et al. (1996, <a href="#">041280</a> )	M	539	631	16	0.76		
	N	514	642	16	0.73		
Santiago et al. (2001, <a href="#">019841</a> )	N	50				0.80 <sup>d</sup>	
	N	250				0.33	
Rigas et al. (2000, <a href="#">010454</a> )	Face mask	480	1,100	27.6	0.86		
<b>BOLUS EXPOSURE</b>							
Hu et al. (1992, <a href="#">042794</a> )	Mouthpiece	250			0.96	0.46	

Ultman et al. (1994, <a href="#">041746</a> )	Mouthpiece	250	500 <sup>e</sup>	15	0.30	
	Mouthpiece	250	500	15		0.47
Ultman et al. (2004, <a href="#">057197</a> )	M	490	450 <sup>e</sup>	32.7	0.87	
	M	517	574	27	0.91	
Nodelman and Ultman (1999, <a href="#">015112</a> )	Nasal Cannula	150	500	18		0.90
	Nasal Cannula	1,000	500	120		0.45
	Mouthpiece	150	500	18		0.80 0.95
	Mouthpiece	1,000	500	120		0.25 0.90

<sup>a</sup>M = mouth exposure by natural breathing; N = nasal exposure by natural breathing; M/N = pooled data from mouth and nasal exposure; mouthpiece = exposure by mouthpiece; F<sub>RT</sub> = total RT uptake; F<sub>UA</sub> = upper airway uptake; F<sub>LRT</sub> = lower RT uptake.

<sup>b</sup>f<sub>B</sub> is either measured or is computed from flows and V<sub>T</sub>.

<sup>c</sup>Total RT uptake reported by Gerrity et al. (1988, [040899](#)) and Gerrity et al. (1994, [041314](#)) did not include the contribution from UA uptake efficiency during expiration. The data include an expiratory UA contribution, assuming it equals inspiratory UA uptake efficiency.

<sup>d</sup>F<sub>UA</sub> from Santiago et al. (2001, [019841](#)) represents nasal absorption (F<sub>nose</sub>).

<sup>e</sup>V<sub>T</sub> is computed from flow and f<sub>B</sub>.

## Target Sites for Ozone Dose

1 A primary uptake site of O<sub>3</sub> delivery to the lungs is believed to be the centriacinar region  
2 (CAR). The CAR refers to the zone at the junction of the conducting airways and the gas exchange  
3 region. This area is also considered the proximal alveolar region (PAR) and is defined as the first  
4 generation distal to the terminal bronchioles. Contained within the CAR, the respiratory bronchioles  
5 were confirmed as the site receiving the greatest O<sub>3</sub> dose (<sup>18</sup>O mass/lung weight) in resting O<sub>3</sub>  
6 exposed rhesus monkeys, when not considering the nose (Plopper et al., 1998, [087203](#)).  
7 Furthermore, the greatest cellular injury occurred in the vicinity of the respiratory bronchioles and  
8 was dependent on the delivered O<sub>3</sub> dose to these tissues. However, <sup>18</sup>O label was detected to a lesser  
9 extent in other regions of the tracheobronchial airway tree, showing that O<sub>3</sub> is delivered to these  
10 compartments as well, resulting in a smaller dose. Models predict that the net O<sub>3</sub> dose (O<sub>3</sub> flux to air-  
11 liquid interface) gradually decreases distally from the trachea toward the end of the tracheobronchial  
12 region (TB) and then rapidly decreases in the pulmonary region (Miller et al., 1985, [040307](#)).  
13 However, the tissue dose (O<sub>3</sub> flux to liquid-tissue interface) is low in the trachea, increases to a  
14 maximum in the terminal bronchioles and the CAR, and then rapidly decreases distally into the  
15 pulmonary region. These models are limited by the exclusion of the upper respiratory tract as well as  
16 reactions occurring between ELF constituents and O<sub>3</sub> after the 16th generation, representing the  
17 CAR region (Miller et al., 1985, [040307](#)).

## Nasopharyngeal Removal and Dose of Ozone

18 In both animals and humans, about 50% of the absorbed O<sub>3</sub> is removed in the head (nose,  
19 mouth, and pharynx), about 7% in the larynx/trachea, and about 43% in the lungs (Hatch et al., 1989,  
20 [041799](#); Hu et al., 1992, [042794](#)). The nasopharyngeal region provides a defense against O<sub>3</sub> entering  
21 the lungs by removing half of the inhaled O<sub>3</sub> from the airstream. The limiting factors in nasal O<sub>3</sub>  
22 uptake are simultaneous diffusion and chemical reaction of O<sub>3</sub> in the nasal ELF layer (Santiago et al.,  
23 2001, [019841](#)). The lining layer in the nose is thicker than in the lungs, but, like for the lungs,

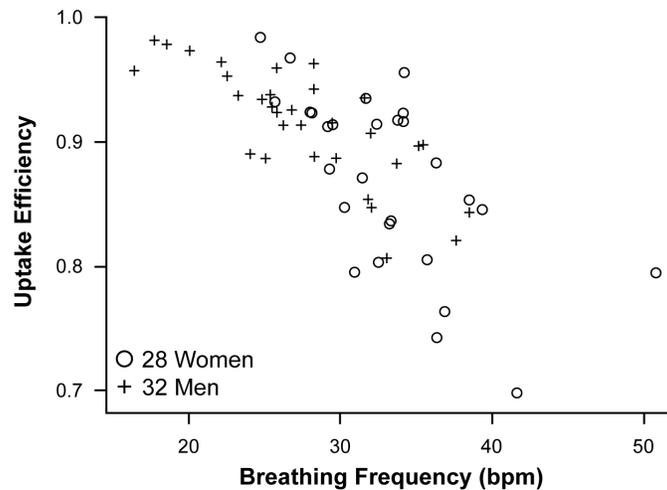
1 mathematical estimates predict that O<sub>3</sub> penetrates less than the thickness of the ELF layer leaving the  
2 reaction products as likely the agents damaging the nasal tissue. The percentage of O<sub>3</sub> taken up is  
3 inversely related to flow rate and weakly related to inlet O<sub>3</sub> concentration. It was hypothesized that  
4 the nonlinear reaction kinetics of the nose could result from the depleting substrates in the nasal ELF  
5 becoming the limiting factor of the reaction (Santiago et al., 2001, [019841](#)).

6 Uptake efficiencies have been calculated for various segments of the upper airways  
7 (Table 5-1). Gerrity et al. (1995, [042785](#)) reported unidirectional uptake efficiencies of O<sub>3</sub> inhaled  
8 from a mouthpiece of 17.6% from the mouth to vocal cords, 12.8% from the vocal cords to the upper  
9 trachea (totaling 27.0%), 11.5% from the upper trachea to the main bifurcation carina (totaling  
10 35.5%), and essentially zero between the carina and the bronchus intermedius (totaling 32.5%).  
11 These values are lower than those calculated by Hu et al. (1992, [042794](#)) that reported uptake  
12 efficiencies of 21, 36, 44, and 46% between the mouth and the vocal cords, the upper trachea, the  
13 main bifurcation carina, and the bronchus intermedius, respectively. The lower efficiencies seen in  
14 Gerrity et al. (1995, [042785](#)) may have resulted from the mouthpiece scrubbing O<sub>3</sub> from the breath  
15 during inhalation. Overall, the nasopharyngeal region removes half of the inhaled O<sub>3</sub> by reactions in  
16 the nasal ELF. The exact uptake efficiency will change due to variations in flow rate and inhaled  
17 concentration.

### **Pulmonary Ozone Uptake and Dose**

18 O<sub>3</sub> uptake in rats is approximately 54% efficient (Hatch et al., 1989, [041799](#)), while in humans  
19 at rest it ranges from 80-95% efficient (Hu et al., 1992, [042794](#)). Approximately 43% of inhaled O<sub>3</sub>  
20 is absorbed in the lungs of both humans and animals. Uptake efficiency is affected by changes in a  
21 number of variables, including tidal volume (V<sub>T</sub>), breathing frequency (f<sub>B</sub>), exposure time, minute  
22 volume, and O<sub>3</sub> concentration. Simulations from the Overton et al. (1996, [080733](#)) single-path  
23 anatomical respiratory tract model, where the upper and lower respiratory tracts were modeled but  
24 uptake by the upper airways was not considered, predicted that fractional uptake and PAR O<sub>3</sub> dose  
25 increased with V<sub>T</sub>. Likewise, experimental studies found that O<sub>3</sub> uptake is positively correlated with  
26 changes in V<sub>T</sub> (Gerrity et al., 1988, [040899](#); Ultman et al., 2004, [057197](#)). Also, O<sub>3</sub> exposure leads to  
27 a reflex mediated increase in f<sub>B</sub> and reduction in V<sub>T</sub>, hypothesized to be protective by decreasing the  
28 dose delivered in the lung (Gerrity et al., 1994, [041314](#)). While maintaining a constant minute  
29 volume, a decrease in V<sub>T</sub> will result in an increase in f<sub>B</sub>. Nasal flow rate (Santiago et al., 2001,  
30 [019841](#)) and f<sub>B</sub> are inversely related to O<sub>3</sub> uptake, such that an increase in f<sub>B</sub> will decrease uptake  
31 efficiency (Figure 5-3) (Gerrity et al., 1988, [040899](#); Ultman et al., 2004, [057197](#); Wiester et al.,  
32 1996, [041280](#)). Modeling also predicted a decrease in fractional uptake with increased f<sub>B</sub>, but an  
33 increase in PAR dose with increased f<sub>B</sub> (Overton et al., 1996, [080733](#)). Similarly, increased f<sub>B</sub> (80 -  
34 160 bpm) and rapid shallow breathing in rats resulted in a decrease in midlevel tracheal <sup>18</sup>O content  
35 and an increase in <sup>18</sup>O content in the mainstem bronchi (Alfaro et al., 2004, [053551](#)). This  
36 dependence may be a result of frequency-induced alterations in contact time that affects the first-

1 order absorption rate for O<sub>3</sub> (Postlethwait et al., 1994, [044219](#)). Also, an association with O<sub>3</sub> uptake  
2 efficiency was found with minute volume and exposure time.

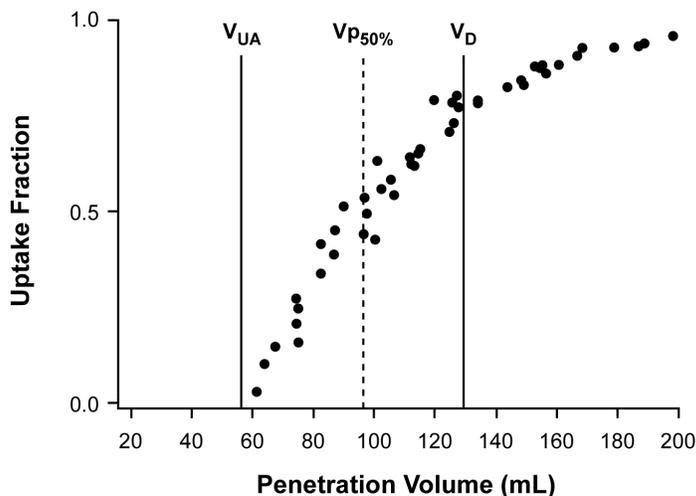


Source: Used with permission from Health Effects Institute, Ultman et al. (2004, [057197](#))

**Figure 5-3. Total ozone uptake efficiency as a function of breathing frequency at a minute ventilation of 30 L/min. Subjects breathed 0.25 ppm ozone oronasally through a breathing mask.**

**The uptake efficiency was well correlated with breathing frequency ( $r = -0.723$ ,  $p < 0.001$ ) and tidal volume (not illustrated;  $r = 0.490$ ,  $p < 0.001$ ).**

3 Increasing flow leads to deeper penetration of O<sub>3</sub> into the lung, such that a smaller fraction of  
4 O<sub>3</sub> is absorbed in the upper airways and shifts uptake to the central and lower airways and  
5 respiratory airspaces (Hu et al., 1994, [041323](#); Nodelman and Ultman, 1999, [015112](#); Ultman et al.,  
6 1994, [041746](#)). Hu et al. (1994, [041323](#); Ultman et al., 1994, [041746](#)) found that O<sub>3</sub> absorption  
7 increases relative to the respiratory tract penetration volume (V<sub>p</sub>) of a bolus O<sub>3</sub> dose (Figure 5-4).  
8 Ozone uptake efficiency and V<sub>p</sub> are not affected by bolus O<sub>3</sub> concentration (Gerrity et al., 1988,  
9 [040899](#); Hu et al., 1992, [042794](#); Kabel et al., 1994, [095597](#)), indicating that O<sub>3</sub> uptake is a linear  
10 absorption process, where the diffusion and chemical reaction rates of O<sub>3</sub> are proportional to the O<sub>3</sub>  
11 concentration. This relationship was not true for nasal cavity uptake, which was proportional to O<sub>3</sub>  
12 concentration in the inlet air (Santiago et al., 2001, [019841](#)), or in exercising individuals, where  
13 uptake efficiency had a weak but significant negative dependence on O<sub>3</sub> concentration (Rigas et al.,  
14 2000, [010454](#)). Overall O<sub>3</sub> inhalation uptake is over 80% efficient, but the exact efficiency that  
15 determines how much O<sub>3</sub> is available at longitudinally distributed compartments in the lung is  
16 sensitive to changes in V<sub>T</sub>, f<sub>B</sub>, and exposure time. Increased f<sub>B</sub> will shift the O<sub>3</sub> uptake from the upper  
17 airways to the central airways and respiratory airspaces.



Source: Adapted with permission from Health Effects Institute, Ultman et al. (2004, [057197](#))

**Figure 5-4. Ozone uptake fraction as a function of volumetric penetration ( $V_p$ ) in a representative subject.** Each point represents the ozone uptake of a bolus inspired through a mouthpiece by the subject. The volumes,  $V_{UA}$  and  $V_D$ , are the volume of the upper airways and anatomical dead space, respectively, and  $V_{p50\%}$  is the  $V_p$  at which 50% of the inspired bolus was absorbed. In 47 healthy subjects, Ultman et al. (2004, [057197](#)) found that  $V_{p50\%}$  was well correlated with  $V_D$  and better correlated with the volume of the conducting airways, i.e.,  $V_D$  minus  $V_{UA}$ .

### Mode of Breathing

1 Ozone uptake and distribution is highly sensitive to the mode of breathing. Variability in  
 2 conducting airways volume had a weaker influence on  $O_3$  absorption during nasal breathing  
 3 compared to oral breathing. This could be a result of  $O_3$  scrubbing in the nasal passageways that are  
 4 bypassed by oral breathing. Studies by Ultman and colleagues using bolus inhalation demonstrate  
 5 that  $O_3$  uptake fraction is greater during nasal breathing than during oral breathing at each  $V_p$  (Kabel  
 6 et al., 1994, [095597](#); Nodelman and Ultman, 1999, [015112](#); Ultman et al., 1994, [041746](#)). However,  
 7 oral breathing results in deeper penetration of  $O_3$  into the lung with a higher absorbed fraction in the  
 8 pharyngeal, lower airways, and respiratory airways (Nodelman and Ultman, 1999, [015112](#)). Similar  
 9 results were obtained from  $O_3$  uptake studies in dogs (Yokoyama and Frank, 1972, [039756](#));  
 10 however earlier human studies suggest that oral or oronasal breathing results in a higher  $O_3$  uptake  
 11 efficiency than nasal breathing (Gerrity et al., 1988, [040899](#); Wiester et al., 1996, [041280](#)). These  
 12 human studies measured total respiratory tract absorption after continuous  $O_3$  exposure using a  
 13 pharyngeal sampling tube, which may decrease sensitivity and lead to measurement errors.

### Interindividual Variability

14 Similarly exposed individuals vary in the amount of actual dose received with intersubject  
 15 differences in fractional  $O_3$  uptake by the respiratory tract accounting for the majority of total

1 variation in O<sub>3</sub> uptake efficiency (Bush et al., 1996, [080763](#); Rigas et al., 2000, [010454](#); Santiago et  
2 al., 2001, [019841](#)). Interindividual variability accounted for between 10-50% of the absolute  
3 variability in O<sub>3</sub> uptake measurements (Rigas et al., 2000, [010454](#); Santiago et al., 2001, [019841](#)).  
4 When concentration, time, and minute ventilation are held constant, fractional absorption ranges  
5 from 0.80 to 0.91 (Rigas et al., 2000, [010454](#)). It has been hypothesized that interindividual variation  
6 in O<sub>3</sub> uptake is the result of substituting a dose surrogate, such as exposure concentration or inhaled  
7 dose, for the actual O<sub>3</sub> dose delivered to the tissues.

8 Variability in local dose may be attributed to differences in the pulmonary physiology. Since  
9 the conducting airways (CA) remove the majority of inhaled O<sub>3</sub> before it reaches the gas exchange  
10 region, the volume and surface area of the upper airways will influence O<sub>3</sub> uptake. Models predict  
11 that fractional O<sub>3</sub> uptake and PAR dose (flux of O<sub>3</sub> to the PAR surfaces divided by exposure  
12 concentration) increase with decreasing TB volume and decreasing TB region expansion. On the  
13 contrary, alveolar expansion had minimal effect on uptake efficiency as little O<sub>3</sub> reaches the  
14 peripheral lung (Bush et al., 2001, [016665](#); Overton et al., 1996, [080733](#)). Ozone uptake is virtually  
15 complete by the time O<sub>3</sub> reaches the alveolar spaces of the lung (Postlethwait et al., 1994, [044219](#)).  
16 Experimental studies have found that differences in CA volumes may account for 75% of the  
17 variation in absorption between subjects (Ultman et al., 2004, [057197](#)). In support of this concept,  
18 regression analysis showed that O<sub>3</sub> absorption is positively correlated with anatomical dead space  
19 (V<sub>D</sub>) and CA volume (i.e., V<sub>D</sub> minus V<sub>UA</sub>), but not total lung capacity (TLC), forced vital capacity  
20 (FVC), or functional residual capacity (FRC) (Bush et al., 1996, [080763](#); Hu et al., 1994, [041323](#);  
21 Postlethwait et al., 1994, [044219](#); Ultman et al., 2004, [057197](#)). Variability in V<sub>D</sub> is correlated more  
22 with the variability in the CA than the upper airways. Similarly, uptake was correlated with changes  
23 in individual bronchial cross-sectional area, indicating that changes in cross-sectional area available  
24 for gas diffusion are related to overall O<sub>3</sub> retention (Reeser et al., 2005, [195718](#); Ultman et al., 2004,  
25 [057197](#)). These studies provide support to the pulmonary physiology, especially the CA volume and  
26 surface area, playing a key role in variability of O<sub>3</sub> uptake between individuals.

27 When absorption data between genders is normalized to V<sub>p</sub>/V<sub>D</sub>, then the variability attributed  
28 to gender differences is no longer distinguishable (Bush et al., 1996, [080763](#)). A physiologically  
29 based pharmacokinetic (PBPK) model simulating O<sub>3</sub> uptake indicates that regional extraction of O<sub>3</sub>  
30 is relatively insensitive to age, but extraction per unit surface area is two- to eightfold higher in  
31 infants compared to adults, due to the fact that children under age 5 have much a much smaller  
32 airway surface area in the extrathoracic (nasal) and pulmonary regions (Sarangapani et al., 2003,  
33 [054581](#)).

### **Correlation of Dose and Response**

34 Two studies have investigated the correlation of O<sub>3</sub> uptake with the pulmonary function  
35 responses to O<sub>3</sub> exposure (Gerrity et al., 1994, [041314](#); Reeser et al., 2005, [195718](#)). These studies  
36 found that the large subject-to-subject variability in %ΔFEV<sub>1</sub> response to O<sub>3</sub> does not appear to have

1 a dosimetric explanation. Reeser et al. (2005, [195718](#)) found no significant relationship between  
2  $\% \Delta FEV_1$  and fractional absorption of  $O_3$  using the bolus method. Contrary to previous findings, the  
3 percent change in dead space volume of the respiratory tract ( $\% \Delta V_D$ ) did not correlate with  $O_3$   
4 uptake, possibly due to the contraction of dead space caused by airway closure. Gerrity et al. (1994,  
5 [041314](#)) found that intersubject variability in  $FEV_1$  and airway resistance was not related to  
6 differences in the  $O_3$  dose delivered to the lower airways, whereas minute ventilation was predictive  
7 of  $FEV_1$  decrement. No study has yet demonstrated that subjects show a consistent pattern of  $O_3$   
8 retention when re-exposed over weeks of time, as has been shown to be the case for the  $FEV_1$   
9 response, or that within-subject variation in  $FEV_1$  response is related to fluctuations in  $O_3$  uptake.

10 On the contrary, cellular injury and inflammation have been found to correlate with the site-  
11 specific  $O_3$  dose. Contained within the CAR, the respiratory bronchioles were confirmed as the site  
12 receiving the greatest  $O_3$  dose ( $^{18}O$  mass/lung weight) and sustained the greatest cellular injury in  $O_3$   
13 (0.4 and 1.0 ppm) exposed resting rhesus monkeys (Plopper et al., 1998, [087203](#)). The respiratory  
14 bronchioles, having the highest concentration of local  $O_3$  dose, were also the site of significant GSH  
15 reduction.

### Co-Pollutant and Sequential Ozone Exposure

16 Previous continuous  $O_3$  exposure (0.12 or 0.36 ppm) decreased bolus  $O_3$  uptake, possibly due  
17 to depletion of compounds able to react with  $O_3$  (Asplund et al., 1996, [082505](#); Rigas et al., 1997,  
18 [083602](#)). Conversely,  $O_3$  (0.36 ppm) bolus uptake was increased with prior  $NO_2$  (0.36 or 0.72 ppm)  
19 or  $SO_2$  (0.36 ppm) exposure (Rigas et al., 1997, [083602](#)). It was hypothesized that this increased  
20 fractional absorption could be due to increased production of reactive substrates in the ELF due to  
21 oxidant-induced airway inflammation.

### Physical Activity

22 Exercise increases the overall exposure of the lung due in most part to the increased volume of  
23 air passing through the lung. Exercise increases breathing frequency and flow rate. According to  
24 present thinking, doubling minute ventilation is assumed to lead to a doubling of dose, however, the  
25 linearity of the dose relative to ventilation relationship has not been carefully studied. A recent study  
26 by Sawyer et al. (2007, [195142](#)) showed that doubling minute ventilation led to only a 1.6-fold  
27 higher dose of  $O_3$  in the lower airway. In addition to increasing the quantity of  $O_3$  in the lung,  
28 exercise also has been shown to lead to a switch to oronasal breathing. By increasing flow to what is  
29 common in moderate exercise, the upper airways absorbed a smaller fraction of the  $O_3$  (~0.50 at  
30 quiet breathing to 0.10 at exercise); however, the trachea and more distal conducting airways  
31 received higher doses than during quiet breathing (0.65 absorbed in the lower conducting airways,  
32 and 0.25 absorbed in the respiratory zone) (Hu et al., 1994, [041323](#)). The same shift in the  $O_3$  dose  
33 distribution to deeper into the lung occurred in other studies mimicking the effects of exercise  
34 (Nodelman and Ultman, 1999, [015112](#)).

### 5.1.3.2. Recent Publications

1 Few new studies have investigated the uptake of O<sub>3</sub> in the respiratory tract since the end of the  
2 last O<sub>3</sub> assessment (U.S. EPA, 2006, [088089](#)). The studies that have been conducted agree with the  
3 results presented above and do not change the dosimetry conclusions of the last document.

4 Past studies have shown that O<sub>3</sub>-induced epithelial damage to the lung occurs with a  
5 reproducible pattern of severity between daughter branches of individual bifurcations that is  
6 dependent on the O<sub>3</sub> concentration-time profile of the inhaled gas. A 3-dimensional computational  
7 fluid dynamics model was created to investigate the dose-response relationship leading to the  
8 distribution of damage in a single airway bifurcation (Taylor et al., 2007, [195717](#)). The model  
9 consisted of one parent branch and two symmetrical daughter branches with a branching angle of 90°  
10 and a sharp carinal ridge. Various flow scenarios were simulated using Reynolds numbers (Re)  
11 ranging from 100 to 500. The Re that corresponds to a certain airway generation is dependent upon  
12 both lung size and minute ventilation, such that the range in Re from 100-500 would encompass  
13 generations 1-5, 3-7, and 6-10 for an adult during quiet breathing, light exertion, and heavy exercise,  
14 respectively, whereas the same Re range corresponds to generations 0-4, 1-6, and 4-8 for a 4-year-  
15 old child. Consistent with early physical models of Schroter and Sudlow (1969, [071359](#)), the model  
16 predicted that during inspiration, the velocity and O<sub>3</sub> concentration distribution were axisymmetric  
17 throughout the parent branch, but skewed towards the inner wall within the daughter branches.  
18 During expiration, the model predicted that the velocity and O<sub>3</sub> concentration distribution was  
19 slightly skewed towards the outer walls of the daughter branches. Hot spots of wall flux existed at  
20 the carina during inspiration and expiration with Re >100. Additional hot spots were found during  
21 expiration on the parent branch wall downstream of the branching region.

22 Past studies investigating nasal uptake of O<sub>3</sub> have shown that the nose partially protects the  
23 rest of the respiratory tract from damage from inspired O<sub>3</sub> (Gerrity et al., 1988, [040899](#); Santiago et  
24 al., 2001, [019841](#)). Sawyer et al. (2007, [195142](#)) further investigated nasal uptake of O<sub>3</sub> in healthy  
25 adults during exercise. Fractional O<sub>3</sub> uptake, acoustic rhinometry (AR), and nasal NO measurements  
26 were taken on ten adults (8 W, 2 M) exposed to 0.2 ppm O<sub>3</sub> before and after moderate exercise at  
27 two flow rates (10 and 20 L/min). The percent nasal uptake of O<sub>3</sub> was ~50% greater at 10 L/min  
28 compared to 20 L/min both pre- and postexercise. However, the inhaled O<sub>3</sub> delivery rate to the lung  
29 (i.e., flow rate X [O<sub>3</sub> ppm] X nasal O<sub>3</sub> penetration) was 1.6-fold greater at the higher flow than at the  
30 lower flow (2.5 compared to 0.9 ppm·L/min). Exercise did not affect O<sub>3</sub> uptake at either flow rate,  
31 but did significantly increase nasal volume (V<sub>n</sub>) and AR measurements of nasal cross-sectional area  
32 (MCA, CSA2, and CSA3) (p < 0.05). Conversely, exercise decreased nasal resistance (R<sub>n</sub>) (p < 0.01)  
33 and NO production (p > 0.05). The change in V<sub>n</sub> and CSA2:MCA ratio was correlated with the  
34 percent change in nasal uptake, however the overall effect was small and sensitive to elimination of  
35 outliers and gender segregation.

36 Smoking history, with its known increase in mucus production, was not found to significantly  
37 affect the fractional uptake of a bolus dose of O<sub>3</sub> in apparently healthy smokers with limited smoking

1 history (Bates et al., 2009, [195727](#)). Despite similar internal O<sub>3</sub> dose distribution, the smokers  
2 exhibited greater pulmonary responses to O<sub>3</sub> bolus exposures, measured as FEV<sub>1</sub> decrements and  
3 increases in the normalized slope of the alveolar plateau (S<sub>N</sub>). This is contrary to previous studies  
4 conducted in smokers with a greater smoking history that found decreased O<sub>3</sub> induced decrements in  
5 FEV<sub>1</sub> in smokers (Emmons and Foster, 1991, [042430](#); Frampton et al., 1997, [082692](#)).

6 Recent studies have reiterated the importance of intersubject variation in O<sub>3</sub> uptake. The  
7 intersubject variability in nasal O<sub>3</sub> uptake determined by Sawyer et al. (2007, [195142](#)) ranged from  
8 26.8 to 65.4% (pre- and postexercise). A second study investigating the use of the CO<sub>2</sub> expirogram to  
9 quantify pulmonary responses to O<sub>3</sub> found that intersubject variability accounted for 50% of the  
10 overall variance in the study (Taylor et al., 2006, [195731](#)).

11 In summary, O<sub>3</sub> uptake efficiency is sensitive to a number of factors. As discussed before, the  
12 characteristics of the ELF layer is a key determinant in the dose of O<sub>3</sub> that reaches the tissue layer.  
13 Fractional absorption will decrease with increased flow and increase proportional to V<sub>T</sub>. Decreased  
14 uptake efficiency due to increased f<sub>B</sub> and oronasal breathing, as occurs during exercise, will shift the  
15 O<sub>3</sub> dose distribution deeper and lead to a greater dose to the lower respiratory tract. Individual total  
16 airway O<sub>3</sub> uptake efficiency is also sensitive to large changes in O<sub>3</sub> concentration, exposure time, and  
17 V<sub>E</sub>. Major sources of variability in absorption of O<sub>3</sub> include O<sub>3</sub> concentration, exposure time,  
18 breathing frequency, minute volume, and tidal volume, but the interindividual variation is the  
19 greatest source of variability uptake efficiency. However, to this date, studies have failed to show  
20 that the large differences in biological response between subjects (FEV<sub>1</sub>, BAL cell inflammatory  
21 response, etc.) are explainable by the differences in O<sub>3</sub> uptake. Recent studies have provided  
22 evidence for hot spots of O<sub>3</sub> flux around bifurcations in the airways.

#### 5.1.4. Species Homology, Sensitivity, and Animal-to-Human Dose Extrapolation

##### 5.1.4.1. Summary of Findings from 2006 Ozone AQCD

23 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) discussed the suitability of animal models for  
24 comparison with human O<sub>3</sub> exposure and concluded that the acute and chronic functional responses  
25 of laboratory animals to O<sub>3</sub> appear qualitatively homologous to human responses. Thus, animal  
26 studies can provide important data in determining cause-effect relationships between exposure and  
27 health outcome that would be impossible to collect in human studies. Still, care must be taken when  
28 comparing quantitative dose-response relationships in animal models to humans due to obvious  
29 interspecies differences.

30 Physiological and anatomical differences exist between experimental species. Primates are  
31 oronasal breathers with a dichotomous branching lung structure, while rodents are obligate nasal  
32 breathers with a monopodial branching lung structure. In addition, rodents have fewer terminal  
33 bronchioles, the major site of O<sub>3</sub> uptake, compared to humans or canines (McBride, 1992, [078532](#)).

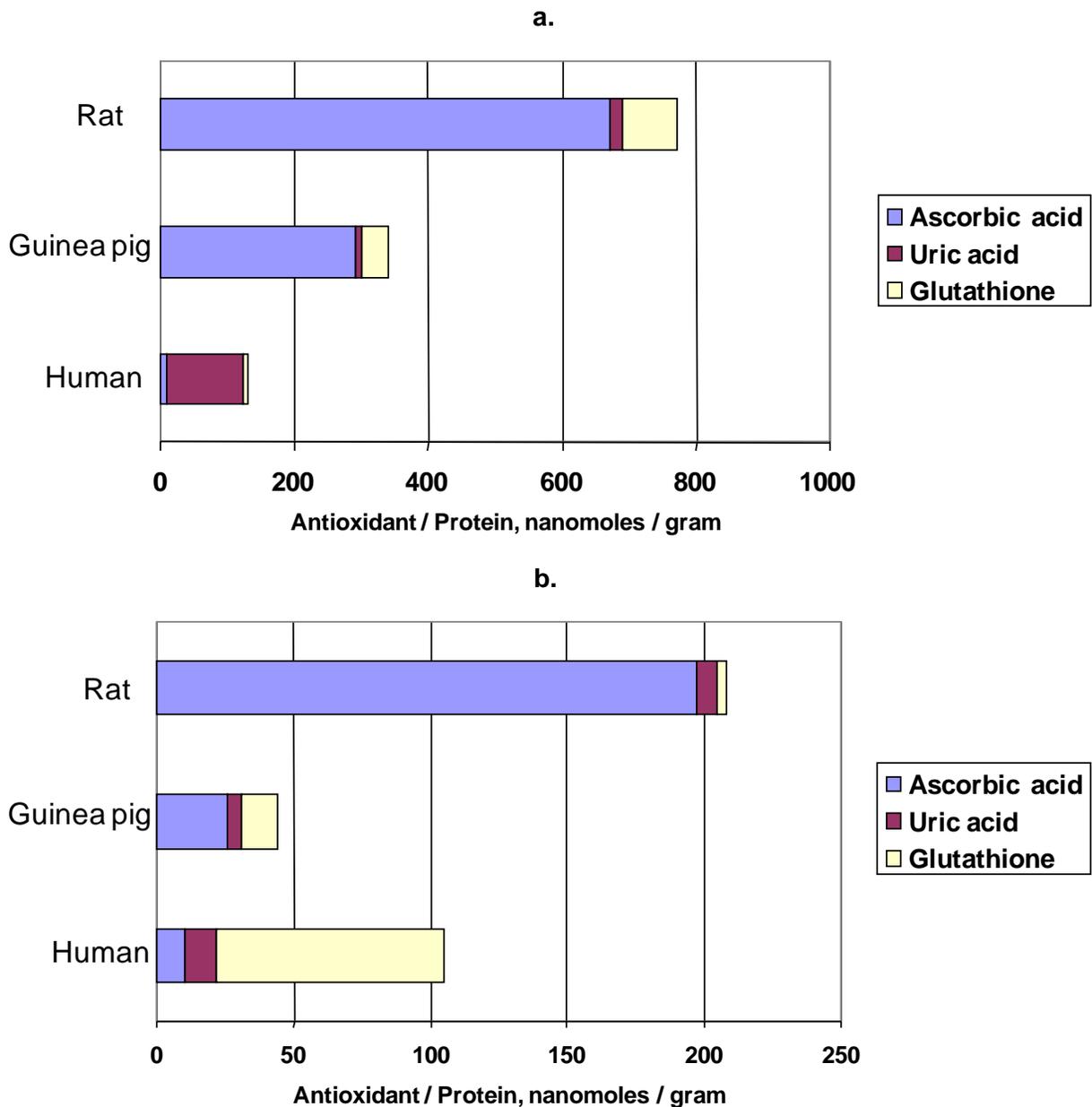
1 Past studies of the effect of body size on resting oxygen consumption also suggest that rodents inhale  
2 more volume of air per lung mass than primates. These distinctions as well as differences in nasal  
3 structure between primates and rodents could affect the site and amount of O<sub>3</sub> uptake. Also, because  
4 of their higher body surface to volume ratio, rodents can rapidly lower body temperature during  
5 exposure leading to lowered O<sub>3</sub> dose and toxicity (Iwasaki et al., 1998, [086165](#); Slade et al., 1997,  
6 [082708](#); Watkinson et al., 2003, [050547](#)). In addition to lowering the O<sub>3</sub> dose to the lungs, this  
7 hypothermic response may cause: (1) lower metabolic rate, (2) altered enzyme kinetics, and (3)  
8 altered membrane function. The thermoregulatory mechanisms also may affect disruption of heart  
9 rate which may lead to: (1) decreased cardiac output (CO), (2) lowered blood pressure (BP), and (3)  
10 decreased tissue perfusion (Watkinson et al., 2003, [050547](#)). These responses have not been  
11 observed in humans except at very high exposures, thus further complicating extrapolation of effects  
12 from animals to humans.

13 Sensitivity to health effects from O<sub>3</sub> varies between and within species, as well as between  
14 endpoints. Rodents appear to have a slightly higher tachypneic response to O<sub>3</sub> and are less sensitive  
15 to changes in pulmonary function test than humans (U.S. EPA, 1996, [017831](#)). However, rats do  
16 experience attenuation of pulmonary function and tachypneic ventilatory responses, similar to  
17 humans (Wiester et al., 1996, [080829](#)). Hatch et al. (1986, [040472](#)) reported that guinea pigs were  
18 the most responsive to O<sub>3</sub>-induced inflammatory cell and protein influx. Rabbits were the least  
19 responsive and rats, hamsters, and mice were intermediate responders. Further analysis of this study  
20 by Miller et al. (1988, [041545](#)) found that the protein levels in guinea pigs increased more rapidly  
21 with predicted pulmonary tissue dose than in rats and rabbits. Alveolar macrophages isolated from  
22 guinea pigs and humans mounted similar qualitative and quantitative cytokine responses to in vitro  
23 O<sub>3</sub> (0.1-1.0 ppm for 60 minutes) exposure (Arsalane et al., 1995, [077430](#)).

24 Humans and animal models are similar in the pattern of regional O<sub>3</sub> dose, but absolute values  
25 differ. Hatch et al. (1994, [038953](#)) reported that exercising humans exposed to oxygen-18 labeled O<sub>3</sub>  
26 (0.4 ppm) accumulated 4-5 times higher concentrations of O<sub>3</sub> reaction product in BAL cells,  
27 surfactant and protein fractions compared to resting rats similarly exposed (0.4 ppm). It was  
28 necessary to expose resting rats to 2 ppm O<sub>3</sub> to achieve the same BAL accumulation of <sup>18</sup>O reaction  
29 product that was observed in humans exposed to 0.4 ppm with intermittent heavy exercise. The  
30 concentration of <sup>18</sup>O reaction product in BAL paralleled the accumulation of BAL protein and  
31 cellular effects of the O<sub>3</sub> exposure observed such that these responses to 2.0 ppm O<sub>3</sub> were similar to  
32 those of the 0.4 ppm O<sub>3</sub> in exercising humans.

33 As O<sub>3</sub> absorption and activity relies on ELF antioxidant substances as described in Section 5.2,  
34 variability in antioxidant concentrations and metabolism between species may affect dose and O<sub>3</sub>-  
35 induced health outcomes. Guinea pigs and mice have a lower basal activity of GSH transferase and  
36 GSH peroxidase, and lower vitamin E levels in the lung compared to rats (Ichinose et al., 1988,  
37 [041805](#); Sagai et al., 1987, [041704](#)). Nasal lavage fluid analysis shows that humans have a higher  
38 proportion of their nasal antioxidants as UA and low levels of AH<sub>2</sub> whereas mice, rats, or guinea pigs

1 have high levels of AH<sub>2</sub> and undetectable levels of UA (Figure 5-5a). GSH is not detected in the  
2 nasal lavage of most of these species, but is present in monkey nasal lavage. Guinea pigs and rats  
3 have a higher antioxidant to protein ratio in nasal lavage and BAL fluid than humans (Hatch, 1992,  
4 [043901](#)). The BALF profile differs from the nasal lavage (Figure 5-5b). Humans have a higher  
5 proportion of GSH and less AH<sub>2</sub> making up their BALF content compared to the guinea pigs and rats  
6 (Hatch, 1992, [043901](#); Slade et al., 1993, [042865](#)). Similar to the nose, rats have the highest  
7 antioxidant to protein mass ratio found in BALF (Slade et al., 1993, [042865](#)). Antioxidant defenses  
8 also vary with age (Servais et al., 2005, [195667](#)) and exposure history (Duan et al., 1996, [080791](#)).  
9 Duan et al. (1993, [086326](#); 1996, [080791](#)) reported that differences in antioxidant levels between  
10 species and lung regions did not appear to be the primary factor in O<sub>3</sub> induced tissue injury.  
11 However, a close association between site-specific O<sub>3</sub> dose, the degree of epithelial injury, and  
12 reduced glutathione depletion was later revealed in monkeys (Plopper et al., 1998, [087203](#)).



Source: Adapted with permission from CRC Press, Inc., Hatch (1992, [043901](#)) and with permission from Slade et al. (1993, [042865](#))

**Figure 5-5. Species comparison of antioxidant / protein ratios of: (a) nasal lavage fluid and, (b) bronchoalveolar lavage fluid.**

### 5.1.4.2. Recent Publications

- 1 There have been few new publications examining interspecies differences in dosimetry and
- 2 response to O<sub>3</sub> since the last AQCD. These studies do not overtly change the conclusions discussed
- 3 above from the previous document (U.S. EPA, 2006, [088089](#)).

1 A quantitative comparison of O<sub>3</sub> transport in the airways of rats, dogs, and humans was  
2 conducted using a three-compartment airways model, based on upper and lower airway casts and  
3 mathematical calculation for alveolar parameters (Tsuji no et al., 2005, [195842](#)). The model was  
4 designed as cylindrical tubes with constant volume and one-dimensional gas movement and no  
5 airway branching patterns. It used data for solubility of O<sub>3</sub> as well as measured nasopharyngeal  
6 removal rates of O<sub>3</sub> published previously. This model examined how interspecies anatomical and  
7 physiological differences affect intra-airway O<sub>3</sub> concentrations and the amount of gas absorbed (10%  
8 O<sub>3</sub> exposure). Peak, real-time, and mean O<sub>3</sub> concentrations were higher in the upper and lower  
9 airways of humans compared to rats and dogs, but lowest in the alveoli of humans. The amount of O<sub>3</sub>  
10 absorbed was lowest in humans when normalized by body weight ( $8.47 \times 10^{-8}$  g/kg compared to  
11  $1.1 \times 10^{-7}$  in rats and  $1.46 \times 10^{-7}$  in dogs). The intra-airway concentration decreased distally in all  
12 species. Sensitivity analysis demonstrated that V<sub>T</sub>, f<sub>B</sub>, and upper and lower airways surface area had  
13 a significant impact on model results. The model is limited in that it did not account for chemical  
14 reactions in the ELF or consider gas diffusion as a driving force for O<sub>3</sub> transport. Also, the model  
15 was run at a respiratory rate of 16/min simulating a resting individual, however exercise may cause a  
16 further deviation from animal models as was seen in Hatch et al. (1994, [038953](#)).

17 To further understand the genetic basis for age-dependent differential response to O<sub>3</sub>, adult  
18 (15 weeks old) and neonatal (15-16 days old) mice from 8 genetically diverse strains were examined  
19 for O<sub>3</sub>-induced (0.8 ppm for 5 hours) pulmonary injury and lung inflammation (Vancza et al., 2009,  
20 [596419](#)). Ozone exposure increased polymorphonuclear leukocytes (PMN) influx in all strains of  
21 mice tested, but significantly in only some sensitive strains, suggesting a genetic background effect.  
22 This strain difference was not due to differences in delivered dose of O<sub>3</sub> to the lung, evidenced by  
23 <sup>18</sup>O lung enrichment. The sensitivity of strains for O<sub>3</sub>-induced increases in BAL protein and PMNs  
24 was different for different strains of rats suggesting that genetic factors contribute to heightened  
25 responses. Interestingly, adult mice accumulated more than twice the levels of <sup>18</sup>O reaction product  
26 of O<sub>3</sub> than corresponding strain neonates. Thus, it appeared that the infant mice showed a two- to  
27 threefold higher response than the adults when expressed relative to the accumulated O<sub>3</sub> reaction  
28 product in their lungs. The apparent decrease in delivered O<sub>3</sub> dose in neonates could be a result of a  
29 more rapid loss of body temperature in infant rats incident to maternal separation and chamber air  
30 flow.

31 The three-dimensional detail of the nasal passages of immature Rhesus macaque monkeys  
32 were analyzed for developing predictive dosimetry models and exposure-dose-response relationships  
33 (Carey et al., 2007, [195752](#)). In doing so the authors report that the relative amounts of the five  
34 epithelial cell types in the nasal airways of monkeys remains consistent between infancy and  
35 adulthood (comparing to (Gross et al., 1982, [040121](#); Gross et al., 1987, [625447](#))). Ozone exposures  
36 (0.5 ppm, 8 h/day under acute [5 days] and episodic conditions [5 replicates of the acute paradigm  
37 spaced a week apart]) confirmed that the ciliated respiratory and transitional epithelium were the  
38 most sensitive cell types in the nasal cavity, showing 50-80% decreases in epithelial thickness and

1 epithelial cell volume. The character and location of nasal lesions resulting from O<sub>3</sub> exposure are  
2 similar between adult and infant monkeys similarly exposed. However, infant monkeys did not  
3 undergo nasal airway epithelial remodeling or adaptation that occurs in adult animals and they may  
4 develop persistent necrotizing rhinitis following episodic longer-term exposures.

5 In summary, for all species there are limitations that must be considered when attempting to  
6 extrapolate to human O<sub>3</sub> exposures. Rats required 4-5 times higher exposure to O<sub>3</sub> to achieve  
7 comparable increases in BAL protein and PMNs to exercising humans. New studies have shown that  
8 varied O<sub>3</sub> response in different mouse strains was not due to differences in delivered dose of O<sub>3</sub> to  
9 the lung but more likely genetic sensitivity, and that infant mice show greater toxicity relative to the  
10 their smaller lung dose than adults. Even though interspecies differences limit quantitative  
11 comparison between species, the acute and chronic functional responses of laboratory animals to O<sub>3</sub>  
12 appear qualitatively homologous to those of the human making them a useful tool in determining  
13 mechanistic and cause-effect relationships with O<sub>3</sub> exposure.

## 5.2. Possible Pathways/Modes of Action

### 5.2.1. Introduction

14 As described in the previous section, O<sub>3</sub> is a highly reactive oxidant gas with low water  
15 solubility. Its diffusion into the fluid/tissue compartment of the respiratory tract occurs by reactive  
16 absorption. This process depends on the availability of substrates such as antioxidants, lipids,  
17 proteins, and carbohydrates and results in their oxidative modification. Because of its chemical  
18 reactivity, inhaled O<sub>3</sub> directly targets components residing on the airways and alveolar surfaces,  
19 including ELF and surface macrophages. Although the O<sub>3</sub> molecule is consumed and may not reach  
20 the apical plasma membrane of airways and alveolar epithelium, secondary oxidation products  
21 transmit signals to the epithelium, nociceptive sensory nerve fibers and, if present, dendritic cells,  
22 mast cells and eosinophils. Thus, O<sub>3</sub> effects are mediated by components of ELF and by the multiple  
23 cell types found in the respiratory tract.

24 Three distinct short-term responses have been well-characterized in humans challenged with  
25 O<sub>3</sub>: decreased pulmonary function, airways inflammation, and increased bronchial reactivity. In  
26 addition, evidence has been accumulating that O<sub>3</sub> exposure exacerbates, and possibly causes, asthma  
27 and allergic airways disease in humans. Effects on the nasal airways and distal lung of humans,  
28 including inflammation and injury, have also been described. Animal studies have demonstrated a  
29 wide range of respiratory system effects. While the respiratory tract is the primary target tissue,  
30 cardiovascular and other organ effects occur following short- and long-term exposures of animals to  
31 O<sub>3</sub>. Mechanisms responsible for these effects are incompletely understood.

32 This section of the ISA highlights findings of studies published since the last O<sub>3</sub> AQCD  
33 (U.S. EPA, 2006, [088089](#)) which provide insight into the biological pathways underlying the effects

1 of O<sub>3</sub>. Older studies which represent the current state of the science are also discussed. Studies  
2 conducted at more environmentally-relevant concentrations of O<sub>3</sub> are of greater interest, since  
3 mechanisms responsible for effects at low O<sub>3</sub> concentrations may not be identical to those occurring  
4 at high O<sub>3</sub> concentrations. In fact, some evidence suggests a concentration-dependent hierarchy of  
5 effects. The following subsections describe the current understanding of potential pathways and  
6 modes of action responsible for the pulmonary and extrapulmonary effects of O<sub>3</sub> exposure.

### 5.2.2. Formation of Secondary Oxidation Products in the Respiratory Tract

7 Since O<sub>3</sub> does not diffuse far into the aqueous layer of the ELF without reacting, it is not likely  
8 to directly impact the underlying cells of the respiratory tract (Pryor, 1992, [042725](#)). This does not  
9 preclude direct reactions with the plasma membranes of cells extending beyond the ELF such as  
10 surface macrophages. The secondary oxidation products formed in the ELF following O<sub>3</sub> exposure  
11 are primarily responsible for ozone's effects at the molecular, cellular and tissue level. The amount  
12 and type of secondary oxidation product formed are important determinants of the anatomic sites of  
13 reaction and injury due to O<sub>3</sub> exposure, as will be discussed below.

14 Although not itself a free radical, ozone's effects are primarily mediated through free radical  
15 reactions. Free radicals are generated during O<sub>3</sub>-mediated oxidation reactions (Pryor, 1994, [075987](#)).  
16 Subsequent reactions of these radical species produce cytotoxic nonradicals such as ozonides and  
17 aldehydes (Cueto et al., 1992, [042770](#); Pryor, 1976, [038940](#)). These effects are reduced by the  
18 presence of the lipid-soluble free radical scavenger alpha-tocopherol (Fujita et al., 1987, [004280](#);  
19 Pryor, 1976, [038940](#); Pryor, 1994, [075987](#)). Although O<sub>3</sub> can react with all hydrocarbons, its  
20 reactivity towards specific groups varies greatly (Pryor, 1992, [042725](#)). Polyunsaturated fatty acids  
21 are one preferred target of O<sub>3</sub>. Following reaction of O<sub>3</sub> with unsaturated fatty acids in the ELF,  
22 measurable amounts of aldehydes were found in human bronchoalveolar lavage (BAL) fluid  
23 (Frampton et al., 1999, [040757](#); Mudway and Kelly, 2000, [010452](#)). Peroxidation of membrane  
24 lipids is an important mechanism underlying O<sub>3</sub>-induced injury (Mudway and Kelly, 2000, [010452](#);  
25 Pryor, 1976, [038940](#)). This could occur by free-radical reactions initiated by O<sub>3</sub> in the ELF or by  
26 direct effects of O<sub>3</sub> on membranes of cells, like surface macrophages, which extend beyond the ELF.  
27 Markers of lipid peroxidation have been demonstrated in lung tissue and BAL fluid following O<sub>3</sub>  
28 exposure and are enhanced in alpha-tocopherol deficient animals (Mudway and Kelly, 2000,  
29 [010452](#)). Ozone-mediated lipid peroxidation leads to the rapid formation of eicosanoids, another  
30 class of secondary oxidation products (discussed below). Ozonized cholesterol species have been  
31 measured in BAL fluid (Pulfer et al., 2005, [076663](#)) and in isolated surfactant (Pulfer and Murphy,  
32 2004, [076673](#)), indicating that O<sub>3</sub> reacts with the cholesterol found in surfactant. In addition, O<sub>3</sub>  
33 attacks ELF proteins through reactions with cysteine, methionine, tryptophan and tyrosine residues  
34 (Mudway and Kelly, 2000, [010452](#)). This results in protein oxidation and carbonylation (Mudway  
35 and Kelly, 2000, [010452](#)).

1 The ELF contains numerous antioxidants including alpha-tocopherol, albumin, ascorbate,  
2 ceruloplasmin, glutathione, lactoferrin, mucins, urate and transferrin (Freed et al., 1999, [011829](#);  
3 Mudway et al., 2006, [196536](#)). Ascorbate, glutathione and urate are present in relatively high  
4 concentrations in the surface liquid of human conducting airways and are known to be preferred  
5 targets of O<sub>3</sub>. These antioxidants are thought to be the first line of defense against inhaled O<sub>3</sub>,  
6 preventing free radical reactions with cellular proteins and lipids (Mudway and Kelly, 2000,  
7 [010452](#)). In vitro studies have demonstrated consumption of water-soluble antioxidants and the  
8 formation of oxidation products by O<sub>3</sub> as well as a reactive hierarchy with O<sub>3</sub> (Cross et al., 1992,  
9 [625299](#); Mudway and Kelly, 1998, [000273](#)). When examined as a single antioxidant in solution,  
10 urate exhibited the greatest reactivity, followed by ascorbate and glutathione (Mudway and Kelly,  
11 1998, [000273](#)). Results using mixtures have demonstrated greater complexity (Mudway and Kelly,  
12 2000, [010452](#)).

13 Although ELF constituents such as antioxidants may protect against the deleterious effects of  
14 O<sub>3</sub>, there is some evidence that antioxidants may paradoxically facilitate O<sub>3</sub>-mediated damage. This  
15 apparent contradiction should be viewed in terms of the concentration-dependent role of the ELF  
16 antioxidants. Studies in vitro using red cell ghosts as a target showed that aqueous phase reactions  
17 between O<sub>3</sub> and the low molecular weight antioxidants ascorbate and glutathione generated  
18 secondary oxidation products capable of perturbing membrane proteins and lipids (Ballinger et al.,  
19 2005, [076649](#)). Reactions between O<sub>3</sub> and these antioxidant species exhibited a biphasic  
20 concentration response, with oxidation of protein and lipid occurring at lower, but not higher,  
21 concentrations of antioxidant. In this way, endogenous reactants led to the formation of secondary  
22 oxidation products which were injurious and also led to quenching reactions which were protective.  
23 Aqueous phase reactions between O<sub>3</sub> and urate or bovine serum albumin did not result in membrane  
24 oxidation (Ballinger et al., 2005, [076649](#)). Further, the presence of urate or bovine serum albumin  
25 protected against lipid and protein oxidation resulting from the reaction of O<sub>3</sub> and ascorbate  
26 (Ballinger et al., 2005, [076649](#)). Thus, the formation of secondary oxidation products mediated by  
27 some antioxidants was opposed by quenching reactions involving other antioxidants.

28 Local scavenging of inhaled O<sub>3</sub> by antioxidants in specific respiratory regions has been  
29 demonstrated in vivo (Gunnison and Hatch, 1999, [087204](#); Mudway et al., 1999, [001270](#)). Urate, but  
30 not ascorbate or glutathione, was depleted in nasal lavage fluid during exposure of human subjects to  
31 0.2 ppm O<sub>3</sub> for 2 hours indicating that urate is the predominant antioxidant with respect to O<sub>3</sub>  
32 reactivity in the nasal cavity (Mudway et al., 1999, [001270](#)). In addition, depletion of urate during O<sub>3</sub>  
33 exposure was associated with a small but significant increase in plasma urate levels (Mudway et al.,  
34 1999, [001270](#)). Efforts to identify the predominant antioxidant(s) in other respiratory tract regions  
35 and in other species have failed to yield definitive results. In one study, glutathione was increased,  
36 rather than decreased, in BAL fluid and bronchial wash fluid 1.5 h following a 2 h exposure of  
37 human subjects to 0.2 ppm O<sub>3</sub> (Blomberg et al., 1999, [001267](#)).

1            Since exposure to O<sub>3</sub> often leads to airway inflammation characterized by neutrophilia and  
2 since neutrophil-derived oxidants often scavenge ELF antioxidants, concentrations of ELF  
3 antioxidants were examined during airways neutrophilia which generally occurs 4-6 hours  
4 postexposure to O<sub>3</sub> (Gunnison and Hatch, 1999, [087204](#); Long et al., 2001, [057301](#); Mudway et al.,  
5 1999, [011833](#)). In humans exposed to 0.2 ppm O<sub>3</sub> for 2 hours, urate, glutathione and alpha-  
6 tocopherol levels remained unchanged in BAL fluid 6 hours postexposure while ascorbate was  
7 decreased significantly in both BAL fluid and plasma (Mudway et al., 1999, [011833](#)). A second  
8 study involving the same protocol reported a loss of ascorbate from bronchial wash fluid and BAL  
9 fluid, representing proximal and distal airway ELF respectively, as well as an increase in oxidized  
10 glutathione in both compartments (Mudway et al., 2001, [025327](#)). No change was observed in ELF  
11 urate levels in response to O<sub>3</sub> (Mudway et al., 2001, [025327](#)). Further, O<sub>3</sub> exposure (0.8 ppm,  
12 4 hours) in female rats resulted in a 50% decrease in BAL fluid ascorbate immediately postexposure  
13 (Gunnison and Hatch, 1999, [087204](#)). These studies suggested a role for ascorbate and glutathione in  
14 protecting against oxidative stress associated with inflammation. On the other hand, a study in  
15 hamsters exposed to 3 ppm O<sub>3</sub> for 6 hours found no depletion of ascorbate, glutathione or alpha-  
16 tocopherol in BAL fluid (Long et al., 2001, [057301](#)). Instead an increase in BAL fluid urate and a  
17 decrease in plasma ascorbate were observed (Long et al., 2001, [057301](#)).

18            Although it is known that ELF antioxidants are variably distributed among regions of the  
19 respiratory tract, mechanisms underlying this variability are not well-understood. It is thought that  
20 both plasma ultrafiltrate and locally secreted substances contribute to the antioxidant content of the  
21 ELF (Freed et al., 1999, [011829](#); Mudway et al., 2006, [196536](#)). In the case of urate, the major  
22 source appears to be the plasma (Peden et al., 1995, [076189](#)). Repletion of urate in nasal lavage fluid  
23 was demonstrated during sequential nasal lavage in human subjects (Mudway et al., 1999, [001270](#)).  
24 When these subjects were exposed to O<sub>3</sub>, nasal lavage urate was significantly decreased while  
25 plasma urate levels was significantly increased (Mudway et al., 1999, [001270](#)). In addition,  
26 concentrations of urate were increased by cholinergic stimulation of the airways which suggests that  
27 increased mucosal gland secretions can be an important source (Peden et al., 1995, [076189](#)).  
28 Regulation of ascorbate, glutathione and alpha-tocopherol concentrations within the ELF is less clear  
29 than that of urate (Mudway et al., 2006, [196536](#)). In a sequential nasal lavage study in humans,  
30 wash-out of ascorbate and glutathione occurred, indicating the absence of rapidly acting repletion  
31 mechanisms (Mudway et al., 1999, [001270](#)). Other studies discussed above demonstrated increases  
32 in BALF glutathione and decreases in BALF and plasma ascorbate levels several hours following O<sub>3</sub>  
33 exposure (Blomberg et al., 1999, [001267](#); Mudway et al., 1999, [011833](#); Mudway et al., 2001,  
34 [025327](#)). Furthermore, high levels of dehydroascorbate, the oxidized form of ascorbate, have been  
35 reported in human ELF (Mudway et al., 2006, [196536](#)). Other investigators have demonstrated  
36 cellular uptake of oxidized ascorbate by several cell types leading to intracellular reduction and  
37 export of reduced ascorbate (Welch et al., 1995, [644675](#)).

1 A further consideration is the compromised status of ELF antioxidants in disease states such as  
2 asthma (Mudway and Kelly, 2000, [010452](#)). This could possibly be due to ongoing inflammation  
3 which causes antioxidant depletion or to abnormal antioxidant transport or synthesis (Mudway and  
4 Kelly, 2000, [010452](#)). For example, basal ascorbate levels were significantly lower and basal levels  
5 of oxidized glutathione and urate were significantly higher in bronchial wash fluid and BAL fluid of  
6 mild asthmatics compared with healthy control subjects (Mudway et al., 2001, [025327](#)). Differences  
7 in ELF antioxidant content have also been noted between species. These observations have led to the  
8 suggestion that the amount and composition of ELF antioxidants, the capacity to replenish  
9 antioxidants in the ELF or the balance between beneficial and injurious interactions between  
10 antioxidants and O<sub>3</sub> may contribute to O<sub>3</sub> sensitivity which varies between individuals and species  
11 (Mudway and Kelly, 2000, [010452](#); Mudway et al., 1999, [001270](#); Mudway et al., 2006, [196536](#)).  
12 The complexity of these interactions was demonstrated by a study in which O<sub>3</sub> exposure resulted in  
13 similar increases in airway neutrophils and decreases in pulmonary function in both mild asthmatics  
14 and healthy controls, despite differences in ELF antioxidant concentrations prior to O<sub>3</sub> exposure  
15 (Mudway et al., 2001, [025327](#)). Further, the O<sub>3</sub>-induced increase in oxidized glutathione and  
16 decrease in ascorbate observed in ELF of healthy controls was not observed in mild asthmatics  
17 (Mudway et al., 2001, [025327](#)). While the authors concluded that basal ascorbate and oxidized  
18 glutathione concentrations were not predictive of responsiveness to O<sub>3</sub>, they also suggested that the  
19 increased basal urate concentrations in the mild asthmatics may have played a protective role  
20 (Mudway et al., 2001, [025327](#)). Thus compensatory mechanisms resulting in enhanced total  
21 antioxidant capacity may play a role in modulating responses to O<sub>3</sub>.

22 Several studies in animals evaluated the relationships between <sup>18</sup>O-labeled O<sub>3</sub> dose markers,  
23 injury markers and ascorbate concentrations following O<sub>3</sub> exposure. In female rats exposed to  
24 0.8 ppm O<sub>3</sub> for 4 hours, BAL indicators of injury and inflammation (protein and neutrophil number)  
25 and <sup>18</sup>O reaction product were increased inversely with the reduction in ascorbate (Gunnison and  
26 Hatch, 1999, [087204](#)). In another study, aging rats (9 and 24 months old) were shown to have 49%  
27 and 64% lower ascorbate in lung tissue, respectively, than 2-month-old rats (Vincent et al., 1996,  
28 [080778](#)). However, aging-induced ascorbate loss did not increase the accumulation of <sup>18</sup>O reaction  
29 products following O<sub>3</sub> exposure (0.4-0.8 ppm, 2-6 hours). Pregnancy and lactation also caused lower  
30 ascorbate content in BAL and nasal lavage fluid and was associated with an increase in accumulation  
31 of <sup>18</sup>O reaction products following O<sub>3</sub> exposure (Gunnison and Hatch, 1999, [087204](#)). Kari et al.  
32 (1997, [086171](#)) observed that a 3-week caloric restriction (75%) in rats abrogated the toxicity of O<sub>3</sub>  
33 (2 ppm, 2 hours), measured as BAL fluid increases in protein, fibronectin and neutrophils, which  
34 was seen in normally fed rats. Accompanying this resistance to O<sub>3</sub> toxicity, was a 30% higher basal  
35 BAL fluid ascorbate concentration, a rapid accumulation of ascorbate into the lungs to levels 60%  
36 above normal and reduction (30%) in the accumulation of <sup>18</sup>O reaction product in the lungs. These  
37 investigations demonstrated an inverse relationship between ascorbate levels and O<sub>3</sub> dose and  
38 provide evidence for ascorbate playing a protective role following O<sub>3</sub> exposure in these studies.

1 Many investigations have focused on antioxidant deficiency and supplementation as  
2 modulators of O<sub>3</sub>-mediated effects. Ascorbate deficiency has been shown to increase the effects of  
3 acute, but not chronic, O<sub>3</sub> exposure in guinea pigs and humans (Kodavanti et al., 1995, [077440](#);  
4 Slade et al., 1989, [059465](#)). Supplementation with ascorbate and alpha-tocopherol was protective in  
5 healthy adults who were on an ascorbate-deficient diet and exposed to 0.4 ppm O<sub>3</sub> for 2 hours while  
6 exercising (Samet et al., 2001, [019034](#)). In this study, the protective effect consisted of a smaller  
7 reduction in forced expiratory volume in one second (FEV<sub>1</sub>) following O<sub>3</sub> exposure (Samet et al.,  
8 2001, [019034](#)). However the inflammatory response (influx of neutrophils and levels of IL-6)  
9 measured in BAL fluid 1 hour after O<sub>3</sub> exposure was not different between supplemented and non-  
10 supplemented subjects (Samet et al., 2001, [019034](#)). Supplementation with ascorbate and alpha-  
11 tocopherol also protected against pulmonary function decrements and nasal inflammatory responses  
12 which were associated with high levels of ambient O<sub>3</sub> in asthmatic children living in Mexico City  
13 (Romieu et al., 2002, [034711](#); Sienna-Monge et al., 2004, [196422](#)). Similarly, supplementation with  
14 ascorbate, alpha-tocopherol and beta-carotene improved pulmonary function in Mexico City  
15 streetworkers (Romieu et al., 1998, [086756](#)). However, ascorbate and alpha-tocopherol  
16 supplementation failed to ameliorate the pulmonary function decrements or airways neutrophilia  
17 observed in humans exposed to 0.2 ppm O<sub>3</sub> for 2 hours (Mudway et al., 2006, [196536](#)). It was  
18 suggested that supplementation may be ineffective in the absence of antioxidant deficiency (Mudway  
19 et al., 2006, [196536](#)). Furthermore, protective effects of supplementation with alpha-tocopherol  
20 alone have not been observed in humans (Mudway and Kelly, 2000, [010452](#)).

21 Recent studies in animals demonstrated protection against O<sub>3</sub>-induced effects using gamma-  
22 tocopherol supplementation in models of allergic rhinosinusitis (Wagner et al., 2009, [201574](#)) and  
23 lower airway allergic inflammation (Wagner et al., 2007, [596420](#)). Previous studies demonstrated  
24 that supplementation with alpha-tocopherol was ineffective in these models (Wagner et al., 2007,  
25 [596420](#)). Other investigators found that alpha-tocopherol deficiency led to an increase in liver lipid  
26 peroxidation (Sato et al., 1980, [039738](#)) and a drop in liver alpha-tocopherol levels following O<sub>3</sub>  
27 exposure (Vasu et al., 2010, [201561](#)). A recent study used alpha-tocopherol transfer protein null mice  
28 as a model of alpha-tocopherol deficiency and demonstrated an altered adaptive response of the lung  
29 genome to O<sub>3</sub> exposure (Vasu et al., 2010, [201561](#)). Taken together, these studies provide evidence  
30 that the tocopherol system modulates O<sub>3</sub>-induced responses.

31 Other antioxidants have been shown to confer resistance to O<sub>3</sub>-induced injury. In a recent  
32 study, lung hyperpermeability in response to O<sub>3</sub> was unexpectedly reduced in mice deficient in the  
33 glutamate-cysteine ligase modifier subunit gene compared with sufficient mice (Johansson et al.,  
34 2010, [644476](#)). Since the lungs of these mice exhibited 70% glutathione depletion, protection against  
35 O<sub>3</sub>-induced injury was unexpected (Johansson et al., 2010, [644476](#)). However it was found that  
36 several other antioxidant defenses, including metallothionein, were upregulated in response to O<sub>3</sub> to  
37 a greater degree in the glutathione-deficient mice compared with sufficient mice (Johansson et al.,  
38 2010, [644476](#)). The authors suggested that resistance to O<sub>3</sub>-induced lung injury was due to

1 compensatory augmentation of antioxidant defenses (Johansson et al., 2010, [644476](#)). Antioxidant  
2 effects have also been attributed to Clara cell secretory protein (CCSP) and surfactant protein A  
3 (SP-A). CCSP was found to modulate the susceptibility of airways epithelium to injury in mice  
4 exposed to O<sub>3</sub> (0.2 or 1 ppm for 8 hours) by an unknown mechanism (Plopper et al., 2006, [596410](#)).  
5 SP-A protected against O<sub>3</sub>-induced airways inflammation and injury, possibly by acting as a  
6 sacrificial substrate (Haque et al., 2007, [597606](#)).

7 A role for plasma antioxidants in modulating O<sub>3</sub>-induced respiratory effects has also been  
8 suggested (Aibo et al., 2010, [378559](#)). In this study, pretreatment of rats with a high dose of  
9 acetaminophen resulted in increased levels of plasma cytokines and the influx of inflammatory cells  
10 into the lung following 6 h exposure to 0.25 and 0.5 ppm O<sub>3</sub> (Aibo et al., 2010, [378559](#)). These  
11 effects were not observed in response to O<sub>3</sub> alone. Although not measured in this study, glutathione  
12 depletion in the liver is known to occur in acetaminophen toxicity. Since liver glutathione is the  
13 source of plasma glutathione, acetaminophen treatment may have lowered plasma glutathione levels  
14 and altered the redox balance in the vascular compartment. These findings indicate an  
15 interdependence between respiratory tract, plasma and liver responses to O<sub>3</sub>, possibly related to  
16 glutathione status.

17 Another important consideration is the non-uniformity of the injury response to O<sub>3</sub> throughout  
18 the respiratory tract. Several mechanisms have been proposed to explain this phenomenon. First,  
19 dosimetry may be a key determinant since the sites receiving the largest dose might be expected to  
20 exhibit the greatest injury or inflammation (Plopper et al., 1998, [087203](#); Postlethwait et al., 2000,  
21 [003000](#)). An important corollary is that the uneven distribution of mucus in the respiratory tract  
22 airways may influence the capacity of O<sub>3</sub> to reach the aqueous layer (Mudway and Kelly, 2000,  
23 [010452](#)). Secondly, the non-homogeneous formation of cytotoxic products in the ELF may account  
24 for the variable response (Postlethwait et al., 2000, [003000](#)). The thickness of the ELF varies along  
25 the respiratory tract, being greater in the upper airways and less more distally. Further the  
26 composition of the ELF varies along the respiratory tract. Thus, the amount of protective  
27 antioxidants and other scavengers in various respiratory tract regions is likely to limit the formation  
28 of cytotoxic products. Similarly, the availability of reactants which are precursors of potent cytotoxic  
29 products may facilitate their formation in a particular region. For example, the formation of highly  
30 electrophilic aldehydes from unsaturated fatty acids may occur in all respiratory tract regions while  
31 the formation of oxidized surfactant lipids is likely restricted to the alveolar region and respiratory  
32 bronchioles where surfactant is found. Thus, region-specific formation of particular oxidation  
33 products may dictate patterns of epithelial injury in the respiratory tract.

34 The relationship between site-specific O<sub>3</sub> dose, epithelial injury and glutathione concentration  
35 was investigated by Plopper (1998, [087203](#)). Adult rhesus monkeys were exposed for 2 hours to 0.4  
36 and 1.0 ppm O<sub>3</sub>, which was labeled with <sup>18</sup>O, and tissues were analyzed immediately postexposure  
37 for dose, epithelial injury and glutathione levels. Results indicated that exposure to 1 ppm O<sub>3</sub>  
38 resulted in the greatest epithelial injury in the respiratory bronchioles although injury was observed

1 at all of the airway sites but not in the lung parenchyma. Exposure to 0.4 ppm O<sub>3</sub> resulted in  
2 epithelial injury only in the respiratory bronchioles. Local O<sub>3</sub> dose was found to be highly variable  
3 among the different sites with the greatest levels found in the respiratory bronchioles and lowest  
4 levels found in the parenchyma following 1 ppm O<sub>3</sub>. Glutathione levels varied in the different  
5 airways sites in monkeys exposed to filtered air. Exposure to 1 ppm O<sub>3</sub> decreased glutathione levels  
6 only in the respiratory bronchioles. This study demonstrated a close relationship between the  
7 exposure dose of O<sub>3</sub> (uptake of <sup>18</sup>O) and the degree of initial epithelial injury at a particular site in  
8 the respiratory tract. Glutathione depletion observed only at that site suggests that glutathione played  
9 a protective role during O<sub>3</sub> exposure.

10 While the formation of secondary oxidation products is the key event leading to O<sub>3</sub>-mediated  
11 effects, scavenging and/or metabolism of those products is likely to be an important determinant of  
12 outcomes. One such mechanism may be scavenging of oxidized lipids via the macrophage receptor  
13 with collagenous structure (MARCO) expressed on the cell surface of alveolar macrophages. A  
14 recent study demonstrated increased gene expression of MARCO in the lungs of an O<sub>3</sub>-resistant C3H  
15 mouse strain (HeJ) but not in an O<sub>3</sub>-sensitive, genetically nearly identical strain (OuJ) (Dahl et al.,  
16 2007, [196986](#)). Upregulation of MARCO occurred in mice exposed to 0.3 ppm O<sub>3</sub> for 24-48 hours;  
17 inhalation exposure for 6 hours at this concentration was insufficient for this response. Animals  
18 lacking the MARCO receptor exhibited greater inflammation and injury, as measured by BAL  
19 neutrophils, protein and isoprostanes, following exposure to 0.3 ppm O<sub>3</sub> (Dahl et al., 2007, [196986](#)).  
20 MARCO also protected against the inflammatory effects of oxidized surfactant lipids (Dahl et al.,  
21 2007, [196986](#)). Scavenging of oxidized lipids may limit O<sub>3</sub>-induced injury since ozonized  
22 cholesterol species formed in the ELF (Pulfer and Murphy, 2004, [076673](#); Pulfer et al., 2005,  
23 [076663](#)) stimulate apoptosis and cytotoxicity (Gao et al., 2009, [200764](#); Sathishkumar et al., 2007,  
24 [097758](#); Sathishkumar et al., 2007, [197785](#); Sathishkumar et al., 2009, [201549](#)) in vitro. While these  
25 studies have focused on the alveolar compartment (alveolar macrophages, surfactant lipids),  
26 comparable pathways have yet to be elucidated in the conducting airways. A second mechanism  
27 likely to impact O<sub>3</sub>-mediated effects is the metabolism of secondary oxidation products catalyzed by  
28 antioxidant enzymes such as glutathione peroxidase, glutathione S-transferases (GST) and  
29 NADPH:quinone oxidoreductase 1 (NQO1). Evidence for the importance of GST and NQO1 in  
30 modulating the effects of O<sub>3</sub> is presented below (see Gene-Environment Interactions).

31 Secondary oxidation products formed as a result of O<sub>3</sub> exposure initiate numerous responses at  
32 the cellular, tissue and whole organ level of the respiratory system. These responses include the  
33 activation of neural reflexes, injury and inflammation, hyperpermeability, increased bronchial  
34 reactivity and altered host defenses, as will be discussed below. In addition, the enhancement of  
35 asthma and allergic responses demonstrated as a result of O<sub>3</sub> exposure is likely due to secondary  
36 oxidation products. Exposure to O<sub>3</sub> also results in effects on other organ systems such as the  
37 cardiovascular, hepatic and central nervous systems. Mechanisms underlying these extrapulmonary  
38 responses are not well understood. It is unlikely that lipid ozonides and other secondary oxidation

1 products, which are bioactive and cytotoxic in the respiratory system, gain access to the vascular  
2 space (Chuang et al., 2009, [197202](#)). However O<sub>3</sub> exposure may result in systemic oxidative stress,  
3 as suggested by studies in humans reporting an association between O<sub>3</sub> exposure and both levels of  
4 plasma 8-isoprostanes and the presence of peripheral blood lymphocyte micronuclei (Chen et al.,  
5 2006, [196504](#); Chen et al., 2007, [145956](#)).

### 5.2.2.1. Summary

6 The initial key event in ozone's toxicity pathway is the formation of secondary oxidation  
7 products in the respiratory tract. Pathways for the removal of those products are also of great  
8 importance. Due to the highly reactive nature of O<sub>3</sub>, direct reactions most likely involve components  
9 of the ELF and/or plasma membranes of surface macrophages which extend beyond the ELF.  
10 Reaction products likely mediate ozone's effects on respiratory tract epithelium.

### 5.2.3. Activation of Neural Reflexes

11 Acute O<sub>3</sub> exposure results in reversible effects on lung function parameters through activation  
12 of neural reflexes. The involvement of bronchial C-fibers, a type of nociceptive sensory nerve, has  
13 been demonstrated in dogs (Coleridge et al., 1993, [038695](#); Schelegle et al., 1993, [039203](#)) and the  
14 involvement of nociceptive sensory nerves has been demonstrated in humans (Passannante et al.,  
15 1998, [030114](#)). Furthermore there is evidence that substance P (SP), a tachykinin which is known to  
16 be released from C-fibers, plays a role in O<sub>3</sub>-mediated effects (Hazbun et al., 1993, [043914](#); Krishna  
17 et al., 1997, [084262](#)).

18 The response to O<sub>3</sub> in humans is characterized by substernal discomfort, especially on deep  
19 inspiration, accompanied by involuntary truncation of inspiration (Hazucha et al., 1989, [041909](#)).  
20 This leads to decreased inspiratory capacity and to decreased forced vital capacity (FVC) and forced  
21 expiratory volume in one second (FEV<sub>1</sub>), as measured by spirometry, and is accompanied by a  
22 decreased tidal volume and increased respiratory frequency in human subjects during exercise  
23 (Hazucha et al., 1989, [041909](#)). For example, these pulmonary function responses have been noted  
24 immediately after a 1-h exposure to 0.3 ppm O<sub>3</sub>, resolving by 6 hours after exposure (Schelegle et  
25 al., 1991, [042491](#)), and during and immediately after a 4-h exposure to 0.2 ppm O<sub>3</sub> in exercising  
26 humans (Aris et al., 1993, [038275](#); Balmes et al., 1996, [080830](#)). Although spirometric changes  
27 began to return to baseline shortly after exposure, small residual spirometric decrements were  
28 reported at 24 hours postexposure (Hazucha et al., 1996, [043923](#)). Spirometric changes in FEV<sub>1</sub> and  
29 FVC were not due to changes in respiratory muscle strength (Hazucha et al., 1989, [041909](#)).  
30 Changes in FVC or symptoms were not modified by treatment with bronchodilators such as atropine  
31 (Beckett et al., 1985, [039758](#)). Thus, parasympathetic involvement in the O<sub>3</sub>-mediated decreases in  
32 lung volume was not significant (Mudway and Kelly, 2000, [010452](#)). However, the loss of vital  
33 capacity was reversible with intravenous administration of the rapid-acting opioid agonist,  
34 sufentanyl, indicating an involvement of opioid receptor-containing nerve fibers and/or more central

1 neurons (Passannante et al., 1998, [030114](#)). The effects of sufentanyl may be attributed to blocking  
2 C-fiber stimulation by O<sub>3</sub> since activation of opioid receptors downregulates C-fiber function  
3 (Belvisi et al., 1992, [644681](#)). There is some evidence that eicosanoids play a role in the neural  
4 reflex since cyclooxygenase inhibition with indomethacin (Alexis et al., 2000, [013072](#); Schelegle et  
5 al., 1987, [041706](#)) or ibuprofen, which also blocks some lipoxygenase activity (Hazucha et al., 1996,  
6 [043923](#)), before exposure to O<sub>3</sub> significantly blunted the spirometric responses. In the latter study,  
7 ibuprofen treatment resulted in measurable decreases in BAL levels of PGE2 and TXB2 at 1 hour  
8 postexposure (Hazucha et al., 1996, [043923](#)). Although an earlier study demonstrated that PGE2  
9 stimulated bronchial C-fibers (Coleridge et al., 1976, [038612](#); Coleridge et al., 1993, [038695](#)) and  
10 suggested that PGE2 mediated O<sub>3</sub>-induced decreases in pulmonary function, no correlation was  
11 observed between the degree of ibuprofen-induced inhibition of BAL PGE2 levels and blunting of  
12 the spirometric response to O<sub>3</sub> (Hazucha et al., 1996, [043923](#)). Nonetheless, recent studies continue  
13 to provide evidence that arachidonic acid metabolites, as well as oxidative stress, contribute to  
14 human responsiveness to O<sub>3</sub> (Alfaro et al., 2007, [196567](#)).

15 A delay in onset of O<sub>3</sub>-induced pulmonary function responses has been noted in numerous  
16 studies. Recently the delay was characterized in terms of changes in breathing frequency (Schelegle  
17 et al., 2007, [195841](#)). In humans exposed to O<sub>3</sub>, no change in breathing frequency was observed until  
18 a certain cumulative inhaled dose of O<sub>3</sub> had been reached. Subsequently, the magnitude of the  
19 change in breathing frequency was correlated with the inhaled dose rate (Schelegle et al., 2007,  
20 [195841](#)). These investigators proposed that initial reactions of O<sub>3</sub> with ELF resulted in a time-  
21 dependent depletion of ELF antioxidants, and that activation of neural reflexes occurred only after  
22 the antioxidant defenses were overwhelmed (Schelegle et al., 2007, [195841](#)).

23 There is a large range of pulmonary function responses to O<sub>3</sub> among healthy young adults  
24 (Balmes et al., 1996, [080830](#); Hazucha et al., 2003, [048168](#)). Since individual responses are  
25 relatively consistent across time, it is thought that responsiveness reflects an intrinsic characteristic  
26 of the subject (Mudway and Kelly, 2000, [010452](#)). Older adults are generally not responsive to O<sub>3</sub>  
27 (Hazucha et al., 2003, [048168](#)), while obese young women may be more responsive than lean young  
28 women (Bennett et al., 2007, [418827](#)). The lack of spirometric responsiveness is not attributable to  
29 the presence of endogenous endorphins, which could potentially block C-fiber stimulation by O<sub>3</sub>, as  
30 demonstrated in a study involving intravenous administration of naloxone immediately following the  
31 O<sub>3</sub> exposure to weak responders (Passannante et al., 1998, [030114](#)). Currently, the mechanisms  
32 underlying the inter-individual variation in responsiveness to O<sub>3</sub> are not known. It has been proposed  
33 that some of the variation in response may be genetically determined (Yang et al., 2005, [077211](#)).  
34 More discussion on this topic is found below (Section 5.2.9.1).

35 In addition to the spirometric changes, mild airways obstruction occurs as a result of O<sub>3</sub>  
36 exposure. This pulmonary function decrement is generally measured as specific airway resistance  
37 (sRaw) which is the product of airway resistance and thoracic gas volume. Increased sRaw occurred  
38 fairly rapidly in exercising humans, peaking at 1-6 hours and resolving by 24 hours following O<sub>3</sub>

1 exposure (Aris et al., 1993, [038275](#); Balmes et al., 1996, [080830](#); Hazucha et al., 1996, [043923](#);  
2 Schelegle et al., 1991, [042491](#)). Small but statistically significant increases in sRaw during O<sub>3</sub>  
3 exposure (0.2 ppm for 4 hours with intermittent exercise) and immediately following O<sub>3</sub> exposure  
4 (0.3 ppm for 1 hour, moderate exercise or 0.4 ppm for 2 hours, intermittent exercise) were observed  
5 in several studies (Aris et al., 1993, [038275](#); Balmes et al., 1996, [080830](#); Hazucha et al., 1996,  
6 [043923](#); Schelegle et al., 1991, [042491](#)). These changes in sRaw correlated with changes in  
7 inflammatory and injury endpoints measured 18 hours postexposure, as will be discussed below, but  
8 not with the time course or degree of spirometric change measured during exposure (Aris et al.,  
9 1993, [038275](#); Balmes et al., 1996, [080830](#); Schelegle et al., 1991, [042491](#)). In addition, a small but  
10 persistent increase in airways resistance associated with narrowing of small peripheral airways  
11 (measured as changes in isoV FEF<sub>25-75</sub>) was demonstrated in O<sub>3</sub>-exposed humans (0.35 ppm for  
12 130 minutes with intermittent exercise) (Weinmann et al., 1995, [077206](#); Weinmann et al., 1995,  
13 [038645](#)). A similar study (0.4 ppm O<sub>3</sub> for 2 hours with intermittent exercise) found decreases in  
14 FEF<sub>25-75</sub> concomitant with increases in residual volume, which is suggestive of small airways  
15 dysfunction (Kreit et al., 1989, [041817](#)). In separate studies, a statistically significant increase in  
16 residual volume (Hazucha et al., 1989, [041909](#)) and a statistically significant decrease in FEF<sub>25-75</sub>  
17 (Horstman et al., 1995, [075834](#)) were observed following O<sub>3</sub> exposure.

18 Mechanisms underlying the rapid increase in airways resistance following O<sub>3</sub> exposure are  
19 incompletely understood. However pretreatment with atropine was found to decrease baseline sRaw  
20 and prevent O<sub>3</sub>-induced increases in sRaw (Beckett et al., 1985, [039758](#)), indicating the involvement  
21 of muscarinic cholinergic receptors of the parasympathetic nervous system. Interestingly, atropine  
22 pretreatment partially blocked the decrease in FEV<sub>1</sub>, but had no effect on the decrease in FVC,  
23 breathing rate, tidal volume or respiratory symptoms (Beckett et al., 1985, [039758](#)). Thus pulmonary  
24 function decrements measured as FEV<sub>1</sub> may reflect both restrictive and obstructive type changes in  
25 airways responses. Using a beta-adrenergic agonist, it was shown that smooth muscle contraction,  
26 not increased airways mucus secretion, was responsible for O<sub>3</sub>-induced increases in airways resistance  
27 (Beckett et al., 1985, [039758](#)). Furthermore, tachykinins may contribute to O<sub>3</sub>-mediated increases in  
28 airways resistance. Bronchopulmonary C fibers mediate local axon responses by releasing  
29 tachykinins such as SP. Tachykinins bind to neurokinin (NK) receptors resulting in responses such as  
30 bronchoconstriction. In one study in which bronchial biopsies were performed and studied by  
31 immunohistochemistry, SP was substantially diminished in submucosal sensory nerves 6 hours  
32 following O<sub>3</sub> exposure (0.2 ppm O<sub>3</sub> for 2 hours with exercise) (Krishna et al., 1997, [084262](#)). A  
33 statistically significant correlation was observed between loss of SP immunoreactivity from neurons  
34 in the bronchial mucosa and changes in FEV<sub>1</sub> measured 1 hour postexposure (Krishna et al., 1997,  
35 [084262](#)). Another study found that SP was increased in lavage fluid of human subjects immediately  
36 after O<sub>3</sub> challenge (0.25 ppm O<sub>3</sub> for 1 hour with heavy exercise) (Hazbun et al., 1993, [043914](#)) These  
37 results provide evidence that the increased airways resistance observed following O<sub>3</sub> exposure is due

1 to vagally-mediated responses and possibly by local axon reflex responses through  
2 bronchopulmonary C fiber-mediated release of SP.

3 In responsive individuals, a striking degree of response attenuation occurs following repeated  
4 daily exposures to O<sub>3</sub>. This phenomena has been reported for both lung function and symptoms such  
5 as upper airway irritation, nonproductive cough and substernal discomfort and pain upon deep  
6 inspiration (Folinsbee et al., 1980, [038880](#); Hackney et al., 1977, [038282](#); Horvath et al., 1981,  
7 [039221](#)). Repeated daily exposures also led to an attenuation of the sRaw response in exercising  
8 humans (Christian et al., 1998, [029925](#)). It is well-established that a young O<sub>3</sub> responder will no  
9 longer be responsive on the fourth or fifth day of consecutive daily O<sub>3</sub> exposure (0.4 ppm O<sub>3</sub> for  
10 4 hours or 0.2 ppm O<sub>3</sub> for 4 hours) and that after developing this tolerance it takes up to 7-10 days of  
11 non-exposure in order for the subject to regain O<sub>3</sub> responsiveness (Christian et al., 1998, [029925](#);  
12 Devlin et al., 1997, [083577](#); Folinsbee et al., 1980, [038880](#); Hackney et al., 1977, [038282](#); Horvath  
13 et al., 1981, [039221](#); Linn et al., 1982, [039646](#)). One group reported persistent small airway  
14 dysfunction despite attenuation of the FEV<sub>1</sub> response on the third day of consecutive O<sub>3</sub> exposure  
15 (Frank et al., 2001, [093491](#)). Studies in animals also indicate an attenuation of the physiologic  
16 response as measured by breathing patterns and tidal volume following five consecutive days of O<sub>3</sub>  
17 exposure (Tepper et al., 1989, [041991](#)). The mechanisms underlying this attenuation in humans and  
18 animal models are not well understood (Devlin et al., 1997, [083577](#)), although some studies have  
19 implicated an alteration in lung antioxidant capacity, enhanced mucus production or factors related  
20 to epithelial hyperplasia following O<sub>3</sub> exposure (Devlin et al., 1997, [083577](#)). These potential  
21 mechanisms and others are discussed below. Adaptation of O<sub>3</sub>-induced bradycardic responses, which  
22 also result from activation of neural reflexes, have also been reported in animal studies (Hamade and  
23 Tankersley, 2009, [596386](#); Watkinson et al., 2001, [016245](#)).

24 Finally, the degree of acute decrease of vital capacity in young, healthy adults does not  
25 correlate (positively) with the degree of neutrophilic inflammation observed in their airways or the  
26 degree of airways obstruction elicited by O<sub>3</sub> exposure (Aris et al., 1993, [038275](#); Aris et al., 1995,  
27 [075945](#); Balmes et al., 1996, [080830](#); Schelegle et al., 1991, [042491](#)), implying that different  
28 mechanisms are at work. Further evidence is provided by the finding that pretreatment with  
29 ibuprofen attenuated O<sub>3</sub>-induced lung function changes and increases in BAL fluid PGE<sub>2</sub> levels, but  
30 had no effect on neutrophilia (Hazucha et al., 1996, [043923](#)).

### 5.2.3.1. New Cellular and Molecular Insights

31 Recent studies in animals provide new information regarding the effects of O<sub>3</sub> on reflex  
32 responses mediated by bronchopulmonary C-fibers, a type of nociceptive sensory nerve. Ozone  
33 exposure in mice was found to selectively activate a subset of receptors on bronchopulmonary C-  
34 fibers which are TRPA1 ion channels (Taylor-Clark and Udem, 2010, [377143](#)). TRPA1 ion  
35 channels are members of the TRP family of ion channels, which are known to mediate the responses  
36 of sensory neurons to inflammatory mediators (Caceres et al., 2009, [628549](#)). In addition to TRPA1

1 ion channels possibly playing a key role in O<sub>3</sub>-induced decrements in pulmonary function, they may  
2 mediate allergic asthma (Caceres et al., 2009, [628549](#)). Activation of TRPA1 ion channels following  
3 O<sub>3</sub> exposure is likely due to the formation of secondary products such as aldehydes and  
4 prostaglandins (Taylor-Clark and Undem, 2010, [377143](#)). Ozonation of unsaturated fatty acids in the  
5 ELF results in the generation of aldehydes (Frampton et al., 1999, [040757](#)). For example  
6 4-hydroxynonenal and 4-oxononenal are derived from the peroxidation of omega-6 unsaturated fatty  
7 acids (Taylor-Clark et al., 2008, [628565](#); Trevisani et al., 2007, [628590](#)). 4-oxononenal is a stronger  
8 electrophile than 4-hydroxynonenal and exhibits greater potency towards the TRPA1 channels  
9 (Taylor-Clark et al., 2008, [628565](#)). TRPA1 channels can be activated by aldehydes and other  
10 electrophiles through covalent modification of cysteine and lysine residues (Trevisani et al., 2007,  
11 [628590](#)). In addition, PGE<sub>2</sub> is known to sensitize TRPA1 channels (Bang et al., 2007, [628545](#)) and,  
12 as noted previously, PGE<sub>2</sub> (or other products of cyclooxygenase-catalyzed reactions) has been  
13 proposed to mediate the pulmonary function changes observed following O<sub>3</sub> exposure in humans.

14 In addition to stimulating central nervous system reflexes, bronchopulmonary C fibers mediate  
15 local axon responses by releasing neuropeptides such as SP, neurokinin (NK) A and calcitonin gene-  
16 related peptide (CGRP). Oslund et al. (2008, [195654](#)) demonstrated that NK-1 receptor blockade had  
17 no effect on O<sub>3</sub>-stimulated physiologic responses such as tidal volume and breathing frequency in  
18 rats over the 8-h exposure period. However, SP and NK receptors contributed to vagally-mediated  
19 bronchoconstriction in guinea pigs 3 days after a single exposure to O<sub>3</sub> (2 ppm for 4 hours) (Verhein  
20 et al., 2011, [670295](#)).

### 5.2.3.2. Summary

21 A key event in ozone's toxicity pathway is the activation of neural reflexes which leads to  
22 decrements in pulmonary function. Evidence is accumulating that secondary oxidation products are  
23 responsible for this effect. Eicosanoids have been implicated in humans while eicosanoids and  
24 aldehydes are effective in animal models. Different receptors on bronchial C-fibers have been shown  
25 to mediate separate effects of O<sub>3</sub> on pulmonary function. Nociceptor sensory nerves are involved in  
26 the involuntary truncation of respiration which results in decreases in FVC, FEV<sub>1</sub>, tidal volume and  
27 an increase in respiratory frequency and pain upon deep inspiration. Opioids block these responses  
28 while atropine does not. New evidence in an animal model suggests that TRPA1 receptors on  
29 bronchial C-fibers mediate this pathway. Ozone exposure also results in activation of vagal sensory  
30 nerves and a mild increase in airways obstruction measured as increased sRaw. Atropine and beta-  
31 adrenergic agonists blocked this response in one study indicating that the airway obstruction was due  
32 to bronchoconstriction. Other studies in humans implicated SP release from bronchial C-fibers  
33 resulting in airway narrowing due to either neurogenic edema or bronchoconstriction. New evidence  
34 in an animal model suggests that the SP-NK receptor pathway caused bronchoconstriction following  
35 O<sub>3</sub> exposure. Considerable inter-individual variability exists in O<sub>3</sub> responsiveness measured by  
36 decrements in pulmonary function. Further, attenuation of these pulmonary function decrements

1 occurs following O<sub>3</sub> exposure for several consecutive days. Mechanisms responsible for these effects  
2 are not known but may be related to inherent differences in neural sensitivity.

#### 5.2.4. Respiratory Tract Injury and Inflammation

3 As described above, O<sub>3</sub> reacts with components of the ELF resulting in the generation of  
4 secondary oxidation products. Higher concentrations of these products may directly injure  
5 respiratory tract epithelium. Lower concentrations may initiate cellular responses including cytokine  
6 generation, adhesion molecule expression and modification of tight junctions leading to  
7 inflammation and increased permeability across airways epithelium (Dahl et al., 2007, [196986](#);  
8 Mudway and Kelly, 2000, [010452](#)). Subsequent epithelial remodeling may also occur (Mudway and  
9 Kelly, 2000, [010452](#)).

10 Injury and inflammation have been observed in many different regions of the respiratory tract  
11 following O<sub>3</sub> exposure (Plopper et al., 1998, [087203](#); Postlethwait et al., 2000, [003000](#)). The nasal  
12 airways, conducting airways and distal airways (i.e. respiratory bronchioles or centriacinar region  
13 depending on the species) have all been identified as sites of O<sub>3</sub>-mediated injury and inflammation  
14 (Mudway and Kelly, 2000, [010452](#)). One study found greater injury in conducting airways  
15 downstream of bifurcations where local doses of O<sub>3</sub> were higher (Postlethwait et al., 2000, [003000](#)).  
16 Although the extent of O<sub>3</sub>-induced injury is variable along the respiratory tract, common features of  
17 the injury response have been noted (Mudway and Kelly, 2000, [010452](#)). In the conducting airways,  
18 necrosis of ciliated cells and degranulation of secretory cells has been observed and in the alveolar  
19 region, necrosis of Type I pneumocytes occurs.

20 Further, O<sub>3</sub>-induced injury and inflammation responses are variable between species. For  
21 example, Dormans et al. (1999, [040766](#)) found that rats, mice, and guinea pigs all exhibited  
22 O<sub>3</sub>-induced (0.2 - 0.4 ppm for 3-56 days) inflammation; however, guinea pigs were the most  
23 sensitive with respect to alveolar macrophage elicitation and pulmonary cell density in the  
24 centriacinar region. Mice were the most sensitive to bronchiolar epithelial hypertrophy and  
25 biochemical changes (e.g. lactate dehydrogenase, glutathione reductase, glucose-6-phosphate  
26 dehydrogenase activity), and had the slowest recovery from O<sub>3</sub> exposure. All species displayed  
27 increased collagen in the ductal septa and large lamellar bodies in Type II pneumocytes at the longest  
28 exposure and highest concentration, whereas this response occurred in the rat and guinea pig at  
29 lower O<sub>3</sub> levels (0.2 ppm) as well. Since no dose metric was measured, it is possible that some of  
30 these differences may be attributable to disparate total inhaled dose or local organ dose. Overall, the  
31 authors rated mice as most susceptible, followed by guinea pigs, then rats (Dormans et al., 1999,  
32 [040766](#)). Rats were also less sensitive to epithelial necrosis and inflammatory responses from O<sub>3</sub>  
33 (1.0 ppm for 8 h) than monkeys and ferrets, which manifested a similar response (Sterner-Kock et  
34 al., 2000, [013033](#)). These data suggest that ferrets may be a good animal model for O<sub>3</sub>-induced  
35 airway effects due to the similarities in pulmonary structure between primates and ferrets.

1 While injury and inflammation often accompany each other, in many cases epithelial injury  
2 precedes observable inflammatory effects and in other cases inflammation leads to injury of the  
3 surrounding cells and tissues. In addition to being species-dependent, the acute injury response is  
4 focal, site-specific and dependent on exposure parameters and the time that elapsed since exposure  
5 (Postlethwait et al., 2000, [003000](#)). The presence of shed epithelial cells in the BAL, increases in  
6 levels of BAL lactate dehydrogenase and protein and increased epithelial permeability have been  
7 observed and are indicative of epithelial injury. In addition, histologic analysis has demonstrated  
8 damage to tight junctions between epithelial cells, suggesting an increase in epithelial permeability.

9 Several studies have measured epithelial permeability as the flux of the small solute <sup>99m</sup>Tc-  
10 DTPA which was introduced into the air spaces in different regions of the respiratory tract. An early  
11 study demonstrated increased pulmonary epithelial permeability, measured as the clearance of  
12 <sup>99m</sup>Tc-DTPA, in humans exposed for 2 h to 0.4 ppm O<sub>3</sub> while exercising moderately (Kehrl et al.,  
13 1987, [040824](#)). Another study found that increased epithelial permeability occurred at 1-3 hours and  
14 18-20 hours postexposure and did not resolve for several days (Foster and Stetkiewicz, 1996,  
15 [079920](#)). Increased bronchial permeability was also observed in dogs immediately after and 18 hours  
16 postexposure to 0.2 ppm O<sub>3</sub> for 6 hours (Freed et al., 1996, [080798](#)). Increased epithelial  
17 permeability has been proposed to play a role in allergic sensitization (Matsumura, 1970, [050626](#)), in  
18 activation of neural reflexes and in stimulation of smooth muscle receptors (Dimeo et al., 1981,  
19 [039662](#)). Studies in animals have also demonstrated increased vascular permeability, as measured by  
20 BAL protein and albumin (Costa et al., 1985, [040273](#); Hu et al., 1982, [039418](#)).

21 An important hallmark of acute O<sub>3</sub> exposure in humans and animals is neutrophilic airways  
22 inflammation. Although neutrophil influx into nasal airways has been demonstrated in human  
23 subjects (Graham and Koren, 1990, [042299](#)), most studies of neutrophil influx have focused on the  
24 lower airways (Aris et al., 1993, [038275](#); Hazucha et al., 1996, [043923](#)). The time course of this  
25 response and its resolution is slower than that of the decrements in pulmonary function (Hazucha et  
26 al., 1996, [043923](#)). In general, airways neutrophilia is observable within 1-2 hours, peaks at  
27 4-6 hours and is returning to baseline levels at 24 h following exposure to O<sub>3</sub> in exercising humans  
28 involving 0.4 ppm for 2 hours (Devlin et al., 1991, [040359](#)) or 0.3 ppm for 1 hour (Schelegle et al.,  
29 1991, [042491](#)). Since the influx and persistence of neutrophils in airways following O<sub>3</sub> exposure  
30 correlates with the temporal profile of epithelial injury (Hu et al., 1982, [039418](#)), neutrophils are  
31 likely to be injurious. However, neutrophils can contribute to the repair of O<sub>3</sub>-injured epithelium by  
32 removing necrotic epithelial cells (Mudway and Kelly, 2000, [010452](#); Vesely et al., 1999, [051045](#)).  
33 The degree of airways inflammation due to O<sub>3</sub> is thought to have more important long-term  
34 consequences than the more quickly resolving changes in pulmonary function since airways  
35 inflammation is often accompanied by tissue injury (Balmes et al., 1996, [080830](#)).

36 The influx of inflammatory cells in the airways of human subjects has been assessed by  
37 bronchoscopy and by morphometric measurements in bronchial mucosal biopsies. Bronchoscopy can  
38 be used to sample fluid from all of the airways and from the lung parenchyma distal to the wedged

1 bronchoscope tip or just the more proximal portion. While many studies have documented a distal  
2 lung inflammatory response using conventional (pooled) BAL, a lesser number of studies have  
3 documented inflammation in the proximal airways using “proximal” BAL sampling (i.e., liquid  
4 aspirated from a 20-30 mL initial lavage aliquot after wedging the bronchoscope or from the left  
5 main bronchus transiently isolated by inflation of proximal and distal balloons) or by using bronchial  
6 mucosal biopsy (Aris et al., 1993, [038275](#); Schelegle et al., 1991, [042491](#)). Airways neutrophilia was  
7 observed at 1 and 6 hours postexposure in proximal airways BAL but only at 6 hours postexposure  
8 in BAL from all of the airways combined (Schelegle et al., 1991, [042491](#)). This result demonstrated  
9 that measurements made in proximal airways BAL better reflected the earliest phase of airways  
10 inflammation than measurements made in conventional multi-aliquot (pooled) BAL.

11 Inter-individual variability in the neutrophilic response has been noted (Devlin et al., 1991,  
12 [040359](#); Holz et al., 1999, [058731](#); Schelegle et al., 1991, [042491](#)). One study demonstrated a  
13 threefold difference in airways neutrophilia, measured as percent of total cells in proximal BAL,  
14 among human subjects exposed to 0.3 ppm O<sub>3</sub> for 1 hour while exercising (Schelegle et al., 1991,  
15 [042491](#)), while a 20-fold difference was demonstrated in BAL neutrophils following exposure to  
16 0.08-0.10 ppm O<sub>3</sub> for 6.6 hours while exercising (Devlin et al., 1991, [040359](#)). Reproducibility of  
17 intra-individual responses to 0.25 ppm O<sub>3</sub>, measured as sputum neutrophilia, was demonstrated by  
18 Holz (1999, [058731](#)). Few studies have examined the dose-responsiveness of airways neutrophilia in  
19 O<sub>3</sub>-exposed humans (Devlin et al., 1991, [040359](#); Holz et al., 1999, [058731](#)). No dose-  
20 responsiveness was observed in healthy human subjects exposed for 1 hour to 0.125 and 0.25 ppm  
21 O<sub>3</sub> and a statistically significant increase in sputum neutrophilia was observed only at the higher  
22 dose (Holz et al., 1999, [058731](#)). However, dose-dependent and statistically significant increases in  
23 BAL neutrophils and the inflammatory mediator IL-6 were reported following exposure to 0.08 and  
24 0.1 ppm O<sub>3</sub> for 6.6 hours in exercising humans (Devlin et al., 1991, [040359](#)). Additional evidence is  
25 provided by a meta-analysis of the O<sub>3</sub> dose-inflammatory response in controlled human exposure  
26 studies involving exposure to 0.08-0.6 ppm O<sub>3</sub> for 60-396 minutes (Mudway and Kelly, 2004,  
27 [399328](#)). Results demonstrated a linear relationship between inhaled O<sub>3</sub> dose (determined as the  
28 product of concentration, ventilation and time) and BAL neutrophils at 0-6 hours and 18-24 hours  
29 following O<sub>3</sub> exposure (Mudway and Kelly, 2004, [399328](#)).

30 Ozone exposure results in alterations in other airways inflammatory cells besides neutrophils.  
31 Numbers of lymphocytes and total cells in BAL fluid were decreased early after O<sub>3</sub> exposure,  
32 preceding the neutrophil influx (Blomberg et al., 1999, [001267](#); Krishna et al., 1997, [084262](#);  
33 Mudway and Kelly, 2000, [010452](#)). The decrease in total cells was thought to reflect decreases in  
34 airway macrophages, although it was not clear whether the cells were necrotic or whether membrane  
35 adhesive properties were altered making them more difficult to obtain by lavage (Blomberg et al.,  
36 1999, [001267](#); Frampton et al., 1997, [086111](#); Mudway and Kelly, 2000, [010452](#); Mudway et al.,  
37 1999, [011833](#); Pearson and Bhalla, 1997, [082686](#)). Recent studies have demonstrated increases in  
38 numbers of sputum monocytes and dendritic-like cells (Alexis et al., 2010, [628538](#)) (discussed

1 further in section 5.2.7). Increases in submucosal mast cells were observed 1.5 hours after a 2-h  
2 exposure of healthy human subjects to 0.2 ppm O<sub>3</sub> (Blomberg et al., 1999, [001267](#)) and increases in  
3 BAL mast cell number were observed 18 hours after O<sub>3</sub> exposure (Frampton et al., 1997, [086111](#)).  
4 Mast cells may play an important role in mediating neutrophil influx since they are an important  
5 source of several pro-inflammatory cytokines and since their influx precedes that of the neutrophils  
6 (Blomberg et al., 1999, [001267](#); Stenfors et al., 2002, [030473](#)). Further, a study using mast cell-  
7 deficient mice demonstrated decreased neutrophilic inflammation in response to O<sub>3</sub> compared with  
8 wild type mice (Kleeberger et al., 1993, [044203](#)). The mechanisms involved in clearing O<sub>3</sub>-provoked  
9 inflammation remain to be clarified.

10 The cellular and molecular signals involved in injury and inflammatory responses following  
11 O<sub>3</sub> exposure have been extensively evaluated (U.S. EPA, 2006, [088089](#)). Eicosanoids are one class  
12 of secondary oxidation products which may be formed rapidly following O<sub>3</sub> exposure and which  
13 may mediate injury and inflammation. Eicosanoids are metabolites of arachidonic acid, a 20-carbon  
14 polyunsaturated fatty acid, which is released from membrane phospholipids by phospholipase  
15 A<sub>2</sub>-mediated catalysis. Activation of phospholipase A<sub>2</sub> occurs by several cell signaling pathways  
16 and may be triggered by O<sub>3</sub>-mediated lipid peroxidation of cellular membranes (Rashba-Step et al.,  
17 1997, [628562](#)). Additionally, cellular phospholipases A<sub>2</sub>, C and D may be activated by lipid  
18 ozonation products (Kafoury et al., 1998, [016913](#)). While the conversion of arachidonic acid to  
19 prostaglandins, leukotrienes and other eicosanoid products is generally catalyzed by  
20 cyclooxygenases and lipoxygenases, non-enzymatic reactions also occur during oxidative stress  
21 leading to the generation of a wide variety of eicosanoids and reactive oxygen species. Further, the  
22 release of arachidonic acid from phospholipids is accompanied by the formation of  
23 lysophospholipids which are precursors for platelet activating factors. Thus, formation of  
24 eicosanoids, reactive oxygen species and platelet activating factors accompanies O<sub>3</sub>-mediated lipid  
25 peroxidation.

26 Additional cell signaling mediators are generated subsequent to O<sub>3</sub> exposure. Secondary  
27 reaction products may stimulate airway macrophages to produce cytokines such as IL-1, IL-6 and  
28 TNF- $\alpha$  which in turn activate IL-8 production by epithelial cells. Ozone exposure is also known to  
29 upregulate the vascular endothelial adhesion molecules P-selectin and ICAM-1 (Blomberg et al.,  
30 1999, [001267](#); Krishna et al., 1997, [084262](#)) and to increase the expression of pro-inflammatory  
31 mediators GM-CSF, Gro- $\alpha$  and IL-8 (Mudway and Kelly, 2000, [010452](#)). In addition, lung epithelial  
32 cells may release ATP in response to O<sub>3</sub> exposure (Ahmad et al., 2005, [196429](#)). ATP and its  
33 metabolites (catalyzed by ecto-enzymes) can bind to cellular purinergic receptors resulting in  
34 activation of cell signaling pathways (Picher et al., 2004, [644780](#)). One such metabolite, adenine, is  
35 capable of undergoing oxidation leading to the formation of urate which, if present in high  
36 concentrations, could activate inflammasomes and result in caspase 1 activation and the maturation  
37 and secretion of IL-1 $\beta$  and IL-18 (Dostert et al., 2008, [155753](#)).

1 Many studies have focused on cell signaling pathways leading to airways neutrophilia in  
2 humans or animal models which generally peaks 4-6 hours after exposure. Although IL-8 has been  
3 proposed to play a role in neutrophil chemotaxis, measurements of IL-8 in lavage fluid from humans  
4 exposed to O<sub>3</sub> show increases that are too late to account for this effect (Mudway and Kelly, 2000,  
5 [010452](#)). However, the profiles of PGE<sub>2</sub> and IL-6 responses suggest that they may play a role in  
6 neutrophil chemotaxis. A study in mice demonstrated that PAF may be important in this response  
7 (Longphre et al., 1999, [001199](#)), while macrophage inflammatory protein-2 (MIP-2) and ICAM-1  
8 have also been implicated in a rat model (Bhalla and Gupta, 2000, [015036](#)). Other studies have  
9 investigated mechanisms involved in earlier or later phases of neutrophilic airways inflammation and  
10 inflammation occurring in the nasal airways and more distal lung (U.S. EPA, 2006, [088089](#)).

11 One set of studies in humans focused on the earliest phase of airways inflammation (1-2 hours  
12 following exposure). Exercising subjects were exposed to 0.2 ppm O<sub>3</sub> for 2 hours and bronchial  
13 biopsy tissues were obtained 1.5 and 6 hours after exposure (Blomberg et al., 1999, [001267](#); Bosson  
14 et al., 2003, [051687](#); Bosson et al., 2009, [399331](#); Stenfors et al., 2002, [030473](#)). Results  
15 demonstrated upregulation of vascular endothelial adhesion molecules P-selectin and ICAM-1 at  
16 both 1.5 and 6 hours (Blomberg et al., 1999, [001267](#); Stenfors et al., 2002, [030473](#)). Submucosal  
17 mast cell numbers were increased at 1.5 hours in the biopsy samples without an accompanying  
18 increase in neutrophil number (Blomberg et al., 1999, [001267](#)). Pronounced neutrophil infiltration  
19 was observed at 6 h in the bronchial mucosa (Stenfors et al., 2002, [030473](#)). Surprisingly,  
20 suppression of the NFκB and AP-1 pathways at 1.5 hours and a lack of increased IL-8 at 1.5 or  
21 6 hours in bronchial epithelium was observed (Bosson et al., 2009, [399331](#)). The authors suggested  
22 that vascular endothelial adhesion molecules, rather than redox sensitive transcription factors, are  
23 key to early neutrophil recruitment in response to O<sub>3</sub>.

24 Multi-day exposure to O<sub>3</sub> has been found to dampen the inflammatory response, but not the  
25 injury response, compared with a single day exposure (Christian et al., 1998, [029925](#); Devlin et al.,  
26 1997, [083577](#)). In human subjects exposed for 4 hours to 0.2 ppm O<sub>3</sub> during moderate exercise,  
27 decreased numbers of BAL neutrophils were observed after 4 days of consecutive exposure  
28 compared with responses after 1 day (Christian et al., 1998, [029925](#)). Results indicated an  
29 attenuation of the inflammatory response in both proximal airways and distal lung. However  
30 repeated exposure did not result in attenuation of the injury markers lactate dehydrogenase and  
31 protein in the BAL. Similar results were found in a study of humans undergoing heavy intermittent  
32 exercise who were exposed for 2 hours to 0.4 ppm O<sub>3</sub> for 5 consecutive days (Devlin et al., 1997,  
33 [083577](#)). In this latter study, partial recovery of the inflammatory response was noted 10 days  
34 following the exposure (Devlin et al., 1997, [083577](#)). In an animal study conducted in parallel (Van  
35 Bree et al., 2002, [035452](#)), full susceptibility to O<sub>3</sub> challenge following exposure to O<sub>3</sub> for 5  
36 consecutive days required 15-20 days recovery. Further, no attenuation of cellular proliferation in  
37 terminal bronchioles was observed during the 5 consecutive days of O<sub>3</sub> exposure. In a separate study  
38 in rats involving repeated O<sub>3</sub> exposures, a lack of attenuation of the injury marker lavagable protein,

1 the persistence of macrophages in the centriacinar region, and histological evidence of progressive  
2 tissue injury was demonstrated (Tepper et al., 1989, [041991](#)). Thus, the inflammatory response  
3 resembled that of the pulmonary function response which was attenuated with repeated short-term  
4 O<sub>3</sub> exposure in both human subjects and animals (Christian et al., 1998, [029925](#); Hackney et al.,  
5 1977, [038282](#); Horvath et al., 1981, [039221](#)). Findings that injury, measured by BAL markers or by  
6 histopathology, persisted in the absence of inflammation or pulmonary function decrements suggests  
7 that, despite adaptation, repeated exposure to O<sub>3</sub> may have serious long-term consequences such as  
8 airway remodeling. The mechanisms involved in clearing O<sub>3</sub>-provoked inflammation remain to be  
9 clarified.

10 Increases in markers of inflammation and of injury occurred to a comparable degree in  
11 subjects with mild (least sensitive) and more remarkable (more sensitive) spirometric responses to  
12 O<sub>3</sub> (Balmes et al., 1996, [080830](#)). Two other studies using similar exposure protocols found that  
13 acute spirometric changes were not positively correlated with cellular and biochemical indicators of  
14 inflammation (Aris et al., 1993, [038275](#); Schelegle et al., 1991, [042491](#)). However inflammation was  
15 correlated with changes in sRaw (Balmes et al., 1996, [080830](#)). In another study, pretreatment with  
16 ibuprofen had no effect on neutrophilia although it blunted the spirometric response (Hazucha et al.,  
17 1996, [043923](#)). Taken together, results from these studies indicate different mechanisms underlying  
18 the spirometric and inflammatory responses to O<sub>3</sub>.

19 In contrast, a common mechanism underlying both inflammation and impaired pulmonary  
20 function was suggested by (Krishna et al., 1997, [084262](#)). This study, conducted in exercising  
21 humans exposed to 0.2 ppm O<sub>3</sub> for 2 hours, demonstrated a correlation between loss of SP  
22 immunoreactivity from neurons in the bronchial mucosa and numbers of neutrophils and epithelial  
23 cells (shed epithelial cells are an index of injury) in the BAL 6 h postexposure. Furthermore, the loss  
24 of SP immunoreactivity was correlated with the observed changes in FEV<sub>1</sub>. SP is a neuropeptide  
25 released by sensory nerves which mediates neurogenic edema and bronchoconstriction (Krishna et  
26 al., 1997, [084262](#)). Further, another study found that SP was increased in lavage fluid of human  
27 subjects immediately after O<sub>3</sub> challenge (Hazbun et al., 1993, [043914](#)). Taken together, these  
28 findings suggest O<sub>3</sub>-mediated stimulation of sensory nerves leading to activation of central and local  
29 axon reflexes as a common effector pathway leading to impaired pulmonary function and  
30 inflammation.

31 Chronic exposure to O<sub>3</sub> has been studied in animal models. In the nasal airways, exposure to  
32 O<sub>3</sub> for days or weeks results in mucous cell metaplasia of nasal transitional epithelium (Harkema et  
33 al., 1999, [001209](#); Hotchkiss et al., 1991, [042441](#)). This remodeling effect was characterized by  
34 neutrophilic infiltration, a loss of sensitive nasal epithelial cells, the proliferation of resistant  
35 epithelial cells and mucin gene overexpression (Cho et al., 1999, [011985](#)). Bronchiolitis, bronchiolar  
36 metaplasia of alveolar ducts, proliferation of Type 2 pneumocytes and fibrosis were reported  
37 following chronic O<sub>3</sub> exposure (Mudway and Kelly, 2000, [010452](#)). It was suggested that remodeling  
38 of respiratory epithelium may lead to enhanced resistance or tolerance to O<sub>3</sub> (Mudway and Kelly,

1 2000, [010452](#)). Deposition of collagen in the airways and sustained lung function decrements  
2 especially in small airways have also been demonstrated as a response to chronic O<sub>3</sub> exposure  
3 (Chang et al., 1992, [042387](#); Mudway and Kelly, 2000, [010452](#)).

#### 5.2.4.1. New Cellular and Molecular Insights

4 Recent investigations in animal models have elucidated additional mechanisms involved in  
5 O<sub>3</sub>-induced inflammation and injury. In one study, tachykinins working through NK-1 and CGRP  
6 receptors were found to contribute to airways epithelial injury, but not to neutrophil influx, in O<sub>3</sub>-  
7 exposed rats (Oslund et al., 2008, [195654](#); Oslund et al., 2009, [201539](#)). Key roles for CXCR2, a  
8 receptor for the cytokines KC and MIP-2, and for IL-6 in O<sub>3</sub>-mediated neutrophil influx were  
9 demonstrated in mice (Johnston et al., 2005, [596393](#); Johnston et al., 2005, [596394](#)). Activation of  
10 JNK and p38 pathways and cathepsin-S were also found to be important in this response (Williams  
11 et al., 2007, [628609](#); Williams et al., 2008, [628607](#); Williams et al., 2009, [628605](#)). Furthermore,  
12 matrix metalloproteinase-9 (MMP-9) protected against O<sub>3</sub>-induced airways inflammation and injury  
13 in mice (Yoon et al., 2007, [596422](#)).

14 Williams et al. (2007, [597545](#)) found that the toll-like receptor (TLR) adaptor protein MyD88  
15 was important in mediating O<sub>3</sub>-induced neutrophilia in mice exposed to 3 ppm O<sub>3</sub> for 3 hours, with  
16 TLR4 and TLR2 contributing to the speed of the response. Moreover, MyD88, TLR2 and TLR4  
17 contributed to inflammatory gene expression in this model and O<sub>3</sub> upregulated MyD88, TLR4 and  
18 TLR4 gene expression. These results complement those of Hollingsworth et al. (2004, [097816](#)) who  
19 demonstrated airways neutrophilia following acute (2 ppm O<sub>3</sub> for 3 hours) and subchronic O<sub>3</sub>  
20 exposure (0.3 ppm for 3 days) in a mouse model (Hollingsworth et al., 2004, [097816](#)). In this study,  
21 airways neutrophilia was not dependent on TLR4 (Hollingsworth et al., 2004, [097816](#)). Ozone  
22 effects on lung hyperpermeability, which is often correlated with neutrophil influx, were previously  
23 found to require a functioning TLR4 (Kleeberger et al., 2000, [014895](#)).

24 Other studies focused on the role of hyaluronan in mediating a later phase (24 hours) of  
25 O<sub>3</sub>-induced inflammation in mice (Garantziotis et al., 2009, [597603](#); Garantziotis et al., 2010,  
26 [624947](#)). Hyaluronan is an extracellular matrix component which is normally found in the ELF as a  
27 large polymer. Exposure to 2 ppm O<sub>3</sub> for 3 hours resulted in elevated levels of soluble low molecular  
28 weight hyaluronan in the BAL fluid 24 hours postexposure (Garantziotis et al., 2009, [597603](#);  
29 Garantziotis et al., 2010, [624947](#)). Ozone may have caused the depolymerization of hyaluronan to  
30 soluble fragments which are known to be endogenous ligands of the CD44 receptor and TLR4 in the  
31 macrophage (Jiang et al., 2005, [628556](#)). Binding of hyaluronan fragments to the CD44 receptor  
32 activates hyaluronan clearance, while binding to TLR4 results in signaling through MyD88 to  
33 produce chemokines that stimulate the influx of inflammatory cells (Jiang et al., 2005, [628556](#)).  
34 Activation of NFκB occurred in both airway epithelia and alveolar macrophages 24 hours  
35 postexposure to O<sub>3</sub>. Increases in BAL pro-inflammatory factors KC, IL-1β, MCP-1, tumor  
36 necrosis factor-α (TNF-α) and IL-6 observed 24 hours following O<sub>3</sub> exposure were found to be

1 partially dependent on TLR4 while increases in BAL inflammatory cells, which consisted mainly of  
2 macrophages, were dependent on CD44. BAL inflammatory cells number and injury markers  
3 following O<sub>3</sub> exposure were similar in wild-type and TLR4-deficient animals.

#### 5.2.4.2. Summary

4 Injury and inflammation are key events in ozone's toxicity pathway. Secondary oxidation  
5 products have been implicated in a number of these processes. Although there may be inter-species  
6 differences with respect to specific mediators, mechanisms involved in the acute responses to O<sub>3</sub>  
7 include epithelial injury and airways neutrophilia. Longer-term exposures may result in mucus cell  
8 metaplasia of nasal epithelium or airways remodeling and fibrosis. Work from several laboratories in  
9 humans and animal models suggest that O<sub>3</sub> triggers the release of tachykinins such as SP from  
10 airway sensory nerves which could contribute to downstream effects including injury and  
11 inflammation. New investigations show that O<sub>3</sub> exposure leads to the generation of hyaluronan  
12 fragments which activate TLR4 and CD44-dependent signaling pathways in macrophages and result  
13 in a greater turnover of macrophage populations in the lung. Activation of these pathways occurs  
14 later than the acute neutrophilic response suggesting that they may contribute to longer-term effects  
15 of O<sub>3</sub>. The mechanisms involved in clearing O<sub>3</sub>-provoked inflammation remain to be clarified.

16 Similar to the pulmonary function responses discussed in the previous section, considerable  
17 inter-individual variability exists in O<sub>3</sub> responsiveness as measured by airways neutrophilia. Further,  
18 attenuation of the inflammatory response occurs following O<sub>3</sub> exposure for several consecutive days.  
19 However evidence suggests that injury may continue despite the dampening of the inflammatory  
20 response during repeated exposures. Mechanisms responsible for inter-individual variability and  
21 response attenuation, or the lack thereof, are not known. It should be noted that inflammation, as  
22 measured by airways neutrophilia, is not correlated with decrements in pulmonary function as  
23 measured by spirometry. Consequently, spirometric measures are not a good surrogate for the degree  
24 of inflammation in any given individual following O<sub>3</sub> exposure. Furthermore, airways neutrophilia  
25 may not be a good indicator of O<sub>3</sub>-mediated lung injury.

#### 5.2.5. Increased Bronchial Reactivity

26 In addition to causing mild airways obstruction as discussed above, acute O<sub>3</sub> exposure results  
27 in reversible increases in bronchial reactivity by mechanisms which are not well understood. These  
28 effects may be more significant in human subjects with already compromised airways  
29 (Section 5.2.6). Bronchial reactivity is generally determined in terms of a response to a challenge  
30 agent. Non-specific bronchial reactivity in humans is assessed by measuring the effect of inhaling  
31 increasing concentrations of a bronchoconstrictive drug on lung mechanics (sRaw or FEV<sub>1</sub>).  
32 Methacholine is most commonly employed but histamine and other agents are also used. Specific  
33 bronchial reactivity is assessed by measuring effects in response to an inhaled allergen in individuals

1 (or animals) already sensitized to that allergen. An increase in sRaw in response to non-specific or  
2 specific challenge agents indicates airways hyperresponsiveness (AHR).

3 Ozone may sensitize bronchial smooth muscle to stimulation through a direct effect on smooth  
4 muscle or through effects on the sensory nerves in the epithelium or on the motor nerves innervating  
5 the smooth muscle (Holtzman et al., 1979, [039220](#); O'Byrne et al., 1983, [041366](#); O'Byrne et al.,  
6 1984, [040066](#)). One possibility may be related to O<sub>3</sub>-mediated increases in epithelial permeability,  
7 which would improve access of agonist to smooth muscle receptors (Holtzman et al., 1979, [039220](#)).  
8 Neurally-mediated effects have been demonstrated in several studies. In one, pretreatment with  
9 atropine was found to block O<sub>3</sub>-induced AHR, suggesting the involvement of cholinergic  
10 postganglionic pathways (Holtzman et al., 1979, [039220](#)). Other studies in animals demonstrated  
11 that O<sub>3</sub>-induced AHR involved vagally-mediated responses (Freed et al., 1996, [080798](#)) and local  
12 axon reflex responses through bronchopulmonary C fiber-mediated release of SP (Joad et al., 1996,  
13 [082711](#)). Further, pretreatment with capsaicin to deplete nerve fibers of SP blocked O<sub>3</sub>-mediated  
14 bronchial reactivity measured as AHR (Tepper et al., 1993, [628570](#)).

15 Some evidence suggested the involvement of arachidonic acid metabolites (Fabbri et al., 1985,  
16 [040276](#); Seltzer et al., 1986, [040383](#)). An early study found AHR in exercising humans immediately  
17 postexposure to 0.6 ppm O<sub>3</sub> for 2 hours, which was associated with increases in BAL neutrophils and  
18 cyclooxygenase products (Seltzer et al., 1986, [040383](#)). Other investigators found that ibuprofen  
19 pretreatment had no effect on AHR following exposure to 0.4 ppm O<sub>3</sub> for 2 hours, although  
20 spirometric responses were blunted (Hazucha et al., 1996, [043923](#)). This study indicated that the  
21 arachidonic acid metabolites whose generation was blocked by ibuprofen, an inhibitor of  
22 cyclooxygenase and some lipoxygenase activity, (i.e. prostaglandins, thromboxanes and some  
23 leukotrienes) did not play a role in AHR. Experiments in dogs demonstrated a close correlation  
24 between O<sub>3</sub>-induced AHR and airway neutrophilic inflammation measured in tissue biopsies  
25 (Holtzman et al., 1983, [039745](#)). Furthermore, the increased AHR observed in dogs following O<sub>3</sub>  
26 exposure was inhibited by neutrophil depletion (O'Byrne et al., 1983, [041366](#)) and by pre-treatment  
27 with inhibitors of arachidonic acid metabolism. In one of these studies, indomethacin pre-treatment  
28 did not prevent airway neutrophilia in response to O<sub>3</sub> providing evidence that the subset of  
29 arachidonic acid metabolites whose generation was inhibitable by the cyclooxygenase inhibitor  
30 indomethacin (i.e., prostaglandins and thromboxanes) was not responsible for neutrophil influx  
31 (O'Byrne et al., 1984, [040066](#)). Taken together, these findings suggest that arachidonic acid  
32 metabolites, but probably not prostaglandins or thromboxanes, may be involved in the AHR response  
33 following O<sub>3</sub> exposure in dogs.

34 Later it was recognized that increased bronchial reactivity can be both a rapidly occurring and  
35 persistent response to O<sub>3</sub> (Foster and Freed, 1999, [001202](#)). Secondary oxidation products of O<sub>3</sub> and  
36 tachykinins have been proposed as early mediators of the response and inflammation-derived  
37 products have been proposed as mediators of the later response (Foster and Freed, 1999, [001202](#)).  
38 Some studies have suggested an involvement of IL-1 (Park et al., 2004, [644864](#)) and TNF- $\alpha$  (Cho et

1 al., 2001, [016160](#); Shore et al., 2001, [018993](#)). Furthermore, multiday exposure to O<sub>3</sub> has been found  
2 to dampen the AHR response compared with a single day exposure (Dimeo et al., 1981, [039662](#)).

### 5.2.5.1. New Cellular and Molecular Insights

3 Recent studies in animal models provide new evidence for mechanisms underlying increased  
4 bronchial reactivity. In guinea pigs, AHR was found to be mediated by different pathways at 1 and  
5 3 days postexposure to a single dose of O<sub>3</sub> (2 ppm for 4 hours) (Verhein et al., 2011, [670295](#); Yost et  
6 al., 2005, [597549](#)). At 1 day, airway hyperreactivity was due to activation of airway parasympathetic  
7 nerves rather than to a direct effect on smooth muscle (Yost et al., 2005, [597549](#)). This effect  
8 occurred as a result of O<sub>3</sub>-stimulated release of major basic protein from eosinophils (Yost et al.,  
9 2005, [597549](#)). Major basic protein is known to block inhibitory M2 muscarinic receptors which  
10 normally dampen acetylcholine release from parasympathetic nerves (Yost et al., 2005, [597549](#)). The  
11 resulting increase in acetylcholine release caused an increase in smooth muscle contraction  
12 following O<sub>3</sub> exposure (Yost et al., 2005, [597549](#)). Eosinophils played a different role 3 days  
13 postexposure to O<sub>3</sub> in guinea pigs (Yost et al., 2005, [597549](#)). Ozone-mediated influx of eosinophils  
14 into lung airways resulted in a different population present 3 days postexposure compared to those  
15 present at one day (Yost et al., 2005, [597549](#)). At this point, eosinophil-derived major basic protein  
16 increased smooth muscle responsiveness to acetylcholine which also contributed to AHR (Yost et al.,  
17 2005, [597549](#)). However, the major effect of eosinophils was to protect against vagal hyperreactivity  
18 (Yost et al., 2005, [597549](#)). The authors suggested that these beneficial effects were due to the  
19 production of nerve growth factor (Yost et al., 2005, [597549](#)). Further work by these investigators  
20 demonstrated a key role for IL-1beta in mediating AHR three days postexposure to O<sub>3</sub> (Verhein et  
21 al., 2011, [670295](#)). In this study, IL-1beta increased nerve growth factor and SP which acted through  
22 the NK1 receptor to cause vagally-mediated bronchoconstriction (Verhein et al., 2011, [670295](#)). The  
23 mechanism by which SP caused acetylcholine release from parasympathetic nerves following O<sub>3</sub>  
24 exposure was not determined (Verhein et al., 2011, [670295](#)). Two studies by other investigators  
25 demonstrated that SP released from airways nociceptive neurons contributed to O<sub>3</sub>-induced AHR  
26 measured 3 hours postexposure to 2 ppm O<sub>3</sub> in ferrets (Wu et al., 2003, [628616](#); Wu et al., 2008,  
27 [597548](#)). These authors further suggested that SP expression in airway neurons was upregulated by  
28 IL-1 which was released in response to O<sub>3</sub> (Wu et al., 2008, [597548](#)). Taken together, the above  
29 study results indicate that mechanisms involved in O<sub>3</sub>-mediated AHR can vary over time  
30 postexposure and that eosinophils and SP can play a role.

31 Evidence for cytokine and chemokine involvement in the AHR response to O<sub>3</sub> has recently  
32 been described. Williams et al. (2008, [597546](#)) demonstrated that the Th2 cytokine IL-13 contributed  
33 to AHR, as well as to airways neutrophilia, following exposure of mice to 3 ppm O<sub>3</sub> for 3 hours.  
34 Other studies in mice have demonstrated a key role for CXCR2, the chemokine receptor for the  
35 neutrophil chemokines KC and MIP-2, but not for IL-6 in O<sub>3</sub>-mediated AHR (Johnston et al., 2005,  
36 [596394](#); Johnston et al., 2005, [596393](#)). In contrast, CXCR2 and IL-6 were both required for

1 neutrophil influx in this model (Johnston et al., 2005, [596393](#); Johnston et al., 2005, [596394](#)), as  
2 discussed above.

3 Other studies have focused on the role of TLR4. Hollingsworth measured AHR, as well as  
4 airways neutrophilia, in mice 6 and 24 hours following acute (2 ppm O<sub>3</sub> for 3 hours) and subchronic  
5 (0.3 ppm for 3 days) exposure to O<sub>3</sub> (Hollingsworth et al., 2004, [097816](#)). TLR4 is a key component  
6 of the innate immune system and is responsible for the immediate inflammatory response seen  
7 following challenge with endotoxin and other pathogen-associated substances. In the 2004 study, a  
8 functioning TLR4 was required for the full AHR response following O<sub>3</sub> exposure but not for airways  
9 neutrophilia (Hollingsworth et al., 2004, [097816](#)). These findings are complemented by an older  
10 study demonstrating that O<sub>3</sub> effects on lung hyperpermeability required a functioning TLR4  
11 (Kleeberger et al., 2000, [014895](#)). Williams et al. (2007, [597545](#)) found that TLR2, TLR4 and the  
12 TLR adaptor protein MyD88 contributed to AHR in mice exposed to 3 ppm O<sub>3</sub> for 3 hours. Ozone  
13 was also found to upregulate MyD88, TLR4 and TLR4 gene expression in this model (Williams et  
14 al., 2007, [597545](#)).

15 A newly recognized mechanistic basis for O<sub>3</sub>-induced AHR is provided by studies focusing on  
16 the role of hyaluronan following O<sub>3</sub> exposure in mice (Garantziotis et al., 2010, [624947](#))  
17 (Garantziotis et al., 2009, [597603](#)). Briefly, TLR4 and CD44 were found to mediate AHR in response  
18 to O<sub>3</sub> and hyaluronan. Hyaluronan is an extracellular matrix component which is normally found in  
19 the ELF as a large polymer. Exposure to 2 ppm O<sub>3</sub> for 3 hours resulted in enhanced AHR and  
20 elevated levels of soluble low molecular weight hyaluronan in the BAL fluid 24 hours postexposure  
21 (Garantziotis et al., 2009, [597603](#); Garantziotis et al., 2010, [624947](#)). Ozone may have caused the  
22 depolymerization of hyaluronan to soluble fragments which are known to be endogenous ligands of  
23 the CD44 receptor and TLR4 in the macrophage (Jiang et al., 2005, [628556](#)). In the two recent  
24 studies, O<sub>3</sub>-induced AHR was attenuated in CD44 and TLR4-deficient mice (Garantziotis et al.,  
25 2009, [597603](#); Garantziotis et al., 2010, [624947](#)). Hyaluronan fragment-mediated stimulation of  
26 AHR was found to require functioning CD44 receptor and TLR4 (Garantziotis et al., 2009, [597603](#);  
27 Garantziotis et al., 2010, [624947](#)). In contrast, high-molecular-weight hyaluronan blocked AHR in  
28 response to O<sub>3</sub> (Garantziotis et al., 2009, [597603](#)). In another study high-molecular-weight  
29 hyaluronan enhanced repair of epithelial injury (Jiang et al., 2005, [628556](#)). These studies provide a  
30 link between innate immunity and the development of AHR following O<sub>3</sub> exposure, and indicate a  
31 role for TLR4 in increasing bronchial smooth muscle reactivity.

## 5.2.5.2. Summary

32 Increased bronchial reactivity is a key event in the toxicity pathway of O<sub>3</sub>. It can be both a  
33 rapidly occurring and persistent response, although adaptation can also occur during multi-day  
34 exposures. Both direct effects on smooth muscle and neurally-mediated effects on smooth muscle  
35 have been proposed to contribute to AHR following O<sub>3</sub> exposure. Currently, more evidence has  
36 accumulated for the latter mechanism. In humans exposed to O<sub>3</sub>, atropine was found to block the

1 early AHR response indicating the involvement of cholinergic postganglionic pathways. Inhibition  
2 of arachidonic acid metabolism was ineffective in blocking this response in humans while mixed  
3 results were found in animal models. Studies in O<sub>3</sub>-exposed animals have demonstrated a role for SP  
4 release from bronchial C fibers in mediating neurally-mediated effects on smooth muscle. Later  
5 phases of increased bronchial reactivity may involve the induction of IL-1beta which in turn  
6 upregulates SP production. In guinea pigs, eosinophil-derived major basic protein contributed to the  
7 stimulation of cholinergic postganglionic pathways. A novel role for hyaluronan in mediating the  
8 later phase effects of O<sub>3</sub> has recently been demonstrated. High molecular weight polymers of  
9 hyaluronan normally found in the ELF were degraded following O<sub>3</sub> exposure in mice. The resulting  
10 hyaluronan fragments stimulated AHR in a TLR4- and CD44 receptor-dependent manner. Previous  
11 work has shown that O<sub>3</sub>-mediated increases in lung permeability required a functioning TLR4  
12 suggesting a possible relationship between increased epithelial permeability and AHR in this model.  
13 Other cytokines and chemokines have been implicated in the AHR response to O<sub>3</sub> in animals models.

## 5.2.6. Exacerbation and Induction of Asthma and Allergic Responses

14 In individuals with asthma, there is increased responsiveness to bronchoconstrictor challenge.  
15 This results from a combination of structural and physiological factors including increased inner-  
16 wall thickness, smooth muscle responsiveness and mucus secretion. Although inflammation is likely  
17 to contribute, its relationship to AHR is not clear (U.S. EPA, 2006, [088089](#)). However, some  
18 asthmatics have higher baseline levels of neutrophils, lymphocytes, eosinophils and mast cells in  
19 bronchial washes and bronchial biopsy tissue (Stenfors et al., 2002, [030473](#)). Evidence is  
20 accumulating that O<sub>3</sub> exposure exacerbates asthmatic and allergic responses in sensitive individuals.  
21 Further, some studies suggest that O<sub>3</sub> exposure leads to the development of asthmatic and allergic  
22 responses.

23 In order to determine whether asthmatics exhibit greater sensitivity to O<sub>3</sub>, several older studies  
24 compared pulmonary function responses in asthmatic and non-asthmatic subjects following O<sub>3</sub>  
25 exposure. While the majority focused on measurements of FEV<sub>1</sub> and FVC and found no differences  
26 between the two groups (Holz et al., 1999, [058731](#); Koenig et al., 1987, [041521](#); Linn et al., 1978,  
27 [038874](#); Mudway et al., 2001, [025327](#); Scannell et al., 1996, [080755](#); Stenfors et al., 2002, [030473](#)),  
28 there were notable exceptions. In one study, greater airways obstruction in asthmatics compared with  
29 non-asthmatic subjects was observed immediately following a 2-h exposure to 0.4 ppm O<sub>3</sub> with  
30 intermittent exercise (Kreit et al., 1989, [041817](#)). These changes were measured as statistically  
31 significant greater decreases in FEV<sub>1</sub> and FEF<sub>25-75</sub> in the absence of a bronchoconstrictor challenge  
32 (Kreit et al., 1989, [041817](#)). These results suggest that this group of asthmatics responded to  
33 O<sub>3</sub>-exposure with a greater degree of vagally-mediated bronchoconstriction compared with the non-  
34 asthmatics. A second study demonstrated a statistically significant greater decrease in FEV<sub>1</sub> and  
35 FEV<sub>1</sub>/FVC in asthmatics compared with non-asthmatics exposed to 0.12 ppm O<sub>3</sub> for 7.6 hours with  
36 light exercise (Horstman et al., 1995, [075834](#)). These responses were accompanied by wheezing and

1 inhaler use in the asthmatics (Horstman et al., 1995, [075834](#)). Aerosol bolus dispersion  
2 measurements demonstrated a statistically significant greater change in asthmatics compared with  
3 non-asthmatics which was suggestive of O<sub>3</sub>-induced small airway dysfunction (Horstman et al.,  
4 1995, [075834](#)). Furthermore, a statistically significant correlation was observed between the degree  
5 of baseline airway status and the FEV<sub>1</sub> response to O<sub>3</sub> in the asthmatic subjects (Horstman et al.,  
6 1995, [075834](#)). A third study found similar decreases in FVC and FEV<sub>1</sub> in both asthmatics and non-  
7 asthmatics exposed to 0.4 ppm O<sub>3</sub> for 2 hours with mild exercise (Alexis et al., 2000, [013072](#)).  
8 However, a statistically significant decrease in FEF<sub>75</sub>, a measure of small airway function, was  
9 observed in asthmatics but not in non-asthmatics (Alexis et al., 2000, [013072](#)). Taken together these  
10 latter studies indicate that while the magnitude of restrictive type spirometric decline was similar in  
11 asthmatics and non-asthmatics, that obstructive type changes (i.e. bronchoconstriction) were greater  
12 in asthmatics. Further, asthmatics exhibited greater sensitivity to O<sub>3</sub> in terms of small airways  
13 function.

14 Since asthma exacerbations occur in response to allergens and/or other triggers, some studies  
15 have focused on O<sub>3</sub>-induced changes in AHR following a bronchoconstrictor challenge. No  
16 difference in sensitivity to methacholine bronchoprovocation was observed between asthmatics and  
17 non-asthmatics exposed to 0.4 ppm O<sub>3</sub> for 2 hours with moderate exercise (Kreit et al., 1989,  
18 [041817](#)). However, increased bronchial reactivity to inhaled allergens was demonstrated in mild  
19 allergic asthmatics (Jorres et al., 1996, [078122](#); Kehrl et al., 1999, [022101](#); Molfino et al., 1991,  
20 [042379](#)) and in allergen-sensitized guinea pigs following O<sub>3</sub> exposure (Sun et al., 1997, [082724](#)).  
21 Similar, but modest, responses were reported for individuals with allergic rhinitis (Jorres et al., 1996,  
22 [078122](#)). Further, the contractile response of isolated airways was increased by pre-exposure to O<sub>3</sub> in  
23 human subjects sensitized and challenged with allergen (Roux et al., 1999, [001264](#)).

24 In terms of airways neutrophilia, larger responses were observed in asthmatics compared to  
25 non-asthmatics subjects exposed to O<sub>3</sub> in some (Balmes et al., 1997, [086092](#); Basha et al., 1994,  
26 [075950](#); Scannell et al., 1996, [080755](#)) but not all (Mudway et al., 2001, [025327](#)) of the older  
27 studies. Further, statistically significant increases in myeloperoxidase levels (an indicator of  
28 neutrophil activation) in bronchial washes was observed in mild asthmatics compared with non-  
29 asthmatics, despite no difference in O<sub>3</sub>-stimulated neutrophil influx between the 2 groups following  
30 exposure to 0.2 ppm O<sub>3</sub> for 2 hours with mild exercise (Stenfors et al., 2002, [030473](#)).

31 Eosinophils and associated proteins are thought to affect muscarinic cholinergic receptors  
32 which are involved in vagally-mediated bronchoconstriction (Mudway and Kelly, 2000, [010452](#)).  
33 Studies described in Section 5.2.5.1 which demonstrated a key role of eosinophils in O<sub>3</sub>-mediated  
34 AHR may not be entirely relevant to humans given the large numbers of eosinophils normally  
35 present in guinea pig airways compared with humans (Yost et al., 2005, [597549](#)). However airways  
36 eosinophilia often occurs in human allergic airways disease, suggesting greater plausibility of this  
37 mechanism in allergic asthmatics. Furthermore, O<sub>3</sub> exposure sometimes often results in airways  
38 eosinophilia in allergic subjects or animal models. For example, eosinophilia of the nasal and other

1 airways was observed in individuals with preexisting allergic disease following O<sub>3</sub> inhalation (Peden  
2 et al., 1995, [076189](#); Vagaggini et al., 2002, [035191](#)). Further, O<sub>3</sub> exposure increased allergic  
3 responses, such as eosinophilia and augmented intraepithelial mucosubstances, in the nasal airways  
4 of ovalbumin (OVA)-sensitized rats (Wagner et al., 2002, [026079](#)). In contrast, Stenfors (2002,  
5 [030473](#)) found no stimulation of eosinophil influx measured in bronchial washes and BAL fluid of  
6 mild asthmatics following exposure to a lower concentration of O<sub>3</sub>.

7 The role of mast cells in O<sub>3</sub>-mediated asthma exacerbations has been investigated. Mast cells  
8 are thought to play a key role in O<sub>3</sub>-induced airways inflammation, since airways neutrophilia was  
9 decreased in mast cell-deficient mice exposed to O<sub>3</sub> (Kleeberger et al., 1993, [044203](#)). However,  
10 another study found that mast cells were not involved in the development of increased bronchial  
11 reactivity in O<sub>3</sub>-exposed mice (Noviski et al., 1999, [001198](#)). Nonetheless, mast cells release a wide  
12 variety of important inflammatory mediators which may lead to asthma exacerbations (Stenfors et  
13 al., 2002, [030473](#)). A large increase in mast cell number in bronchial submucosa was observed in  
14 non-asthmatics and a significant decrease in mast cell number in bronchial epithelium was observed  
15 in mild asthmatics 6 hours following exposure to 0.2 ppm O<sub>3</sub> for 2 hours during mild exercise  
16 (Stenfors et al., 2002, [030473](#)). While these results point to an O<sub>3</sub>-mediated flux in bronchial mast  
17 cell populations which differed between the non-asthmatics and mild asthmatics, interpretation of  
18 these findings is difficult. Furthermore, mast cell number did not change in airway lavages in either  
19 group in response to O<sub>3</sub> (Stenfors et al., 2002, [030473](#))

20 Cytokine profiles in the airways have been investigated as an indicator of O<sub>3</sub> sensitivity.  
21 Differences in epithelial cytokine expression were observed in bronchial biopsy samples in non-  
22 asthmatic and asthmatic subjects both at baseline and 6 h postexposure to 0.2 ppm O<sub>3</sub> for 2 hours  
23 (Bosson et al., 2003, [051687](#)). The asthmatic subjects had a higher baseline expression of IL-4 and  
24 IL-5 compared to non-asthmatics. In addition, expression of IL-5, IL-8, GM-CSF, and ENA-78 in  
25 asthmatics was increased significantly following O<sub>3</sub> exposure compared to non-asthmatics (Bosson  
26 et al., 2003, [051687](#)). Some of these (IL-4, IL-5 and GM-CSF) are T helper type 2 (Th2)-related  
27 cytokines or neutrophil chemoattractants, and play a role in IgE production, airway eosinophilia and  
28 suppression of Th1-cytokine production (Bosson et al., 2003, [051687](#)). These findings suggest a link  
29 between adaptive immunity and enhanced sensitivity of asthmatics to O<sub>3</sub>.

### 5.2.6.1. New Cellular and Molecular Insights

30 Since asthmatics may have enhanced sensitivity to O<sub>3</sub>, one recent study investigated whether  
31 O<sub>3</sub> exposure exacerbated asthmatic responses in persistent asthmatics. These subjects had been  
32 therapeutically treated with inhaled corticosteroids for several months prior to the study. Exposure of  
33 these subjects to 0.2 ppm O<sub>3</sub> for 2 hours with mild exercise resulted in decrements in FEV<sub>1</sub> and FVC  
34 and an increase in sRaw immediately postexposure (Stenfors et al., 2010, [386512](#)). In addition, large  
35 increases in neutrophil number and myeloperoxidase levels (an indicator of neutrophil activation) in  
36 airway lavages and in mast cell number in bronchial submucosa tissue obtained by biopsy was

1 observed 18 hours postexposure (Stenfors et al., 2010, [386512](#)). No change in bronchial wash or  
2 BAL fluid mast cell number or eosinophil number in any compartment was observed. (Stenfors et  
3 al., 2010, [386512](#)). These results suggest that some standard treatments for asthma may not protect  
4 against the effects of environmental O<sub>3</sub> and that this group may be particularly prone to asthma  
5 exacerbations given that airways neutrophilia occurred despite the inhaled corticosteroid treatment  
6 (Stenfors et al., 2010, [386512](#)).

7 Other recent studies in humans and animals provide evidence that O<sub>3</sub> causes the development  
8 of allergic responses and/or asthma. Several of these suggested that O<sub>3</sub>-mediated activation of innate  
9 immunity contributes to O<sub>3</sub>-induced, as well as to O<sub>3</sub>-amplified, allergic responses. In one study  
10 involving human subjects, the authors hypothesized that O<sub>3</sub> exposure would result in recruitment of  
11 activated innate immune cells to the airways. Healthy individuals were exposed to 0.08 ppm O<sub>3</sub> for  
12 6.6 hours with intermittent exercise and airways inflammation was characterized in induced sputum  
13 18 h postexposure (Alexis et al., 2010, [628538](#)). Previous studies demonstrated that induced sputum  
14 contains liquid and cellular constituents of the lining fluid from central conducting airways (Alexis  
15 et al., 2001, [190013](#)) and also identified these airways as a site of preferential O<sub>3</sub> absorption during  
16 exercise (Hu et al., 1994, [041323](#)). Ozone exposure resulted in sputum neutrophilia and increased  
17 numbers of airways monocytes and dendritic-like cells (Alexis et al., 2010, [628538](#)). In addition,  
18 increased expression of cell surface markers characteristic of innate immunity and antigen  
19 presentation (i.e. CD-14 and HLA-DR) was demonstrated on airways monocytes (Alexis et al., 2010,  
20 [628538](#)). Enhanced antigen presentation contributes to exaggerated T cell responses and promotes  
21 Th2 inflammation and an allergic phenotype (Lay et al., 2007, [196610](#)). Upregulation of pro-  
22 inflammatory cytokines in sputum was also demonstrated in O<sub>3</sub>-exposed subjects (Alexis et al.,  
23 2010, [628538](#)). One of these cytokines, IL-12p70, correlated with numbers of dendritic-like cells in  
24 the sputum, and is an indicator of dendritic cell activation (Alexis et al., 2010, [628538](#)). These  
25 authors have previously reported that O<sub>3</sub> activates monocytes and macrophages (Lay et al., 2007,  
26 [196610](#)) which could play a role in exacerbating existing asthma by activating allergen-specific  
27 memory T-cells. The current study confirms these findings and extends them by suggesting a  
28 potential mechanism whereby O<sub>3</sub>-activated dendritic cells could stimulate naïve T-cells to promote  
29 the development of asthma (Alexis et al., 2010, [628538](#)). A companion study by these same  
30 investigators (described in detail in Section 5.2.9.1) provides evidence of dendritic cell activation,  
31 measured as increased expression of HLA-DR, in a subset of the human subjects (GSTM1 null)  
32 exposed to 0.4 ppm O<sub>3</sub> for 2 hours with intermittent exercise (Alexis et al., 2009, [628542](#))

33 Another recent study demonstrated O<sub>3</sub>-mediated activation of the innate immune system and  
34 linked it to the development of non-specific AHR in a mouse model (Pichavant et al., 2008, [596409](#)).  
35 Repeated exposure to 1 ppm O<sub>3</sub> for 3 hours induced non-specific AHR measured 24 hours following  
36 the last exposure (Pichavant et al., 2008, [596409](#)). This response was found to require NKT cells,  
37 which are effector lymphocytes of innate immunity, as well as IL-17 and airways neutrophilia  
38 (Pichavant et al., 2008, [596409](#)). Since glycolipids such as galactosyl ceramide are ligands for the

1 invariant CD1 receptor on NKT cells and serve as endogenous activators of NKT cells, a role for  
2 O<sub>3</sub>-oxidized lipids in activating NKT cells was proposed (Pichavant et al., 2008, [596409](#)). The  
3 authors contrasted this innate immunity pathway with that of allergen-provoked specific AHR which  
4 involves adaptive immunity, the cytokines IL-4, IL-13, IL-17, and airways eosinophilia (Pichavant  
5 et al., 2008, [596409](#)). Interestingly, NKT cells were required for both the specific AHR provoked by  
6 allergen and the non-specific AHR provoked by O<sub>3</sub> (Pichavant et al., 2008, [596409](#)). Different  
7 cytokine profiles of the NKT cells from allergen and O<sub>3</sub>-exposed mice in mediating was proposed to  
8 account for the different pathways (Pichavant et al., 2008, [596409](#)). More recently, NKT cells have  
9 been found to function in both innate and adaptive immunity (Vivier et al., 2011, [676697](#)).

10 Priming of the innate immune system by O<sub>3</sub> was reported by Hollingsworth et al., (2007,  
11 [597609](#)). In this study, exposure of mice to 2 ppm O<sub>3</sub> for 3 hours led to nonspecific AHR at 24 and  
12 48 hours postexposure, an effect which subsided by 72 hours (Hollingsworth et al., 2007, [597609](#)).  
13 However in mice treated with aerosolized endotoxin immediately following O<sub>3</sub> exposure, AHR was  
14 greatly enhanced at 48 and 72 hours postexposure (Hollingsworth et al., 2007, [597609](#)). Ozone pre-  
15 exposure was found to reduce the number of inflammatory cells, to increase cytokine production and  
16 total protein in the BAL fluid and to increase systemic IL-6 following exposure to endotoxin  
17 (Hollingsworth et al., 2007, [597609](#)). Furthermore, O<sub>3</sub> stimulated the apoptosis of alveolar  
18 macrophages 24 hours postexposure, an effect which was greatly enhanced by endotoxin treatment.  
19 Apoptosis of blood monocytes was also observed in response to the combined exposures  
20 (Hollingsworth et al., 2007, [597609](#)). Ozone pre-exposure enhanced the response of lung  
21 macrophages to endotoxin (Hollingsworth et al., 2007, [597609](#)). Taken together, these findings  
22 demonstrated that O<sub>3</sub> exposure increased innate immune responsiveness to endotoxin. The authors  
23 proposed that this effect was mediated by TLR4-dependent pathways since O<sub>3</sub> increased surface  
24 expression of TLR4 on macrophages (Hollingsworth et al., 2007, [597609](#)). More recently, these  
25 authors demonstrated that hyaluronan contributed to the O<sub>3</sub>-primed response to endotoxin (Li et al.,  
26 2010, [670282](#)). In this study, exposure of mice to 1 ppm O<sub>3</sub> for 3 h resulted in enhanced responses to  
27 endotoxin, which was mimicked by intratracheal instillation of hyaluronan fragments (Li et al., 2010,  
28 [670282](#)). Hyaluronan, like O<sub>3</sub>, was also found to induce TLR4 receptor peripheralization in the  
29 membrane (Hollingsworth et al., 2007, [597609](#); Li et al., 2010, [670282](#)), an effect which is  
30 associated with enhanced responses to endotoxin. This study and previous ones by the same  
31 investigators showed elevation of BAL hyaluronan in response to O<sub>3</sub> exposure (Garantziotis et al.,  
32 2009, [597603](#); Garantziotis et al., 2010, [624947](#); Li et al., 2010, [670282](#)), providing evidence that  
33 ozone's effects on innate immunity are at least in part mediated by hyaluronan fragments. The  
34 authors note that excessive TLR4 signaling can lead to lung injury and suggest that O<sub>3</sub> may be  
35 responsible for an exaggerated innate immune response which may underlie lung injury and  
36 decreased host defense (Li et al., 2010, [670282](#)) (Section 5.2.7.1).

37 An interaction between allergen and O<sub>3</sub> in the induction of nonspecific AHR was shown in  
38 another animal study (Larsen et al., 2010, [628560](#)). Mice were sensitized with the aerosolized

1 allergen OVA on 10 consecutive days followed by exposure to O<sub>3</sub> (0.1-0.5 ppm for 3 hours) (Larsen  
2 et al., 2010, [628560](#)). While allergen sensitization alone did not alter airway responsiveness to a  
3 nonspecific challenge, O<sub>3</sub> exposure of sensitized mice resulted in nonspecific AHR at 6 and 24 hours  
4 postexposure (Larsen et al., 2010, [628560](#)). The effects of O<sub>3</sub> on AHR were independent of airways  
5 eosinophilia and neutrophilia (Larsen et al., 2010, [628560](#)). However, OVA pretreatment led to  
6 goblet cell metaplasia which was enhanced by O<sub>3</sub> exposure (Larsen et al., 2010, [628560](#)). It should  
7 be noted that OVA sensitization using only aerosolized antigen in this study is less common than the  
8 usual procedure for OVA sensitization achieved by one or more initial systemic injections of OVA  
9 and adjuvant followed by repeated inhalation exposure to OVA.

10 Furthermore, O<sub>3</sub> was found to act as an adjuvant for allergic sensitization (Hollingsworth et  
11 al., 2010, [635786](#)). In this study in mice, oropharyngeal aspiration of OVA on day 0 and day 6 failed  
12 to lead to allergic sensitization unless mice were first exposed to 1 ppm O<sub>3</sub> for 2 hours  
13 (Hollingsworth et al., 2010, [635786](#)). The O<sub>3</sub>-mediated response involved Th2 (IL-4, IL-5 and IL-9)  
14 and Th17 cytokines (IL-17) and was dependent on a functioning TLR4 (Hollingsworth et al., 2010,  
15 [635786](#)). Ozone exposure also activated OVA-bearing dendritic cells in the thoracic lymph nodes, as  
16 measured by the presence of the CD86 surface marker, which suggests naïve T-cell stimulation and  
17 the involvement of Th2 pathways (Hollingsworth et al., 2010, [635786](#)). Thus ozone's adjuvant  
18 effects may be due to activation of both innate and adaptive immunity.

19 Results of recent studies demonstrate participation of innate immune pathways and also  
20 suggest involvement of adaptive immune pathways in both the induction and the exacerbation of  
21 allergic responses and AHR by O<sub>3</sub>.

### 5.2.6.2. Summary

22 Collectively these older and more recent studies provide insight into ozone's ability to provoke  
23 asthma exacerbations in humans. Greater airways inflammation and/or greater bronchial reactivity  
24 have been demonstrated in asthmatics compared to non-asthmatics. This pre-existing inflammation  
25 and altered baseline bronchial reactivity may contribute to the enhanced bronchoconstriction seen in  
26 asthmatics exposed to O<sub>3</sub>. Furthermore, inflammation may contribute to O<sub>3</sub>-mediated AHR. Animal  
27 studies have demonstrated a role for eosinophil-derived proteins in mediating these effects. Since  
28 airways eosinophilia occurs in both allergic humans and allergic animal models, this pathway may  
29 underlie the exacerbation of allergic asthma by O<sub>3</sub>. In addition, differences have been noted in  
30 epithelial cytokine expression in bronchial biopsy samples of healthy and asthmatic subjects. A Th2  
31 phenotype, indicative of adaptive immune system activation and enhanced allergic responses, was  
32 observed before O<sub>3</sub> exposure and was increased by O<sub>3</sub> exposure in asthmatics. Since eosinophilia is a  
33 hallmark of a Th2 phenotype, these findings support links between allergic asthma, sensitivity to O<sub>3</sub>  
34 and adaptive immunity. Studies in humans and animal models also provide evidence for activation of  
35 innate immunity by O<sub>3</sub>. In humans, O<sub>3</sub> exposure resulted in increased numbers of airways monocytes  
36 and dendritic-like cells. Altered expression of cell surface markers characteristic of innate immunity

1 and antigen presentation was observed on monocytes and macrophages. Recruitment of these  
2 activated immune cells could lead to activation of allergen-specific memory T-cells in allergic  
3 individuals and result in the exacerbation of existing asthma in response to an allergen trigger. In  
4 animal studies, O<sub>3</sub> exposure primed the innate immune system and led to increased endotoxin-  
5 induced AHR by a mechanism involving hyaluronan and TLR4. The exaggerated immune response  
6 to O<sub>3</sub> + endotoxin could lead to a more pronounced lung injury response to a bacterial trigger.  
7 Enhanced bronchial reactivity, airways eosinophilia, Th2 phenotype, recruitment of activated innate  
8 immune cells, and enhanced responsiveness to endotoxin all provide biological plausibility for  
9 epidemiologic evidence of asthma exacerbations associated with exposure to O<sub>3</sub>. Thus, the influx of  
10 immunomodulatory cells and the activation of innate and adaptive immunity lead to the exacerbation  
11 of asthma and allergic responses which is emerging as a key event in the toxicity pathway of O<sub>3</sub>.

12 Recent studies in humans and animal models also provide evidence that O<sub>3</sub> exposure causes  
13 induction of AHR and allergic responses. Both activation of innate immunity and promotion of  
14 adaptive immunity have been implicated. In humans, O<sub>3</sub> exposure resulted in increased numbers of  
15 dendritic-like cells and levels of a cytokine associated with dendritic cell activation in the sputum,  
16 suggesting the presence of a population of activated dendritic cells which could stimulate naïve  
17 T-cells to promote the development of asthma. Evidence for activated dendritic cells was also found  
18 in GSTM1 null human subjects (Section 5.2.9.1) and in allergen-sensitized animals exposed to O<sub>3</sub>. In  
19 the latter study, O<sub>3</sub> acted as an adjuvant for allergic sensitization and the development of AHR by a  
20 mechanism involving TLR4. In a different animal model, O<sub>3</sub>-induced AHR required the presence of  
21 NKT cells and IL-17, both of which indicate innate immune system activation. Ozone-induced  
22 goblet cell metaplasia has also been demonstrated. These findings suggest that O<sub>3</sub> may be capable of  
23 causing new onset asthma and allergic responses in humans. Thus, promotion of adaptive immunity  
24 and activation of innate immunity leads to the induction of AHR and allergic responses which is  
25 emerging as a key event in the toxicity pathway of O<sub>3</sub>.

### 5.2.7. Impaired Host Defense

26 O<sub>3</sub> impacts host defense by a variety of different mechanisms. Animal models have  
27 demonstrated decreased mucociliary particle clearance and effects on alveolar macrophages,  
28 including inhibited phagocytosis and production of reactive oxygen intermediates, and altered  
29 chemotaxis and adhesion in response to O<sub>3</sub> exposure (U.S. EPA, 2006, [088089](#)). Ozone has been  
30 shown to target SP-A, resulting in a decrease in its function (U.S. EPA, 2006, [088089](#)). In addition,  
31 reduced clearance of bacterial pathogens and enhanced susceptibility to bacterial lung infections  
32 were observed in rodents exposed acutely to O<sub>3</sub> (Gilmour et al., 1993, [039620](#); U.S. EPA, 2006,  
33 [088089](#)). Further, O<sub>3</sub>-induced alterations in immune function have been demonstrated (Jakab et al.,  
34 1995, [039548](#); U.S. EPA, 2006, [088089](#)).

### 5.2.7.1. New Cellular and Molecular Insights

1 As described above, priming of the innate immune system by O<sub>3</sub> was reported by  
2 Hollingsworth et al. (2007, [597609](#)). Besides effects on AHR, exposure of mice to 2 ppm O<sub>3</sub> for  
3 3 hours reduced inflammatory cell influx in the airways in response to endotoxin (Hollingsworth et  
4 al., 2007, [597609](#)). In addition, O<sub>3</sub> exposure stimulated the apoptosis of alveolar macrophages  
5 24 hours postexposure, an effect which was enhanced by a subsequent treatment with endotoxin  
6 (Hollingsworth et al., 2007, [597609](#)). Apoptosis of circulating blood monocytes was also observed in  
7 response to O<sub>3</sub> and endotoxin (Hollingsworth et al., 2007, [597609](#)). The authors attributed these  
8 effects to the increased surface expression of TLR4 and increased signaling in macrophages  
9 observed in the study (Hollingsworth et al., 2007, [597609](#)). It was proposed that the resulting  
10 decrease in airways inflammatory cells could account for O<sub>3</sub>-mediated decreased clearance of  
11 bacterial pathogens observed in numerous animal models (Hollingsworth et al., 2007, [597609](#)). A  
12 more recent study by these investigators provided evidence that hyaluronan mediates O<sub>3</sub>-priming of  
13 innate immunity and suggested that exaggerated innate immune responses may underlie lung injury  
14 and decreased host defense (Li et al., 2010, [670282](#)).

15 Recent studies also demonstrated SP-A oxidation by O<sub>3</sub>. SP-A is an important innate immune  
16 protein which plays a number of roles in host defense including acting as opsonin for the recognition  
17 of some pathogens (Haque et al., 2009, [200767](#)). These investigations demonstrated that O<sub>3</sub>-  
18 mediated carbonylation of SP-A was associated with impaired macrophage phagocytosis in vitro  
19 (Mikeroov et al., 2008, [596405](#)). Furthermore, O<sub>3</sub> exposure in mice was found to increase  
20 susceptibility to pneumonia infection in mice through an impairment of SP-A dependent  
21 phagocytosis (Mikeroov et al., 2008, [201537](#); Mikeroov et al., 2008, [597493](#)).

22 Another recent study demonstrated impaired antigen-specific immunity following subacute O<sub>3</sub>  
23 exposure (0.6 ppm, 10 h/day for 15 days) in mice (Feng et al., 2006, [596381](#)). Specifically, O<sub>3</sub>  
24 exposure altered the lymphocyte subset and cytokine profile and impacted thymocyte early  
25 development leading to immune dysfunction.

### 5.2.7.2. Summary

26 Collectively these older and more recent studies in animal models provide several mechanisms  
27 by which O<sub>3</sub> exposure could enhance susceptibility to lung infections. Both decreased mucociliary  
28 particle clearance and decreased numbers and function of alveolar macrophage have been  
29 implicated. Recent studies suggest that O<sub>3</sub>-mediated oxidation of SP-A oxidation and priming of the  
30 innate immune system may contribute to decreased pathogen clearance. Immune dysfunction outside  
31 of the lung has also been demonstrated. Thus, immune system modulation resulting in impaired host  
32 defense is emerging as a key event in ozone's toxicity pathway.

## 5.2.8. Extrapulmonary Effects

1           Extrapulmonary effects of O<sub>3</sub> have been noted for decades (U.S. EPA, 2006, [088089](#)). One  
2 such effect is hypothermia, which in rodents occurs subsequent to the activation of neural reflexes  
3 and involves the parasympathetic nervous system (Watkinson et al., 2001, [016245](#)). Other  
4 mechanisms are likely to be involved in extrapulmonary effects. It has been proposed that lipid  
5 oxidation products resulting from reaction of O<sub>3</sub> with lipids in the ELF are responsible for systemic  
6 effects, however it is not known whether they gain access to the vascular space (Chuang et al., 2009,  
7 [197202](#)). Alternatively, extrapulmonary release of diffusible mediators may initiate or propagate  
8 inflammatory responses in the vascular or in systemic compartments (Cole and Freeman, 2009,  
9 [597507](#)). For example, one such mediator, the cytokine IL-6, is known to have pleiotropic effects such  
10 as inducing the acute phase response, activating the hypothalamus-pituitary-adrenal axis and altering  
11 serum cholesterol levels (Tarrant, 2010, [644810](#)).

### 5.2.8.1. Cardiovascular Effects

12           Effects of O<sub>3</sub> on the cardiovascular system have been demonstrated in both humans and animal  
13 models (U.S. EPA, 2006, [088089](#)). Several mechanisms have been proposed to account for these  
14 responses (Perepu et al., 2010, [385020](#)). First, O<sub>3</sub> may impair alveolar-arterial oxygen transfer and  
15 reduce the supply of arterial oxygen to the myocardium. This may have a greater impact in  
16 individuals with compromised cardiopulmonary systems. Gong et al. (1998, [029938](#)) provided  
17 evidence of a small decrease in arterial oxygen saturation in human subjects exposed to O<sub>3</sub>. In  
18 addition, Delaunois et al. (1998, [015779](#)) demonstrated pulmonary vasoconstriction in O<sub>3</sub>-exposed  
19 rabbits. Although of interest, the contribution of this pathway to O<sub>3</sub>-induced cardiovascular effects  
20 remains uncertain. Secondly, O<sub>3</sub> may trigger neural reflexes which stimulate the autonomic nervous  
21 system and alter electrophysiologic responses of the heart. For example, bradycardia, altered HRV  
22 and arrhythmia have been demonstrated in animals exposed to O<sub>3</sub> (Arito et al., 1990, [042285](#);  
23 Hamade and Tankersley, 2009, [596386](#); Watkinson et al., 2001, [016245](#)). Third, O<sub>3</sub>-induced  
24 pulmonary inflammation may lead to inflammatory or injury responses in the cardiovascular system  
25 (Cole and Freeman, 2009, [597507](#)).

26           Some recent studies have suggested that O<sub>3</sub> may alter the systemic vasculature. In resting  
27 humans, exposure to fine particulate matter (PM) + O<sub>3</sub> resulted in arterial vasoconstriction and  
28 increased diastolic blood pressure during the 2-h exposure (Brook et al., 2002, [024987](#)). However, a  
29 recent study in humans observed no changes in HRV or blood pressure in healthy nonsmokers  
30 exposed at rest to 0.12 ppm O<sub>3</sub> for 2 hours (Brook et al., 2009, [195611](#)). Thus, the previously  
31 observed effects of the combined O<sub>3</sub> and PM exposure may have been attributable to PM alone. A  
32 role for O<sub>3</sub> in modulating endothelin, a potent vasoconstrictor, has also been proposed. Studies in  
33 animals found that O<sub>3</sub>-induced endothelin system genes in the lung and increased circulating levels  
34 of endothelin (Thomson et al., 2005, [087554](#); Thomson et al., 2006, [097483](#)).

## Recent Cellular and Molecular Insights

1 Ozone-induced perturbations of the cardiovascular system were recently investigated in young  
2 mice and monkeys (Chuang et al., 2009, [197202](#)). Young mice exposed to 0.5 ppm O<sub>3</sub> for 5 days  
3 demonstrated increased heart rate and blood pressure. Decreases in endothelial-dependent  
4 vasorelaxation and NO homeostasis were observed in arterial tissue. Oxidative and nitrosative stress  
5 were demonstrated in lung and aortic tissue following O<sub>3</sub> exposure. Mitochondrial DNA was  
6 damaged in lung and aortas from young mice and infant rhesus monkeys similarly exposed to O<sub>3</sub>.  
7 Since altered NO homeostasis, mitochondrial DNA damage and oxidative stress are known to  
8 contribute to the development of atherosclerosis, young Apo E null mice were exposed  
9 subchronically to O<sub>3</sub> (0.5 ppm O<sub>3</sub> for 5 days/week over 8 weeks). Ozone exposure augmented the  
10 aortic lesion areas compared with controls exposed to filtered air, suggesting an acceleration of  
11 atherogenesis. This is the first study to definitively identify the systemic vasculature as a target of  
12 O<sub>3</sub>-induced effects.

13 A second recent study in animals demonstrated effects on the heart due to chronic O<sub>3</sub> exposure  
14 (Perepu et al., 2010, [385020](#)). Rats were exposed to 0.8 ppm O<sub>3</sub> for 28 and 56 days and isolated  
15 hearts were subjected to ischemia-reperfusion injury. Ozone exposure enhanced the sensitivity to  
16 injury in this model, as demonstrated by decreased cardiac function compared with control rats that  
17 were exposed to filtered air. Further, markers of lipid peroxidation and inflammation were greater in  
18 the hearts of O<sub>3</sub>-exposed rats. This study is the first to definitively identify the heart as a target for  
19 O<sub>3</sub>-induced effects.

20 Further evidence for O<sub>3</sub>-induced effects in the systemic vasculature and heart is provided by a  
21 recent chronic study in rats (Kodavanti et al., In Press, [666323](#)). Episodic exposure to 0.4 ppm O<sub>3</sub> for  
22 16 weeks (5 h/day for 1 day/week) resulted in increased aortic levels of mRNA for biomarkers of  
23 oxidative stress, thrombosis, vasoconstriction and proteolysis. Ozone exposure also increased lectin-  
24 like oxidized-low density lipoprotein receptor-1(LOX-1) mRNA and protein levels in the aorta.  
25 Depletion of cardiac mitochondrial phospholipid fatty acids was also observed. Taken together, these  
26 results suggest a role for circulating oxidized lipids in mediating the effects of O<sub>3</sub>.

### 5.2.8.2. Hepatic Effects

27 Changes in hepatic gene expression have also been noted following O<sub>3</sub> exposure. Specifically,  
28 downregulation of gene families related to lipid, fatty acid and carbohydrate metabolism was  
29 demonstrated in the liver of O<sub>3</sub>-exposed mice (Last et al., 2005, [596400](#)). In addition, transcription of  
30 enzymes involved in xenobiotic metabolism was decreased. Impairment of hepatic drug metabolism  
31 was suggested in an older study which found that mice exposed to O<sub>3</sub> had prolonged pentobarbital  
32 sleeping time (Graham et al., 1985, [040289](#)). Further evidence of hepatic effects is provided by a  
33 recent study in which exposure to 0.25 and 0.5 ppm O<sub>3</sub> for 6 hours resulted in exacerbation of drug-  
34 induced liver injury in mice pre-exposed to acetaminophen. This included a greater increase in

1 hepatic neutrophil accumulation and greater alteration in gene expression profiles in mice exposed to  
2 O<sub>3</sub> and acetaminophen compared with either exposure alone (Aibo et al., 2010, [378559](#)).

### 5.2.8.3. Summary

3 Collectively, these older and more recent studies in animal models provide evidence for  
4 extrapulmonary effects of O<sub>3</sub>. Although it was suggested that these effects are directly mediated by  
5 secondary oxidation products formed in the lung as a result of O<sub>3</sub> exposure, there is no evidence that  
6 these species enter the circulation. Alternatively, extrapulmonary effects may be due to activation of  
7 neural reflexes or to release of diffusible mediators which may initiate or propagate inflammatory  
8 responses in the vascular or systemic compartments. Recent studies suggest that oxidative/nitrosative  
9 stress contributes to O<sub>3</sub>-induced cardiovascular effects. Thus, systemic inflammation and vascular  
10 oxidative/nitrosative stress are emerging as key events in the toxicity pathway of O<sub>3</sub>.

### 5.2.9. Factors Affecting Responses to Ozone

11 Responses to O<sub>3</sub> are variable within the population and the basis for this variability is not clear  
12 (Mudway and Kelly, 2000, [010452](#)). Research has focused on the role of gene-environment  
13 interactions, preexisting conditions, adaptive mechanisms and lifestage in influencing the responses  
14 to O<sub>3</sub>. Co-exposure to other pollutants has also been considered.

#### 5.2.9.1. Gene-Environment Interactions

15 The significant inter-individual variation in responses to O<sub>3</sub> infers that genetic background is  
16 an important determinant of susceptibility to O<sub>3</sub> (Cho and Kleeberger, 2007, [195616](#); Kleeberger et  
17 al., 1997, [095736](#)). Strains of mice which are prone or resistant to O<sub>3</sub>-induced effects have been used  
18 to systematically identify candidate susceptibility genes. Genome wide linkage analyses (also known  
19 as positional cloning) demonstrated quantitative trait loci for O<sub>3</sub>-induced lung inflammation and  
20 hyperpermeability on chromosome 17 (Kleeberger et al., 1997, [095736](#)) and chromosome 4  
21 (Kleeberger et al., 2000, [014895](#)), respectively, using these recombinant inbred strains of mice. More  
22 specifically these studies found that Tnf, whose protein product is the inflammatory cytokine TNF- $\alpha$ ,  
23 and Tlr4, whose protein product is TLR4, were candidate susceptibility genes (Kleeberger et al.,  
24 1997, [095736](#); Kleeberger et al., 2000, [014895](#)). Other investigations in inbred mouse strains found  
25 that differences in expression of certain proteins, such as CCSP (Broeckaert et al., 2003, [055490](#)) and  
26 MARCO (Dahl et al., 2007, [196986](#)), are responsible for phenotypic characteristics, such as  
27 epithelial permeability and scavenging of oxidized lipids, respectively, which confer sensitivity to  
28 O<sub>3</sub>.

29 Genetic polymorphisms have received increasing attention as modulators of O<sub>3</sub>-mediated  
30 effects. Functionally relevant polymorphisms in candidate susceptibility genes have been studied at  
31 the individual and population level in humans and also in animal models. Genes whose protein

1 products are involved in antioxidant defense/oxidative stress and xenobiotic metabolism, such as  
2 glutathione-S-transferase M1 (GSTM1) and NADPH:quinone oxidoreductase 1 (NQO1), have also  
3 been major focuses of these efforts. This is because oxidative stress resulting from O<sub>3</sub> exposure is  
4 thought to contribute to the pathogenesis of asthma and because xenobiotic metabolism detoxifies  
5 secondary oxidation products formed by O<sub>3</sub> which contribute to oxidative stress (Islam et al., 2008,  
6 [097348](#)). TNF- $\alpha$  is of interest since it is linked to a candidate O<sub>3</sub> susceptibility gene and since it plays  
7 a key role in initiating airways inflammation (Li et al., 2006, [090972](#)). Polymorphisms of genes  
8 coding for GST M1, NQO1 and TNF- $\alpha$  have been associated with altered susceptibility to O<sub>3</sub>-  
9 mediated effects (Bergamaschi et al., 2001, [052670](#); Corradi et al., 2002, [035448](#); Li et al., 2006,  
10 [090972](#); Romieu et al., 2004, [056796](#); Yang et al., 2005, [077211](#)). Additional studies have focused on  
11 functional variants in other genes involved in antioxidant defense such as catalase (CAT),  
12 myeloperoxidase, heme oxygenase (HMOX-1) and manganese superoxide dismutase (MnSOD)  
13 (Islam et al., 2008, [097348](#); Wenten et al., 2009, [597084](#)). These studies are discussed below.

14 GSTM1 is a phase II antioxidant enzyme which is transcriptionally regulated by NF-E2-  
15 related factor 2-antioxidant response element (Nrf2-ARE) pathway. A large proportion (40-50%) of  
16 the general public (across ethnic populations) has the GSTM1 null genotype, which has been linked  
17 to an increased risk of adverse health effects due to exposure to air pollutants (London, 2007,  
18 [093279](#)). A role for GSTs in metabolizing electrophiles such as 4-hydroxynonanal, which is a  
19 secondary oxidation product formed following O<sub>3</sub> exposure, has been demonstrated (Awasthi et al.,  
20 2004, [644649](#)). A recent study found that the GSTM1 genotype modulated the time course of the  
21 neutrophilic inflammatory response following acute O<sub>3</sub> exposure (0.4 ppm for 2 hours with  
22 intermittent exercise) in healthy adults (Alexis et al., 2009, [628542](#)). In GSTM1-null and sufficient  
23 subjects, O<sub>3</sub>-induced sputum neutrophilia was similar at 4 hours. However, neutrophilia resolved by  
24 24 hours in sufficient subjects but not in GSTM1-null subjects. It is not known whether this effect  
25 was due to the persistence of pro-inflammatory stimuli, impaired production of downregulators or  
26 impaired neutrophil apoptosis and clearance. In addition, O<sub>3</sub> exposure increased the expression of the  
27 surface marker CD14 in airway neutrophils of GSTM-1 null subjects compared with sufficient  
28 subjects. Furthermore, numbers of airway macrophages were decreased at 4 and 24 hours following  
29 O<sub>3</sub> exposure in GSTM1-sufficient subjects (Alexis et al., 2009, [628542](#)). Airways macrophages in  
30 GSTM1 null subjects were greater in number and found to have greater oxidative burst and  
31 phagocytic capability than those of sufficient subjects. Airways macrophages and dendritic cells  
32 from GSTM1 null subjects exposed to O<sub>3</sub> expressed higher levels of the surface marker HLA-DR,  
33 suggesting activation of the innate immune system (Alexis et al., 2009, [628542](#)). These differences  
34 in inflammatory responses between the GSTM1 null and sufficient subjects may provide biological  
35 plausibility for the differences in O<sub>3</sub>-mediated effects reported in controlled human exposure studies  
36 (Bergamaschi et al., 2001, [052670](#); Corradi et al., 2002, [035448](#)). It should also be noted that  
37 GSTM1 genotype did not affect the acute pulmonary function (spirometric) response to O<sub>3</sub> which  
38 provides additional evidence for separate mechanisms underlying ozone's effects on pulmonary

1 function and inflammation in adults (Alexis et al., 2009, [628542](#)). However, GSTM1 null asthmatic  
2 children were previously found to be more sensitive to the effects of O<sub>3</sub> on pulmonary function than  
3 GSTM1 sufficient asthmatic children (Romieu et al., 2004, [056796](#)).

4 NQO1 catalyzes the 2-electron reduction by NADPH of quinones to hydroquinones.  
5 Depending on the substrate, it is capable of both protective detoxification reactions and redox  
6 cycling reactions resulting in the generation of reactive oxygen species. A recent study using NQO1-  
7 null mice demonstrated that NQO1 contributes to O<sub>3</sub>-induced oxidative stress, AHR and  
8 inflammation in mice (Voynow et al., 2009, [194311](#)). These experimental results may provide  
9 biological plausibility for the increased biomarkers of oxidative stress and increased pulmonary  
10 function decrements observed in O<sub>3</sub>-exposed individuals bearing both the wild-type NQO1 gene and  
11 the null GSTM1 gene (Bergamaschi et al., 2001, [052670](#); Corradi et al., 2002, [035448](#)).

12 Two studies reported relationships between TNF promoter variants and O<sub>3</sub>-induced effects in  
13 humans. In one study, O<sub>3</sub>-induced change in lung function was significantly lower in adult subjects  
14 with TNF promoter variants -308A/A and -308G/A compared with adult subjects with the variant -  
15 308G/G (Yang et al., 2005, [077211](#)). This response was modulated by a specific polymorphism of  
16 LTA (Yang et al., 2005, [077211](#)), a previously identified candidate susceptibility gene whose protein  
17 product is lymphotoxin- $\alpha$  (Kleeberger et al., 1997, [095736](#)). In the second study, an association  
18 between the TNF promoter variant -308G/G and decreased risk of asthma and lifetime wheezing in  
19 children was found (Li et al., 2006, [090972](#)). The protective effect on wheezing was modulated by  
20 ambient O<sub>3</sub> 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 asthma (Li et  
22 al., 2006, [090972](#)).

23 Similarly, a promoter variant of the gene HMOX-1, consisting of a smaller number of (GT)<sub>n</sub>  
24 repeats, was associated with a reduced risk for new-onset asthma in non-Hispanic white children  
25 (Islam et al., 2008, [097348](#)). The number of (GT)<sub>n</sub> repeats in this promoter has been shown to be  
26 inversely related to the inducibility of HMOX-1. A modulatory effect of O<sub>3</sub> was demonstrated since  
27 the beneficial effects of this polymorphism were seen only in children living in low O<sub>3</sub> communities  
28 (Islam et al., 2008, [097348](#)). This study also identified an association between a polymorphism of the  
29 CAT gene and increased risk of new-onset asthma in Hispanic children; however no modulation by  
30 O<sub>3</sub> was seen (Islam et al., 2008, [097348](#)). No association was observed in this study between a  
31 MnSOD polymorphism and asthma (Islam et al., 2008, [097348](#)).

32 Studies to date indicate that some variability in individual responsiveness to O<sub>3</sub> may be  
33 accounted for by functional genetic polymorphisms. Further, the effects of gene-environment  
34 interactions may be different in children and adults.

### 5.2.9.2. Preexisting Diseases and Conditions

35 Several preexisting diseases and conditions have been described which modulate the response  
36 to O<sub>3</sub> exposure. Atopy and asthma are important factors in humans. For example, asthmatics were

1 more susceptible to O<sub>3</sub>-mediated inflammation (Balmes et al., 1997, [086092](#); Basha et al., 1994,  
2 [075950](#); Scannell et al., 1996, [080755](#)), while not exhibiting any increase in responsiveness as  
3 measured by spirometry. Ozone exposure resulted in eosinophilia of the nasal and lower airways in  
4 individuals with preexisting allergic disease (Peden et al., 1995, [076189](#); Vagaggini et al., 2002,  
5 [035191](#)) and increased bronchial reactivity to challenge with inhaled specific antigen in mild allergic  
6 asthmatics (Jorres et al., 1996, [078122](#); Kehrl et al., 1999, [022101](#); Molfino et al., 1991, [042379](#)).  
7 Increased bronchial reactivity was also reported in individuals with allergic rhinitis (Jorres et al.,  
8 1996, [078122](#)). It has been proposed that sensitivity is conferred by the presence of greater numbers  
9 of resident airway inflammatory cells in disease states such as asthma (Mudway and Kelly, 2000,  
10 [010452](#)).

11 In addition, smoking and COPD status are important determinants since responsiveness to O<sub>3</sub>,  
12 as measured by spirometry, is decreased in individuals with these conditions (U.S. EPA, 2006,  
13 [088089](#)). Furthermore, obesity may alter susceptibility. In a reanalysis of the data of Hazucha (2003,  
14 [048168](#)), increasing body mass index in young women was associated with increased O<sub>3</sub>  
15 responsiveness (Bennett et al., 2007, [418827](#)). In animal models, diet-induced obesity augmented  
16 inflammation and injury, as measured by BAL markers, as well as innate AHR, in mice exposed  
17 acutely to O<sub>3</sub> (Johnston et al., 2008, [597625](#)). In contrast, the inflammatory response following sub-  
18 acute exposure to O<sub>3</sub> was dampened by obesity in a different mouse model (Shore et al., 2009,  
19 [201551](#)). Finally, nutritional status may impact the response to O<sub>3</sub>. Many investigations have focused  
20 on antioxidant deficiency as a modulator of O<sub>3</sub>-mediated effects (see above). Although results of  
21 these studies are mixed, studies in humans demonstrate that supplementation with ascorbate and  
22 alpha-tocopherol was protective against O<sub>3</sub>-induced pulmonary function deficits in healthy adults  
23 who were ascorbate-deficient (Samet et al., 2001, [019034](#)) and in asthmatic children living in  
24 Mexico City (Romieu et al., 2002, [034711](#); Sienra-Monge et al., 2004, [196422](#)). Furthermore,  
25 supplementation with ascorbate, alpha-tocopherol and beta-carotene was found to be protective in  
26 Mexico City streetworkers (Romieu et al., 1998, [086756](#)).

### 5.2.9.3. Lifes tage: Postnatal development

27 An interesting set of studies conducted over the last 10 years in the infant rhesus monkey has  
28 identified numerous O<sub>3</sub>-mediated perturbations in the developing lung and immune system (Plopper  
29 et al., 2007, [596412](#)). These investigations were prompted by the dramatic rise in the incidence of  
30 childhood asthma and focused on the possible role of O<sub>3</sub> and allergens in promoting remodeling of  
31 the epithelial-mesenchymal trophic unit during postnatal development of the tracheobronchial  
32 airway wall. Rhesus monkeys were used in these studies because the branching pattern and  
33 distribution of airways in this model are more similar to humans than are those of rodents to humans.  
34 In addition, a model of allergic airways disease, which exhibits the main features of human asthma,  
35 had already been established in the adult rhesus monkey. Studies in infant monkeys were designed to  
36 determine whether repeated exposure to O<sub>3</sub> altered postnatal growth and development, and if so,

1 whether such effects were reversible. In addition, exposure to O<sub>3</sub> was evaluated for its potential to  
2 increase the development of allergic airways disease. Infant rhesus monkeys (30 days old) were  
3 exposed to cyclic episodic O<sub>3</sub> over a 5-month period. This involved biweekly cycles of alternating  
4 O<sub>3</sub> (5 consecutive days of 0.5 ppm O<sub>3</sub>, 8 h/day) and filtered air (9 consecutive days). Some animals  
5 were sensitized to house dust mite allergen (HDMA) and then exposed to HDMA aerosol for 2 h/day  
6 on days 3-5 of either filtered air or O<sub>3</sub> exposure.

7 Key findings are numerous. First, baseline airway resistance and AHR in the infant monkeys  
8 were dramatically increased by combined exposure to both HDMA and O<sub>3</sub> (Joad et al., 2006,  
9 [596390](#); Schelegle et al., 2003, [053778](#)). Secondly, O<sub>3</sub> exposure alone led to a large increase in BAL  
10 eosinophils (Schelegle et al., 2003, [053778](#)) while HDMA exposure alone led to a large increase of  
11 eosinophils in airways tissue (Joad et al., 2006, [596390](#); Schelegle et al., 2003, [053778](#)). Thirdly, the  
12 growth pattern of distal airways was significantly changed by exposure to O<sub>3</sub> alone and in  
13 combination with HDMA. More specifically, longer and narrower airways resulted and the number  
14 of conducting airway generations between the trachea and the gas exchange area was decreased  
15 (Fanucchi et al., 2006, [096491](#)). This latter effect was not ameliorated by a recovery period of  
16 6 months. Fourthly, exposure to both HDMA and O<sub>3</sub> altered the abundance and distribution of  
17 CD25+ lymphocytes in the airways (Miller et al., 2009, [596406](#)). Lastly, several effects were seen at  
18 the level of the epithelial mesenchymal trophic unit in response to O<sub>3</sub>. These include altered  
19 organization of the airways epithelium (Schelegle et al., 2003, [053778](#)), increased abundance of  
20 mucous goblet cells (Schelegle et al., 2003, [053778](#)), disruption of the basement membrane zone  
21 (Evans et al., 2004, [596379](#)), reduced innervation (Larson et al., 2004, [057062](#)), increased  
22 neuroendocrine-like cells (Joad et al., 2006, [596390](#)), and altered orientation and abundance of  
23 smooth muscle bundles (Plopper et al., 2007, [596412](#); Tran et al., 2004, [628626](#)). Six months of  
24 recovery in filtered air led to reversal of some but not all of these effects (Evans et al., 2004, [596379](#);  
25 Kajekar et al., 2007, [567661](#); Plopper et al., 2007, [596412](#)). The authors concluded that cyclic  
26 challenge of infant rhesus monkeys to allergen and O<sub>3</sub> during the postnatal period compromised  
27 airway growth and development and resulted in changes which favor allergic airways responses  
28 (Plopper et al., 2007, [596412](#)).

29 Nasal mucous membranes are also a target of O<sub>3</sub>-mediated effects. The infant rhesus monkey  
30 was used as a model since its nasal airways are similar to those of children (Carey et al., 2007,  
31 [195752](#)). Lesions in airways epithelium in the developing nasal passages of immature monkeys were  
32 determined following both acute (5 consecutive days of 0.5 ppm 8 h/day) and cyclic episodic (as  
33 described above) O<sub>3</sub> exposure. Similar effects were observed in response to acute and episodic O<sub>3</sub>.  
34 Histological analysis demonstrated necrotizing rhinitis in the nasal mucosa lining of the main nasal  
35 chamber and focal regions of epithelial exfoliation, especially in the anterior maxilloturbinate. An  
36 anterior to posterior decrease was observed in the severity of these lesions. Morphometric analysis  
37 demonstrated a 65% reduction in the mean thickness of the nasal epithelium in the anterior  
38 maxilloturbinate and loss of volume density of airway cilia, epithelial cytoplasm and nuclei. The

1 authors reported that the O<sub>3</sub>-induced nasal lesions observed in this study are similar to those reported  
2 for adult monkeys. However, unlike the adult monkeys, no epithelial hyperplasia or metaplasia was  
3 observed in the young monkeys suggesting that persistent necrotizing rhinitis may be the long term  
4 sequelae in the absence of protective adaptations.

5 Effects of O<sub>3</sub> on early postnatal airways development has also been studied in rats. A recent  
6 study demonstrated that O<sub>3</sub> exposure during critical postnatal periods resulted in increased SP nerve  
7 fiber density in lung smooth muscle (Hunter et al., 2010, [382064](#)). The authors proposed that O<sub>3</sub> may  
8 lead to enhanced responsiveness of airway sensory nerves. Another study found increases in  
9 immediate-early gene responses in airways epithelium of rats exposed postnatally to O<sub>3</sub> (Johnston et  
10 al., 2006, [097439](#)). Further, neonatal mice exhibit strain-specific differential susceptibility to O<sub>3</sub>  
11 (Vancza et al., 2009, [596419](#)).

#### 5.2.9.4. Lifes tage: Aging

12 On the other side of the lifestage spectrum is aging. The spirometric response to O<sub>3</sub> is lost in  
13 humans as they age (Drechsler-Parks, 1995, [076085](#); Hazucha et al., 2003, [048168](#)). In mice,  
14 physiological responses to O<sub>3</sub> were also attenuated with age (Hamade et al., 2010, [666324](#)).  
15 Mechanisms accounting for this effect have not been well-studied but could include altered number  
16 and sensitivity of receptors or altered signaling pathways involved in neural reflexes.

#### 5.2.9.5. Adaptation

17 The decrease in pulmonary function and increase in bronchoconstriction, airways  
18 inflammation and bronchial reactivity observed on the first and second days of consecutive daily  
19 exposure in response to O<sub>3</sub> were not seen after 4 or 5 days (see above). Several mechanisms have  
20 been postulated. First, the upregulation of antioxidant defenses (or conversely, a decrease in critical  
21 O<sub>3</sub>-reactive substrates) may protect against O<sub>3</sub>-mediated adverse effects. Increases in antioxidant  
22 content of the BAL have been demonstrated by Devlin (1997, [083577](#)), Tepper (1989, [041991](#)), and  
23 others. Second, IL-6 was demonstrated to be an important mediator of adaptation (McKinney et al.,  
24 1998, [086751](#)). Third, a protective role for increases in mucus producing cells and mucus  
25 concentrations in the airways has also been proposed (Devlin et al., 1997, [083577](#)). Fourth, epithelial  
26 hyperplasia or metaplasia may decrease susceptibility to subsequent O<sub>3</sub> challenge (Carey et al., 2007,  
27 [195752](#); Harkema et al., 1987, [040816](#); Harkema et al., 1987, [041496](#)). These morphologic changes  
28 have been observed in nasal and lower airways. Although there is some evidence to support these  
29 possibilities, there is no consensus on mechanisms underlying adaptation. Recent studies  
30 demonstrating that O<sub>3</sub> activates TRP receptors suggest that modulation of TRP receptor number or  
31 sensitivity by repeated O<sub>3</sub> exposures may also contribute to adaptation.

### 5.2.9.6. Co-Exposures with Particulate Matter

1 Numerous studies have investigated the effects of co-exposure to O<sub>3</sub> and PM because of the  
2 prevalence of these pollutants in ambient air. Results are highly variable and depend on whether  
3 exposures are simultaneous or sequential, the type of PM employed and the endpoint examined. In  
4 humans, simultaneous exposure to O<sub>3</sub> (0.12 ppm for 2 h at rest) and CAPs resulted in a diminished  
5 systemic IL-6 response compared with exposure to CAPs alone (Urch et al., 2010, [387113](#)).  
6 Exposure to O<sub>3</sub> alone did not alter blood IL-6 levels (Urch et al., 2010, [387113](#)). The authors  
7 provided evidence that O<sub>3</sub> mediated a switch to shallow breathing which may have accounted for this  
8 effect (Urch et al., 2010, [387113](#)). Further, simultaneous exposure to CAPs and O<sub>3</sub>, but not exposure  
9 to either alone, resulted in increased diastolic blood pressure in human subjects (Fakhri et al., 2009,  
10 [191914](#)). In some strains of mice, pre-exposure to O<sub>3</sub> (0.5 ppm for 2 hours) modulated the effects of  
11 carbon black PM on heart rate, HRV and breathing patterns (Hamade and Tankersley, 2009, [596386](#)).  
12 Another recent study in mice demonstrated that treatment with carbon nanotubes followed 12 hours  
13 later by O<sub>3</sub> exposure (0.5 ppm for 3 hours) resulted in a dampening of some of the pulmonary effects  
14 of carbon nanotubes measured as markers of inflammation and injury in the BAL (Han et al., 2008,  
15 [596387](#)). The authors suggest that this may represent “cross-tolerance.” Harkema et al. (2005,  
16 [078340](#)) found that epithelial and inflammatory responses in the airways of rats were enhanced by  
17 co-exposure to O<sub>3</sub> and LPS (used as a model of biogenic PM) or to O<sub>3</sub> and OVA (used as a model of  
18 an aeroallergen). Furthermore, one recent study demonstrated maternal-fetal effects of PM exposure  
19 on O<sub>3</sub> responses. In this study, maternal exposure to PM resulted in augmented lung mediators of  
20 inflammation, airway epithelial mucous metaplasia and enhanced O<sub>3</sub>-mediated AHR in young mice  
21 (Auten et al., 2009, [200760](#)). Overall, these findings are hard to interpret but demonstrate the  
22 complexity of interactions between PM and O<sub>3</sub> exposures.

### 5.2.9.7. Summary

23 Collectively, these older and more recent studies provide evidence for mechanisms which may  
24 underlie the variability in responsiveness seen among individuals. Certain functional genetic  
25 polymorphisms, pre-existing conditions and diseases, lifestages and co-exposures contribute to  
26 enhanced susceptibility to O<sub>3</sub>. Adaptation may also be important, but it is incompletely understood,  
27 both in terms of the pathways involved and the resulting consequences.

### 5.2.10. Overall Summary

28 Key events in the toxicity pathway of O<sub>3</sub> have been identified in humans and animal models.  
29 They include the formation of secondary oxidation products in the lung, activation of neural reflexes,  
30 pulmonary injury and inflammation and increased bronchial reactivity. In addition, evidence is  
31 accumulating that immune system modulation may lead to impaired host defense and the

1 exacerbation and/or induction of asthma and allergic responses (Figure 5-6). Systemic inflammation  
 2 and vascular oxidative/nitrosative stress may be critical to the extrapulmonary effects of O<sub>3</sub>.

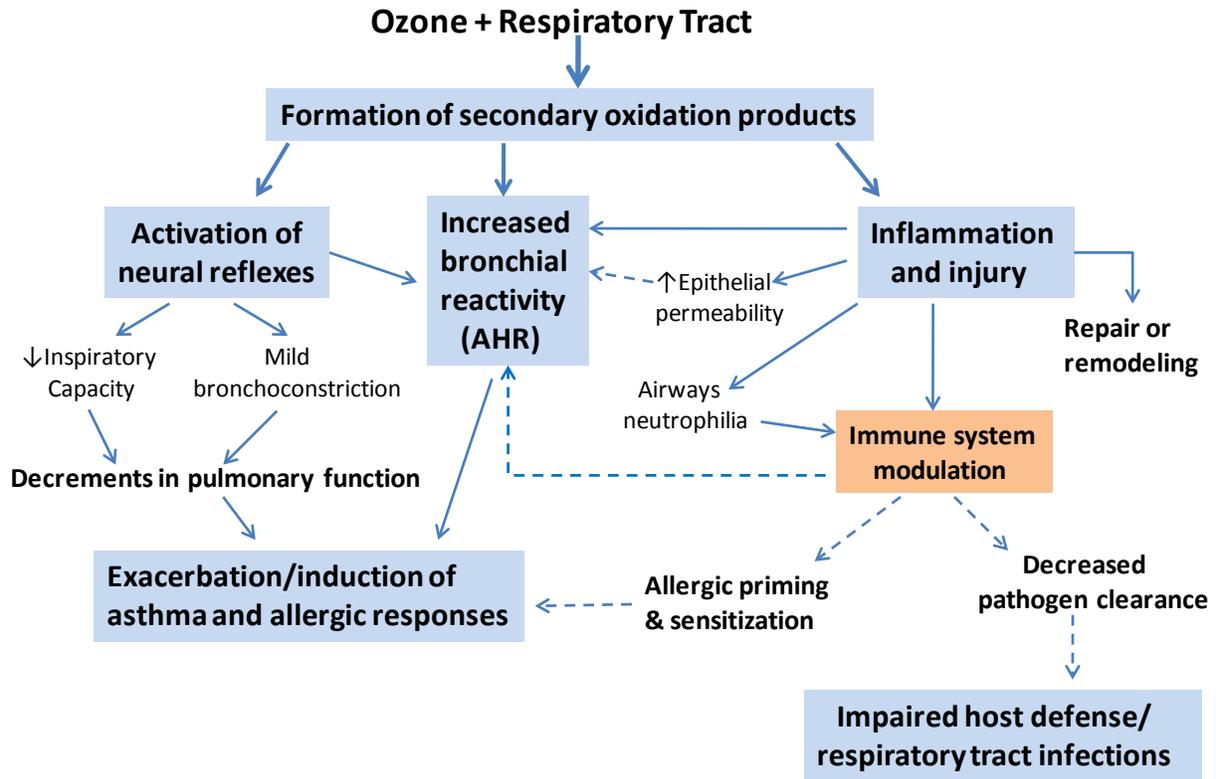


Figure 5-6. Schematic depicting key events in ozone's toxicity pathway. Solid arrows denote pathways for which there is greater certainty. Broken arrows represent pathways of emerging interest.

### 5.2.11. Gaps in Knowledge

3 Despite a vast body of knowledge regarding the effects of O<sub>3</sub> exposure, the current  
 4 understanding of mechanisms underlying important health effects in humans is incomplete.  
 5 Additional research will be useful to elucidate the biologic pathways by which exposure to O<sub>3</sub>:

- 6     ▪ Primes the immune system, including promotion of adaptive immunity and activation of  
 7       innate immunity
- 8     ▪ Alters early postnatal development of the lung and immune system
- 9     ▪ Affects the cardiovascular system

# References

A list of all references considered for inclusion in the dosimetry section of this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=409](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=409)

A list of all references considered for inclusion in the mode of action section of this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=392](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=392)

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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# Chapter 6. Integrated Health Effects of Short-Term Ozone Exposure

## 6.1. Introduction

1 This chapter reviews, summarizes, and integrates the evidence for various health outcomes  
2 associated with short-term exposures to O<sub>3</sub> (hours to days). Numerous controlled human exposure,  
3 epidemiologic and toxicological studies have permitted evaluation of the relationships of short-term  
4 O<sub>3</sub> exposure with a range of endpoints related to respiratory effects (Section 6.2), cardiovascular  
5 effects (Section 6.3), and mortality (Sections 6.2, 6.3, and 6.6). A smaller number of studies are  
6 available to assess the effects of O<sub>3</sub> on other physiological systems such as the central nervous  
7 system (Section 6.4), liver and metabolism (Section 6.5.1), and cutaneous and ocular tissues (Section  
8 6.5.2).

9 Evidence for major health effect categories (e.g., respiratory, cardiovascular, mortality) is  
10 described in individual sections that include a brief summary of conclusions from the 2006 O<sub>3</sub>  
11 AQCD and an evaluation of recent evidence that is intended to build upon evidence from previous  
12 reviews. Within each section, results are organized by health endpoint (e.g., lung function,  
13 pulmonary inflammation) then by specific scientific discipline (e.g., controlled human exposure,  
14 epidemiology, and toxicology). Each major section (e.g., respiratory, cardiovascular, mortality)  
15 concludes with an integrated summary of the findings and a conclusion regarding causality. Based  
16 upon the framework described in Chapter 1, a determination of causality is made for a broad health  
17 effect category, such as respiratory effects, with coherence and plausibility being based on evidence  
18 available across disciplines and also across the suite of related health endpoints, including cause-  
19 specific mortality.

## 6.2. Respiratory Effects

20 Based on evidence integrated across human controlled exposure, epidemiologic, and  
21 toxicological studies, the 2006 O<sub>3</sub> AQCD concluded that there was clear, consistent evidence of a  
22 causal relationship between short-term O<sub>3</sub> exposure and respiratory effects (U.S. EPA, 2006,  
23 [088089](#)). Contributing to this conclusion were consistent and coherent observations across scientific  
24 disciplines of associations of short-term O<sub>3</sub> exposures with pulmonary function decrements and  
25 increases in lung inflammation, lung permeability, airway hyperresponsiveness, respiratory  
26 symptoms, and respiratory-related hospitalizations and emergency department (ED) visits.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

1           Controlled human exposure studies have provided strong and quantifiable exposure-response  
2 data on the human health effects of O<sub>3</sub>. The most salient observations from studies reviewed in the  
3 1996 and 2006 O<sub>3</sub> AQCDs (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)) were that: (1) young  
4 healthy adults exposed to O<sub>3</sub> concentrations  $\geq$  80 ppb develop significant reversible, transient  
5 decrements in pulmonary function if minute ventilation (V<sub>E</sub>) or duration of exposure is increased  
6 sufficiently; (2) children experience similar spirometric responses but lesser symptoms from O<sub>3</sub>  
7 exposure relative to young adults; (3) O<sub>3</sub>-induced spirometric responses are decreased in older  
8 individuals relative to young adults; (4) there is a large degree of intersubject variability in  
9 physiologic and symptomatic responses to O<sub>3</sub>, but responses tend to be reproducible within a given  
10 individual over a period of several months; and (5) subjects exposed repeatedly to O<sub>3</sub> for  
11 several days develop a tolerance to successive exposures, as demonstrated by an attenuation of  
12 spirometric and symptomatic responses, that is lost after about a week without exposure.

13           Substantial evidence for biologically plausible O<sub>3</sub>-induced respiratory morbidity has been  
14 derived from coherence between toxicological and controlled human exposure studies examining  
15 parallel endpoints. For example, O<sub>3</sub>-induced decrements in lung function have also been observed in  
16 animals, and as in humans, tolerance or adaptation has been demonstrated in animal models. Both  
17 humans and rodents exhibit increased airway hyperresponsiveness. This is an important consequence  
18 of exposure to ambient O<sub>3</sub>, because the airways are then predisposed to narrowing upon inhalation of  
19 a variety of ambient stimuli. Additionally, airway hyperresponsiveness tends to resolve more slowly  
20 and appears less subject to attenuation. Increased permeability and inflammation have been observed  
21 in the airways of humans and animals alike after O<sub>3</sub> exposure, and although these aspects are not  
22 necessarily associated with immediate changes in lung function or hyperresponsiveness, the potential  
23 relationship between repetitive bouts of acute inflammation and the development of chronic  
24 respiratory disease is unknown. Another feature of O<sub>3</sub> exposure-related respiratory morbidity is  
25 impaired host defense and reduced resistance to lung infection, which has been strongly supported  
26 by toxicological evidence and to a limited extent by human data. Respiratory infection in early life is  
27 associated with increased incidence of asthma in humans.

28           In epidemiologic studies, acute O<sub>3</sub>-related respiratory morbidity has been assessed most  
29 frequently using lung function. Several studies of healthy children attending camps as well as studies  
30 of outdoor workers, groups exercising outdoors, and children with asthma support O<sub>3</sub> effects on lung  
31 function at ambient levels (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)). In addition to lung  
32 function, ambient O<sub>3</sub> has been positively associated with respiratory symptoms (e.g., cough, wheeze,  
33 shortness of breath), especially in large U.S. panel studies of asthmatic children (Gent et al., 2003,  
34 [052885](#); Mortimer et al., 2000, [013255](#)). The respiratory health effects of acute O<sub>3</sub> exposure are most  
35 clearly indicated in asthmatic children and subjects with increased outdoor exposures. In contrast  
36 with other respiratory health endpoints, the association between short-term O<sub>3</sub> exposure and  
37 respiratory mortality is less clearly indicated. Although O<sub>3</sub> has been consistently associated with  
38 nonaccidental and cardiopulmonary mortality, the contribution of respiratory causes to these findings

1 has been uncertain as the few studies that have examined mortality specifically from respiratory  
2 causes have reported inconsistent associations with ambient O<sub>3</sub> exposures.

3 As discussed throughout this section, consistent with the strong body of evidence presented in  
4 the 2006 O<sub>3</sub> AQCD, recent studies continue to support associations between short-term O<sub>3</sub> exposure  
5 and respiratory health effects, in particular, lung function decrements in controlled human exposure  
6 studies, airway inflammatory responses in toxicological studies, and respiratory-related  
7 hospitalizations and ED visits. Recent epidemiologic studies contribute new evidence on susceptible  
8 populations and of associations of ambient O<sub>3</sub> exposures with biological markers of airway  
9 inflammation and oxidative stress, which is consistent with the extensive evidence from human  
10 controlled exposure and toxicological studies. Furthermore, extending the potential continuum of  
11 well-established O<sub>3</sub>-associated respiratory effects, new multicity studies and a multicontinent study  
12 demonstrate associations between ambient O<sub>3</sub> and respiratory-related mortality.

## 6.2.1. Lung Function

### 6.2.1.1. Controlled Human Exposure

13 This section focuses on studies in which volunteers were exposed, for periods of up to 8 hours  
14 to O<sub>3</sub> concentrations ranging from 40 to 500 ppb, while at rest or during exercise of varying  
15 intensity. Responses to acute O<sub>3</sub> exposures in the range of ambient concentrations include decreased  
16 inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing patterns during exercise; and  
17 symptoms of cough and pain on deep inspiration (PDI). Reflex inhibition of inspiration results in a  
18 decrease in forced vital capacity (FVC) and total lung capacity (TLC) and, in combination with mild  
19 bronchoconstriction, contributes to a decrease in the forced expiratory volume in 1 second (FEV<sub>1</sub>).  
20 As individuals may experience small changes in various health endpoints from exercise, diurnal  
21 variation, or other effects in addition to those of O<sub>3</sub> during the course of an exposure, the term “O<sub>3</sub>-  
22 induced” is used herein to designate effects that have been corrected for such extraneous responses  
23 as measured during filtered air (FA) exposures.

#### **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 exposure to  
25 O<sub>3</sub> in young healthy nonsmoking adults (18-35 years of age). These studies typically use fixed  
26 concentrations of O<sub>3</sub> under carefully regulated environmental conditions and subject activity levels.  
27 The magnitude of respiratory effects (decrements in spirometry and symptomatic response) in these  
28 individuals is a function of O<sub>3</sub> concentration (C), minute ventilation (V<sub>E</sub>), and exposure duration.  
29 Any physical activity will increase minute ventilation and therefore the dose of inhaled O<sub>3</sub>. Dose of  
30 inhaled O<sub>3</sub> to the lower airways is also increased due to a shift from nasal to oronasal breathing with

1 a consequential decrease in O<sub>3</sub> scrubbing by the upper airways. Thus, the intensity of physiological  
2 response following an acute exposure will be strongly associated with minute ventilation.

3 There is a rapid recovery of O<sub>3</sub>-induced spirometric responses and symptoms; 40 to 65%  
4 recovery appears to occur within about 2 hours following exposure (Folinsbee and Hazucha, 1989,  
5 [041732](#)). For example, following a 2-h exposure to 400 ppb O<sub>3</sub> with intermittent exercise,  
6 Nightingale et al. (2000, [000796](#)) observed a 13.5% mean decrement in FEV<sub>1</sub>. By 3 hours  
7 postexposure, however, only a 2.7% FEV<sub>1</sub> decrement persisted. Partial recovery also occurs  
8 following cessation of exercise despite continued exposure to O<sub>3</sub> (Folinsbee et al., 1977, [038283](#))  
9 and at low O<sub>3</sub> concentrations during exposure (Hazucha et al., 1992, [042789](#)). A slower recovery  
10 phase, especially after exposure to higher O<sub>3</sub> concentrations, may take at least 24 hours to complete  
11 (Folinsbee and Hazucha, 2000, [001701](#); Folinsbee et al., 1993, [043781](#)). Repeated daily exposure  
12 studies at higher concentrations typically show that FEV<sub>1</sub> response to O<sub>3</sub> is enhanced on the  
13 second day of exposure. This enhanced response suggests a residual effect of the previous exposure,  
14 about 22 hours earlier, even though the pre-exposure spirometry may be the same as on the  
15 previous day. The absence of the enhanced response with repeated exposure at lower O<sub>3</sub>  
16 concentrations may be the result of a more complete recovery or less damage to pulmonary tissues  
17 (Folinsbee et al., 1994, [044189](#)).

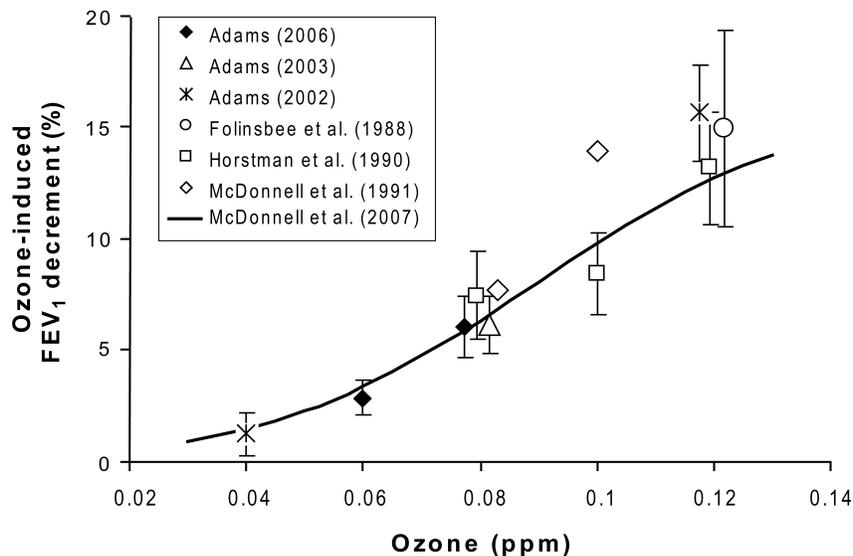
18 For healthy young adults exposed at rest for 2 hours, 500 ppb is the lowest O<sub>3</sub> concentration  
19 reported to produce a statistically significant O<sub>3</sub>-induced group mean FEV<sub>1</sub> decrement (6.4%, n=10,  
20 (Folinsbee et al., 1978, [039060](#)) and 6.7%, n=13, (Horvath et al., 1979, [039222](#))). Airway resistance  
21 was not clearly affected during at-rest exposure to these O<sub>3</sub> concentrations. For exposures of 1-2  
22 hours to ≥ 120 ppb O<sub>3</sub>, statistically significant symptomatic responses and effects on FEV<sub>1</sub> are  
23 observed when V<sub>E</sub> is sufficiently increased by exercise. For instance, with very heavy continuous  
24 exercise (V<sub>E</sub> = 89 L/min), an O<sub>3</sub>-induced group mean decrement of 9.7% in FEV<sub>1</sub> has been reported  
25 for healthy young adults exposed for 1 hour to 120 ppb O<sub>3</sub> (Gong et al., 1986, [040465](#)). Symptoms  
26 are present and decrements in forced expiratory volumes and flows occur at 160-240 ppb  
27 O<sub>3</sub> following 1 hour of continuous heavy exercise (V<sub>E</sub> ≈ 55 to 90 L/min (Adams and Schelegle,  
28 1983, [039822](#); Avol et al., 1984, [040221](#); Folinsbee et al., 1984, [040065](#); Gong et al., 1986, [040465](#))  
29 and following 2 hours of intermittent heavy exercise (V<sub>E</sub> ≈ 65-68 L/min) (Kulle et al., 1985, [040311](#);  
30 Linn et al., 1986, [040481](#); McDonnell et al., 1983, [040680](#)). With heavy intermittent exercise  
31 (15-min intervals of rest and exercise [V<sub>E</sub> = 68 L/min]), symptoms of breathing discomfort and a  
32 group mean O<sub>3</sub>-induced decrement of 3.4% in FEV<sub>1</sub> occurred in young healthy adults exposed for 2  
33 hours to 120 ppb O<sub>3</sub> (McDonnell et al., 1983, [040680](#)).<sup>1</sup>

34 For prolonged (6.6 hours) exposures relative to shorter exposures, significant pulmonary  
35 function responses and symptoms have been observed at lower O<sub>3</sub> concentrations and at a moderate  
36 level of exercise (V<sub>E</sub> = 40 L/min). The results from studies using 6.6 hours of constant or square-  
37 wave (S-W) exposures are illustrated in Figure 6-1. Exposure to 40 ppb for 6.6 hours produces small,

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<sup>1</sup> In total, subjects were exposed to O<sub>3</sub> for 2.5 hours. Intermittent exercise periods, however, were only conducted for the first 2 hours of exposure and FEV<sub>1</sub> was determined 5 minutes after the exercise was completed.

1 statistically insignificant changes in FEV<sub>1</sub> that are relatively similar to responses from FA exposure  
 2 (Adams, 2002, [093690](#)). Volunteers exposed to 60 ppb O<sub>3</sub> experience group mean O<sub>3</sub>-induced FEV<sub>1</sub>  
 3 decrements of about 3% (Adams, 2006, [087681](#); Brown et al., 2008, [195140](#))<sup>1</sup>; those exposed to  
 4 80 ppb have group mean decrements which range from 6 to 8% (Adams, 2003, [042245](#); Adams,  
 5 2006, [087681](#); Horstman et al., 1990, [042187](#); McDonnell et al., 1991, [042384](#)); at 100 ppb, group  
 6 mean decrements range from 8 to 14% (Horstman et al., 1990, [042187](#); McDonnell et al., 1991,  
 7 [042384](#)); and at 120 ppb, group mean decrements of 13 to 16% are observed (Adams, 2002, [093690](#);  
 8 Folinsbee et al., 1988, [040898](#); Horstman et al., 1990, [042187](#)). As illustrated in Figure 6-1, there is a  
 9 smooth dose-response curve without evidence of a threshold for exposures between 40 and 120 ppb  
 10 O<sub>3</sub>. Taken together, these data indicate that mean FEV<sub>1</sub> is clearly decreased by 6.6-h exposures to  
 11 60 ppb O<sub>3</sub> and higher concentrations in subjects performing moderate exercise.



Source: Brown et al. (2008, [195140](#))

**Figure 6-1. Cross-study comparison of mean ozone-induced FEV<sub>1</sub> decrements following 6.6 hours of constant, square-wave exposure to ozone. During each hour of the exposures, subjects were engaged in moderate exercise for 50 minutes and rest for 10 minutes. Following the third hour, subjects had an additional 35 minute rest period for lunch. The McDonnell et al. (2007, [093104](#)) curve illustrates the predicted FEV<sub>1</sub> decrement at 6.6 hours as a function of ozone 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. The data at 0.08 and 0.12 ppm have been offset for illustrative purposes.**

<sup>1</sup> Adams (2006, [087681](#)) did not find effects on FEV<sub>1</sub> at 60 ppb to be statistically significant. In an analysis of the Adams (2006, [087681](#)) data, even after removal of potential outliers, Brown et al. (2008, [195140](#)) found the average effect on FEV<sub>1</sub> at 60 ppb to be small, but highly statistically significant (p < 0.002) using several common statistical tests.

1 As opposed to constant or S-W concentration patterns used in the studies described above,  
2 many more recent studies conducted at the levels of 40-80 ppb have used variable O<sub>3</sub> concentration  
3 patterns. It has been suggested that a triangular (variable concentration) exposure profile can  
4 potentially lead to higher FEV<sub>1</sub> responses than S-W profiles at overall equivalent inhaled O<sub>3</sub> doses.  
5 Hazucha et al. (1992, [042789](#)) were the first to investigate the effects of variable versus constant  
6 concentration exposures on responsiveness to O<sub>3</sub>. In their study, volunteers were randomly exposed  
7 to a triangular concentration profile that increased linearly from 0-240 ppb for the first 4 hours of the  
8 8-h exposure, then decreased linearly from 240 to 0 ppb over the next 4 hours of the 8-h exposure,  
9 and to an S-W exposure of 120 ppb O<sub>3</sub> for 8 hours. While the total inhaled O<sub>3</sub> doses at 4 hours and  
10 8 hours for the S-W and the triangular concentration profile were almost identical, the FEV<sub>1</sub>  
11 response was dissimilar. For the S-W exposure, FEV<sub>1</sub> declined ~5% by the fifth hour and then  
12 remained at that level. With the triangular O<sub>3</sub> profile, there was minimal FEV<sub>1</sub> response over the first  
13 3 hours followed by a rapid decrease in FEV<sub>1</sub> (-10.3%) over the next 3 hours. During the seventh  
14 and eighth hours, mean FEV<sub>1</sub> decrements improved to -6.3% as the O<sub>3</sub> concentration decreased from  
15 120 to 0 ppb (mean = 60 ppb). These findings illustrate that the severity of symptoms and the  
16 magnitude of spirometric responses are time-dependent functions of inhaled dose rate with periods  
17 of both effect development and recovery during the course of an exposure.

18 Subsequently, others have also demonstrated that variable concentration exposures can elicit  
19 greater FEV<sub>1</sub> and symptomatic responses than S-W exposures (Adams, 2003, [042245](#); Adams, 2006,  
20 [196494](#); Adams, 2006, [087681](#)). Adams (2006, [196494](#)) reproduced the findings of Hazucha et al.  
21 (1992, [042789](#)) at 120 ppb. However, Adams (2003, [042245](#); 2006, [087681](#)) found that responses  
22 from an 80 ppb O<sub>3</sub> (average) triangular exposure did not differ significantly from those observed in  
23 the 80 ppb O<sub>3</sub> S-W exposure at 6.6 hours. Nevertheless, FEV<sub>1</sub> and symptoms were significantly  
24 different from pre-exposure at 4.6 hours (when the O<sub>3</sub> concentration was 150 ppb) in the triangular  
25 exposure, but not until 6.6 hours in the S-W exposure. At the lower O<sub>3</sub> concentration of 60 ppb, no  
26 temporal pattern differences in FEV<sub>1</sub> responses between S-W and triangular exposure profiles could  
27 be discerned (Adams, 2006, [087681](#)). However, total symptom scores were significantly increased  
28 for the 60 ppb triangular (but not the S-W) exposure following 5.6 and 6.6 hours of exposure. At  
29 40 ppb, triangular and S-W patterns produced responses similar to FA exposure (Adams, 2002,  
30 [093690](#); Adams, 2006, [087681](#)).

31 For exposures of 60 ppb and greater, these studies (Adams, 2003, [042245](#); Adams, 2006,  
32 [087681](#); Adams, 2006, [196494](#); Hazucha et al., 1992, [042789](#)) demonstrate that during triangular  
33 exposure protocols, volunteers may develop greater spirometric and/or symptomatic responses  
34 during and following peak O<sub>3</sub> concentrations as compared to responses over the same time interval  
35 of S-W exposures. This observation is not unexpected since the inhaled dose rate during peaks of the  
36 triangular protocols approached twice that of the S-W protocols, e.g., 150 ppb versus 80 ppb. At time  
37 intervals toward the end of an exposure, inhaled dose rates for the triangular protocols were less than  
38 those of S-W. At these later time intervals, there is some recovery of responses during triangular  
39 exposure protocols, whereas there is a continued development of or a plateau of responses in the

1 S-W exposure protocols. Thus, responses during triangular protocols relative to S-W protocols may  
2 be expected to diverge and be greater following peak exposures and then converge toward the end of  
3 an exposure. The ensuing discussion on exposures between 40 and 80 ppb will focus on  
4 postexposure effects where the influence of triangular and S-W concentration patterns are minimal,  
5 i.e., FEV<sub>1</sub> pre-to-post effects are similar (although not identical) between triangular and S-W  
6 protocols having equivalent average exposure concentrations.

7 Schelegle et al. (2009, [618629](#)) recently investigated the effects of 6.6 hours variable O<sub>3</sub>  
8 exposure protocols at mean concentrations of 60, 70, 80, and 87 ppb on respiratory symptoms and  
9 pulmonary function in young healthy adults (16 F, 15 M; 21.4 ± 0.6 years). The mean FEV<sub>1</sub>  
10 (±standard error) decrements at 6.6 hours (end of exposure relative to pre-exposure) were -0.80 ±  
11 0.90%, 2.72 ± 1.48%, 5.34 ± 1.42%, 7.02 ± 1.60%, and 11.42 ± 2.20% for exposure to FA, 60, 70,  
12 80, and 87 ppb O<sub>3</sub>, respectively. Statistically significant decrements in FEV<sub>1</sub> and increases in total  
13 subjective symptom scores (p < 0.05) were found following exposure to mean concentrations of 70,  
14 80, and 87 ppb O<sub>3</sub> relative to FA. Statistically significant effects were not found at 60 ppb. One of  
15 the expressed purposes of the Schelegle et al. (2009, [618629](#)) study was to determine the minimal  
16 mean O<sub>3</sub> concentration that produces a statistically significant decrement in FEV<sub>1</sub> and symptoms in  
17 healthy individuals completing 6.6-h exposure protocols. At 70 ppb, Schelegle et al. (2009, [618629](#))  
18 observed significant effects. At 60 ppb, a 3.5% FEV<sub>1</sub> decrement was not found to be statistically  
19 significant. However, the slightly smaller 2.9% FEV<sub>1</sub> decrement at 60 ppb observed by Adams  
20 (2006, [087681](#)) was found to be statistically significant by Brown et al. (2008, [195140](#)).

21 More recently, Kim et al. (In Press, [674869](#)) investigated the effects of a 6.6-h exposure to  
22 60 ppb O<sub>3</sub> on pulmonary function and respiratory symptoms in young healthy adults (32 F, 27 M;  
23 25.0 ± 0.5 year) that were roughly half GSTM1-null and half GSTM1-positive. Sputum neutrophil  
24 levels were also measured in a subset of the subjects (13 F, 11 M). The mean FEV<sub>1</sub> (±standard error)  
25 decrements at 6.6 hours (end of exposure relative to pre-exposure) were significantly different (p =  
26 0.008) between the FA (0.002 ± 0.46%) and O<sub>3</sub> (1.76 ± 0.50%) exposures. The inflammatory  
27 response following O<sub>3</sub> exposure was also significantly (p<0.001) increased relative to the FA  
28 exposure. Respiratory symptoms were not affected by O<sub>3</sub> exposure. There was also no significant  
29 effect of GSTM1 genotype on FEV<sub>1</sub> or inflammatory responses.

30 Consideration of the minimal O<sub>3</sub> concentration producing statistically significant effects  
31 following 6.6-h exposures warrants additional discussion. As discussed above, numerous studies  
32 have demonstrated statistically significant O<sub>3</sub>-induced group mean FEV<sub>1</sub> decrements of 6-8% at  
33 80 ppb. Schelegle et al. (2009, [618629](#)) have now reported statistically significant O<sub>3</sub>-induced group  
34 mean FEV<sub>1</sub> decrement of 6%, as well as respiratory symptoms, at 70 ppb. At 60 ppb, there is  
35 information available from 4 separate studies (Adams, 1998, [670457](#))<sup>1</sup>(Adams, 2006, [087681](#); Kim  
36 et al., In Press, [674869](#); Schelegle et al., 2009, [618629](#)). The group mean O<sub>3</sub>-induced FEV<sub>1</sub>

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<sup>1</sup> The American Petroleum Institute has declined to provide a copy of this report to EPA.

1 decrements observed in these studies were 3.6% by Adams (1998, [670457](#))<sup>1</sup>, 2.8% (triangular  
2 exposure) and 2.9% (S-W exposure) by Adams (2006, [087681](#)), 3.5% by Schelegle et al. (2009,  
3 [618629](#)), and 1.8% by Kim et al. (In Press, [674869](#)). Based on data from these three studies, at  
4 60 ppb, the weighted-average group mean O<sub>3</sub>-induced FEV<sub>1</sub> decrement (i.e., adjusted for FA  
5 responses) is 2.7% (n=150) (Adams, 1998, [670457](#); Adams, 2006, [087681](#); Kim et al., In Press,  
6 [674869](#); Schelegle et al., 2009, [618629](#)). Although not found to be statistically significant in the  
7 original studies, these group mean changes in FEV<sub>1</sub> at 60 ppb are consistent between studies, i.e.,  
8 none observed an average improvement in lung function with following a 6.6-h exposure to 60 ppb  
9 O<sub>3</sub>. Indeed, as was illustrated in Figure 6-1, the FEV<sub>1</sub> responses at 60 ppb fall on a smooth dose-  
10 response curve for exposures between 40 and 120 ppb O<sub>3</sub>. Furthermore, in a re-analysis of the  
11 60 ppb S-W data from Adams (2006, [087681](#)), Brown et al. (2008, [195140](#)) found the mean effects  
12 on FEV<sub>1</sub> to be highly statistically significant (p<0.002) using several common statistical tests even  
13 after removal of 3 potential outliers. The time-course and magnitude of FEV<sub>1</sub> responses at 40 ppb  
14 resemble those occurring during FA exposures (Adams, 2002, [093690](#); Adams, 2006, [087681](#)).  
15 Taken together, the available evidence shows that detectable effects of O<sub>3</sub> on group mean FEV<sub>1</sub>  
16 persist down to 60 ppb, but not 40 ppb in young healthy adults exposed for 6.6 hours during  
17 moderate exercise.

### ***Intersubject Variability in Response of Healthy Subjects***

18 Consideration of group mean changes is important in discerning if observed effects are due to  
19 O<sub>3</sub> exposure rather than chance alone. Inter-individual variability in responses is, however,  
20 considerable and pertinent to assessing the fraction of the population that might actually be affected  
21 during an O<sub>3</sub> exposure. Hackney et al. (1975, [039208](#)) first recognized a wide range in the sensitivity  
22 of subjects to O<sub>3</sub>. The range in the subjects' ages (29 to 49 years) and smoking status (0 to 50 pack  
23 years) in the Hackney et al. (1975, [039208](#)) study are now understood to affect the spirometric and  
24 symptomatic responses to O<sub>3</sub>. Subsequently, DeLucia and Adams (1977, [038281](#)) examined  
25 responses to O<sub>3</sub> in six healthy non-smokers and found that two exhibited notably greater sensitivity  
26 to O<sub>3</sub>. Since that time, numerous studies have documented considerable variability in responsiveness  
27 to O<sub>3</sub> even in subjects recruited to assure homogeneity in factors recognized or presumed to affect  
28 responses.

29 An individual's FEV<sub>1</sub> response to a 2-h O<sub>3</sub> exposure is generally reproducible over  
30 several months and presumably reflects the intrinsic responsiveness of the individual to O<sub>3</sub> (Hazucha  
31 et al., 2003, [048168](#); McDonnell WF 3rd; Horstman et al., 1985, [040283](#)). The frequency distribution  
32 of individual FEV<sub>1</sub> responses following these relatively short exposures becomes skewed as the  
33 group mean response increases, with some individuals experiencing large reductions in FEV<sub>1</sub> (Kulle  
34 et al., 1985, [040311](#); Weinmann et al., 1995, [076022](#)). For 2-h exposures with intermittent exercise  
35 causing a predicted average FEV<sub>1</sub> decrement of 10%, individual decrements ranged from  
36 approximately 0 to 40% in white males aged 18-36 years (McDonnell et al., 1997, [084266](#)). For an

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<sup>1</sup> This information is from page 133 of Adams (2006, [087681](#)).

1 average FEV<sub>1</sub> decrement of 13%, Ultman et al. (2004, [057197](#)) reported FEV<sub>1</sub> responses ranging  
2 from a 4% improvement to a 56% decrement in young healthy adults (32 M, 28 F) exposed for 1  
3 hour to 250 ppb O<sub>3</sub>. One-third of the subjects had FEV<sub>1</sub> decrements of >15%, and 7% of the subjects  
4 had decrements of >40%.

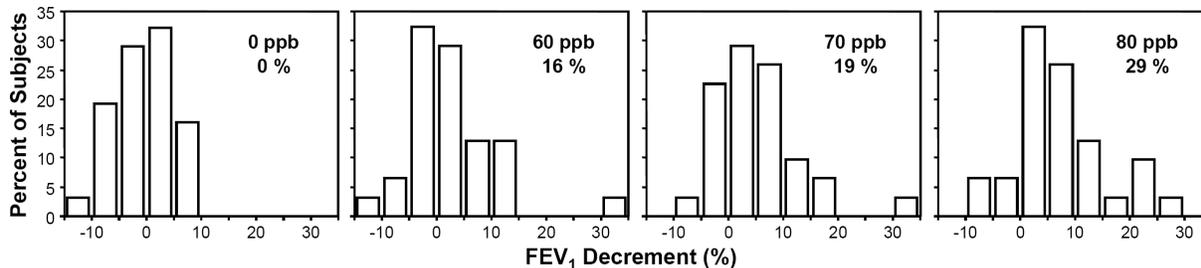
5 Consistent with the 1- to 2-h studies, the distribution of individual responses following 6.6-h  
6 exposure studies becomes skewed with increasing exposure concentration and magnitude of the  
7 group mean FEV<sub>1</sub> response (McDonnell, 1996, [082679](#)). Figure 6-2 illustrates frequency  
8 distributions of individual FEV<sub>1</sub> responses observed in 31 young healthy adults following 6.6-h  
9 exposures between 0 and 80 ppb. Schelegle et al. (2009, [618629](#)) found >10% FEV<sub>1</sub> decrements in  
10 16, 19, 29, and 42% of individuals exposed for 6.6 hours to 60, 70, 80, and 87 ppb, respectively. Just  
11 as there are differences in mean decrements between studies having similar exposure scenarios  
12 (Figure 6-1 at 80 and 120 ppb), there are also differences in the proportion of individuals affected  
13 with >10% FEV<sub>1</sub> decrements. At 80 ppb, the proportion affected with >10% FEV<sub>1</sub> decrements was  
14 17% (n=30) by Adams (2006, [087681](#))<sup>1</sup>, 26% (n=60) by McDonnell (1996, [082679](#)), and 29% (n=31)  
15 by Schelegle et al. (2009, [618629](#)). At 60 ppb, the proportion with >10% FEV<sub>1</sub> decrements was 20%  
16 (n=30) by Adams (1998, [670457](#))<sup>2</sup>, 3% (n=30) by Adams (2006, [087681](#))<sup>5</sup>, 16% (n=31) by Schelegle  
17 et al. (2009, [618629](#)), and 5% (n=59) by Kim et al. (In Press, [674869](#)). Based on these studies, the  
18 weighted average proportion of individuals with >10% FEV<sub>1</sub> decrements is 10% following exposure  
19 to 60 ppb. Due to insufficient data, these proportions were not corrected for responses to FA  
20 exposure where lung function typically improves in healthy adults. For example, uncorrected versus  
21 O<sub>3</sub>-induced (i.e., adjusted for response during FA exposure) proportions of individuals having >10%  
22 FEV<sub>1</sub> decrements in the Adams (2006, [087681](#))<sup>3</sup> study were, respectively, 3% versus 7% at 60 ppb  
23 and 17% versus 23% at 80 ppb. Thus, uncorrected proportions underestimate the actual fraction of  
24 healthy individuals affected.

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<sup>1</sup> Not assessed by Adams (2006, [087681](#)), the proportion was provided in Figure 8-1B of U.S. EPA (2006, [088089](#)).

<sup>2</sup> This information is from page 761 of Adams (2002, [093690](#)).

<sup>3</sup> Not assessed by Adams (2006, [087681](#)), uncorrected and O<sub>3</sub>-induced proportions are from Figures 8-1B and 8-2, respectively, of the 2006 O<sub>3</sub> AQCD (2006, [088089](#)).



Source: Adapted with permission from American Thoracic Society, Schelegle et al. (2009, [618629](#))

**Figure 6-2. Frequency distributions of FEV<sub>1</sub> decrements observed by Schelegle et al. (2009) in young healthy adults (16 F, 15 M) following 6.6-h exposures to ozone or filtered air. □ During each hour of the exposures, subjects were engaged in moderate exercise 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 ozone concentration profile having the average ozone concentration provided in each panel. As average ozone concentration increased, the distribution of responses became asymmetric with a few individuals exhibiting large FEV<sub>1</sub> decrements. The percentage indicated in each panel is the portion of subjects having a FEV<sub>1</sub> decrement in excess of 10%.**

1            Given considerable inter-individual variability in responses, the interpretation of biologically  
2 small group mean decrements requires careful consideration. Following prolonged 6.6-h exposures  
3 to an average level of 60 ppb O<sub>3</sub>, data available from three studies yield a weighted-average group  
4 mean O<sub>3</sub>-induced FEV<sub>1</sub> decrement (i.e., adjusted for FA responses) of 3.3% (n=91) (Adams, 1998,  
5 [670457](#); Adams, 2006, [087681](#); Schelegle et al., 2009, [618629](#)). The data from these studies also  
6 yield a weighted-average proportion (uncorrected for FA responses) of subjects with >10% FEV<sub>1</sub>  
7 decrements of 13% (n=91) (Adams, 1998, [670457](#); Adams, 2006, [087681](#); Schelegle et al., 2009,  
8 [618629](#)). In an individual with relatively “normal” lung function, recognizing technical and  
9 biological variability in measurements, confidence can be given that within-day changes in FEV<sub>1</sub> of  
10 ≥ 5% are clinically meaningful (American Thoracic Society, 1991, [044889](#); Pellegrino et al., 2005,  
11 [626521](#)). Here focus is given to individuals with >10% decrements in FEV<sub>1</sub> since some individuals  
12 in the Schelegle et al. (2009, [618629](#)) study experienced 5-10% FEV<sub>1</sub> decrements following  
13 exposure to FA. The data are not available to the EPA to determine the O<sub>3</sub>-induced proportion for  
14 either the Adams (1998, [670457](#)) or Schelegle et al. (2009, [618629](#)) studies. As already stated,  
15 however, this uncorrected proportion likely underestimates that actual proportion of healthy  
16 individuals experiencing O<sub>3</sub>-induced FEV<sub>1</sub> decrements in excess of 10%. Therefore, by considering  
17 uncorrected responses and those individuals having >10% decrements, 13% is an underestimate of  
18 the proportion of healthy individuals that are likely to experience clinically meaningful changes in  
19 lung function following exposure for 6.6 hours to 60 ppb O<sub>3</sub> during moderate exercise. Although  
20 none of these studies (Adams, 1998, [670457](#); Adams, 2006, [087681](#); Schelegle et al., 2009, [618629](#))  
21 reported FEV<sub>1</sub> decrements at 60 ppb to be statistically significant, Brown et al. (2008, [195140](#)) found  
22 those from Adams (2006, [087681](#)) to be highly statistically significant. The forgoing discussion  
23 shows that even where group mean decrements are biologically small and of debatable statistical

1 significance, a considerable fraction of exposed individuals experience clinically meaningful  
2 decrements in lung function.

### Responses in Individuals with Pre-Existing Disease

3 Individuals with respiratory disease are of primary concern in evaluating the health effects of  
4 O<sub>3</sub> because a given change in function is likely to have more impact on a person with preexisting  
5 function impairment and reduced reserve.

6 Possibly due to the age of subjects studied, patients with COPD performing light to moderate  
7 exercise do not generally experience statistically significant pulmonary function decrements  
8 following 1- and 2-h exposures to ≤ 300 ppb O<sub>3</sub> (Kehrl et al., 1985, [040294](#); Linn et al., 1982,  
9 [039645](#); Linn et al., 1983, [040672](#); Solic et al., 1982, [039610](#)). Following a 4 h exposure to 240 ppb  
10 O<sub>3</sub> during exercise, Gong et al. (1997, [083593](#)) found an O<sub>3</sub>-induced FEV<sub>1</sub> decrement of 8% in  
11 COPD patients which was not statistically different from the decrement of 3% in healthy subjects.  
12 Demonstrating the need for control exposures and presumably due to exercise, four of the patients in  
13 the Gong et al. (1997, [083593](#)) study had FEV<sub>1</sub> decrements of >14% following both the FA and O<sub>3</sub>  
14 exposures. Although the clinical significance is uncertain, small transient decreases in arterial blood  
15 oxygen saturation have also been observed in some of these studies.

16 Based on studies reviewed in the 1996 and 2006 O<sub>3</sub> AQCD (U.S. EPA, 1996, [017831](#);  
17 U.S. EPA, 2006, [088089](#)), asthmatic subjects appear to be at least as sensitive to acute effects of O<sub>3</sub>  
18 as healthy nonasthmatic subjects. Horstman et al. (1995, [075834](#)) found the O<sub>3</sub>-induced FEV<sub>1</sub>  
19 decrement in mild-to-moderate asthmatics to be significantly larger than in healthy subjects (19%  
20 versus 10%, respectively) exposed to 160 ppb O<sub>3</sub> during exercise for 7.6-h exposure. In asthmatics, a  
21 significant positive correlation between O<sub>3</sub>-induced spirometric responses and baseline lung function  
22 was observed, i.e., responses increased with severity of disease. Such differences in pulmonary  
23 function between asthmatics and healthy individuals were not found in shorter duration studies.  
24 Alexis et al. (2000, [013072](#)) and Jörres et al. (1996, [078122](#)) reported a tendency for slightly greater  
25 FEV<sub>1</sub> decrements in asthmatics than healthy subjects. Several studies reported similar responses  
26 between asthmatics and healthy individuals (Basha et al., 1994, [075950](#); Hiltermann et al., 1995,  
27 [078494](#); Scannell et al., 1996, [080755](#)). The lack of differences in the Hiltermann et al. (1995,  
28 [078494](#)) and Basha et al. (1994, [075950](#)) studies was not surprising, however, given extremely small  
29 sample sizes and corresponding lack of statistical power. One study reported a tendency for  
30 asthmatics to have smaller O<sub>3</sub>-induced FEV<sub>1</sub> decrements than healthy subjects (3% versus 8%,  
31 respectively) when exposed to 200 ppb O<sub>3</sub> for 2 hours during exercise (Mudway et al., 2001,  
32 [025327](#)). However, the asthmatics in that study also tended to be older than the healthy subjects,  
33 which could partially explain their lesser response since FEV<sub>1</sub> responses to O<sub>3</sub> diminish with age.

34 Some, but not all, studies have also reported that asthmatics have a somewhat exaggerated  
35 airway inflammatory response to acute O<sub>3</sub> exposure relative to healthy control subjects (e.g., (Basha  
36 et al., 1994, [075950](#); Hiltermann et al., 1997, [084979](#); Hiltermann et al., 1999, [013196](#); Holz et al.,  
37 2002, [041632](#); McBride et al., 1994, [043912](#); Michelson et al., 1999, [001147](#); Newson et al., 2000,

1 [000853](#); Peden, 2001, [025355](#); Peden et al., 1995, [076189](#); Peden et al., 1997, [085842](#); Scannell et  
2 al., 1996, [080755](#); Vagaggini et al., 1999, [001210](#)). For example, at 18 hours post-O<sub>3</sub> exposure  
3 (200 ppb, 4 hours with exercise) and corrected for FA responses, Scannell et al. (1996, [080755](#))  
4 found significantly increased neutrophils in 18 asthmatics (12%) compared to 20 healthy subjects  
5 (4.5%). This difference in inflammatory response was observed despite no group differences in  
6 spirometric responses to O<sub>3</sub>.

7 Vagaggini et al. (2010, [387127](#)) exposed mild-to-moderate asthmatics (n=23; 33 ± 11 years) to  
8 300 ppb O<sub>3</sub> for 2 hours with moderate exercise. Although the group mean O<sub>3</sub>-induced FEV<sub>1</sub>  
9 decrement was only 4%, eight subjects were categorized as “responders” with >10 FEV<sub>1</sub> decrements.  
10 There were no baseline differences between responders and nonresponders. At 6 hours post O<sub>3</sub>  
11 exposure, sputum neutrophils were significantly increased by 15% relative to FA in responders. The  
12 neutrophil increase in responders was also significantly greater than the 0.2% increase in  
13 nonresponders. Across all subjects, there was a significant (r=0.61, p = 0.015) correlation between  
14 changes in FEV<sub>1</sub> and changes in sputum neutrophils. Prior studies have reported that inflammatory  
15 responses do not appear to be correlated with lung function responses in either asthmatic or healthy  
16 subjects (Balmes et al., 1996, [080830](#); Balmes et al., 1997, [086092](#); Devlin et al., 1991, [040359](#);  
17 Holz et al., 1999, [058731](#)). Interestingly, the nonresponders in the Vagaggini et al. (2010, [387127](#))  
18 study experienced a significant O<sub>3</sub>-induced 11.3% increase in sputum eosinophils, while responders  
19 had an insignificant 2.6% decrease. Six of the subjects were NQO1wt and GSTM1 null, but this  
20 phenotype was not found to be associated with the changes in lung function or inflammatory  
21 responses to O<sub>3</sub>.

22 A few recent studies have evaluated the effects of corticosteroid usage on the response of  
23 asthmatics to O<sub>3</sub>. Vagaggini et al. (2007, [196638](#)) evaluated whether corticosteroid usage would  
24 prevent O<sub>3</sub>-induced lung function decrements and inflammatory responses in a group of subjects  
25 with mild persistent asthma (n=9; 25 ± 7 years). In this well designed study, asthmatics were  
26 randomly exposed on four occasions to 270 ppb O<sub>3</sub> or FA for 2 hours with moderate exercise.  
27 Exposures were preceded by four days of treatment with prednisone or placebo. Pretreatment with  
28 corticosteroids prevented an inflammatory response in induced sputum at 6 hours postexposure.  
29 FEV<sub>1</sub> responses were, however, not prevented by corticosteroid treatment and were roughly  
30 equivalent to those observed following placebo. Vagaggini et al. (2001, [025343](#)) also found  
31 budesonide to decrease airway neutrophil influx in asthmatics following O<sub>3</sub> exposure. In contrast,  
32 inhalation of corticosteroid budesonide failed to prevent or attenuate O<sub>3</sub>-induced responses in healthy  
33 subjects as assessed by measurements of lung function, bronchial reactivity and airway inflammation  
34 (Nightingale et al., 2000, [000796](#)). High doses of inhaled fluticasone and oral prednisolone have  
35 each been reported to reduce inflammatory responses to O<sub>3</sub> in healthy individuals (Holz et al., 2005,  
36 [077170](#)).

37 More recently, Stenfors et al. (2010, [386512](#)) exposed persistent asthmatics (n=13; aged  
38 33 years) receiving chronic inhaled corticosteroid therapy to 200 ppb O<sub>3</sub> for 2 hours with moderate  
39 exercise. An average O<sub>3</sub>-induced FEV<sub>1</sub> decrement of 8.4% was observed, whereas, only a 3.0%

1 FEV<sub>1</sub> decrement is predicted for similarly exposed age-matched healthy controls (McDonnell et al.,  
2 2007, [093104](#)). At 18 hours postexposure, there was a significant O<sub>3</sub>-induced increase in BAL  
3 neutrophils, but not eosinophils. Bronchial biopsy also showed a significant O<sub>3</sub>-induced increase in  
4 mast cells. This study suggests that the protective effect of acute corticosteroid therapy against  
5 inflammatory responses to O<sub>3</sub> in asthmatics demonstrated by Vagaggini et al. (2007, [196638](#)) may be  
6 lost with continued treatment regimes.

## Factors Modifying Responsiveness to Ozone

7 Physical activity increases V<sub>E</sub> and therefore the dose of inhaled O<sub>3</sub>. Consequently, the intensity  
8 of physiological response during and following an acute O<sub>3</sub> exposure will be strongly associated  
9 with minute ventilation. Apart from inhaled O<sub>3</sub> dose and related environmental factors (e.g., repeated  
10 daily exposures), individual-level factors, such as health status, age, gender, ethnicity, race, smoking  
11 habit, diet, and SES have been considered as potential modulators of a physiologic response to such  
12 exposures.

13 Children, adolescents, and young adults (<18 years of age) appear, on average, to have nearly  
14 equivalent spirometric responses to O<sub>3</sub>, but have greater responses than middle-aged and older adults  
15 when exposed to comparable O<sub>3</sub> doses (U.S. EPA, 1996, [017831](#)). Symptomatic responses to O<sub>3</sub>  
16 exposure, however, appear to increase with age until early adulthood and then gradually decrease  
17 with increasing age (U.S. EPA, 1996, [017831](#)). For subjects aged 18-36 years, McDonnell et al.  
18 (1999, [010939](#)) reported that symptom responses from O<sub>3</sub> exposure also decrease with increasing  
19 age. Diminished symptomatic responses in children and the elderly might put these groups at  
20 increased risk for continued O<sub>3</sub> exposure. Once lung growth and development reaches the peak  
21 (18-20 years of age in females and early twenties in males), pulmonary function, which is at its  
22 maximum as well, begins to decline progressively with age as does O<sub>3</sub> sensitivity.

23 In healthy individuals, the fastest rate of decline in O<sub>3</sub> responsiveness appears between the  
24 ages of 18 and 35 years (Passannante et al., 1998, [030114](#); Seal et al., 1996, [044251](#)), more so for  
25 females than males (Hazucha et al., 2003, [048168](#)). A model based on laboratory data estimates  
26 approximately a 1.1% reduction in FEV<sub>1</sub> per year over the above age range (Seal et al., 1996,  
27 [044251](#)). During the middle age period (35-55 years), O<sub>3</sub> sensitivity continues to decline but at a  
28 much lower rate. Beyond this age (>55 years), acute O<sub>3</sub> exposure elicits minimal spirometric  
29 changes. Whether the same age-dependent pattern of O<sub>3</sub> sensitivity decline also holds for  
30 nonspirometric pulmonary function, airway reactivity or inflammatory endpoints has not been  
31 determined. Although there is considerable evidence that spirometric and symptomatic responses to  
32 O<sub>3</sub> exposure decrease with age beyond young adulthood, this evidence comes from cross-sectional  
33 analysis and has not been confirmed by longitudinal studies of the same individuals.

34 Several studies have suggested that physiological differences between sexes may predispose  
35 females to a greater susceptibility to O<sub>3</sub>. Lower plasma and nasal lavage fluid (NLF) levels of uric  
36 acid (the most prevalent antioxidant) in females, the initial defense mechanism of O<sub>3</sub> neutralization  
37 in airway surface liquid, may be a contributing factor (Housley et al., 1996, [080811](#)). Consequently,

1 reduced absorption of O<sub>3</sub> in the upper airways may promote its deeper penetration. Dosimetric  
2 measurements have shown that the absorption distribution of O<sub>3</sub> is independent of gender when  
3 absorption is normalized to anatomical dead space (Bush et al., 1996, [080763](#)). Thus, a gender-  
4 related differential removal of O<sub>3</sub> by uric acid seems to be minimal. In general, the physiologic  
5 response of young healthy females to O<sub>3</sub> exposure appears comparable to the response of young  
6 males (Hazucha et al., 2003, [048168](#)). During the follicular phase of the menstrual cycle, lung  
7 function response to O<sub>3</sub> may be enhanced (Fox et al., 1993, [043906](#)), but Seal et al. (1996, [044251](#))  
8 later reported no effect of menstrual cycle phase in their analysis of responses of 150 women. Seal et  
9 al. (1996, [044251](#)) conceded that the methods used by Fox et al. (1993, [043906](#)) more precisely  
10 defined menstrual cycle phase.

11 Only one controlled human exposure study (Seal et al., 1993, [039357](#)) has compared lung  
12 function responses of whites (93 M, 94 F) and blacks (92 M, 93 F) exposed to a range of O<sub>3</sub>  
13 concentrations (0-400 ppb). The main effects of gender-race group and O<sub>3</sub> concentration were  
14 statistically significant (both at  $p < 0.001$ ), although the interaction between gender-race group and  
15 O<sub>3</sub> concentration was not significant ( $p = 0.13$ ). These findings indicate some overall difference  
16 between the gender-race groups that is independent of O<sub>3</sub> concentration, i.e., the concentration-  
17 response curves for the four gender-race groups are parallel. In a multiple comparison procedure on  
18 data collapsed across all O<sub>3</sub> concentrations for each gender-race group, both black men and black  
19 women had significantly larger decrements in FEV<sub>1</sub> than did white men. The authors noted that the  
20 O<sub>3</sub> dose per unit of lung tissue would be greater in blacks and females than whites and males,  
21 respectively. That this difference in tissue dose might have affected responses to O<sub>3</sub> cannot be ruled  
22 out. The college students recruited for the Seal et al. (1993, [039357](#)) study are probably from better  
23 educated and more SES advantaged families, thus reducing potential for these variables as  
24 confounding factors. In a follow-up analysis, Seal et al. (1996, [044251](#)) reported that, of three SES  
25 categories, individuals in the middle SES category showed greater concentration-dependent decline  
26 in percent-predicted FEV<sub>1</sub> (4-5% at 400 ppb O<sub>3</sub>) than low and high SES groups. The authors did not  
27 have an “immediately clear” explanation for this finding.

28 Smokers are less responsive to O<sub>3</sub> than nonsmokers. Spirometric and plethysmographic  
29 pulmonary function decline, nonspecific airway hyperreactivity, and inflammatory response of  
30 smokers to O<sub>3</sub> were all weaker than data reported for nonsmokers. Although all of these responses  
31 are intrinsically related, the functional association between them, as in nonsmokers, has been weak.  
32 Similarly, the time course of development and recovery of these effects as well their reproducibility  
33 was not different from nonsmokers. Chronic airway inflammation with desensitization of bronchial  
34 nerve endings and an increased production of mucus may plausibly explain the pseudo-protective  
35 effect of smoking (Frampton et al., 1997, [082692](#); Torres et al., 1997, [084265](#)).

36 The first line of defense against oxidative stress is antioxidants-rich ELF which scavenge free  
37 radicals and limit lipid peroxidation. Exposure to O<sub>3</sub> depletes the antioxidant level in nasal ELF  
38 probably due to scrubbing of O<sub>3</sub> (Mudway et al., 1999, [001270](#)), however, the concentration and the  
39 activity of antioxidant enzymes either in ELF or plasma do not appear to be related to O<sub>3</sub>

1 responsiveness (Avisar et al., 2000, [012528](#); Blomberg et al., 1999, [001267](#); Samet et al., 2001,  
2 [019034](#)). Carefully controlled studies of dietary antioxidant supplementation have demonstrated  
3 some protective effects of  $\alpha$ -tocopherol and ascorbate on spirometric lung function from O<sub>3</sub> but not  
4 on the intensity of subjective symptoms and inflammatory response including cell recruitment,  
5 activation and a release of mediators (Samet et al., 2001, [019034](#); Trenga et al., 2001, [019845](#)).  
6 Dietary antioxidants have also been reported to attenuate O<sub>3</sub>-induced bronchial hyperresponsiveness  
7 in asthmatics (Trenga et al., 2001, [019845](#)).

8 Several studies (Bergamaschi et al., 2001, [052670](#)) have reported that genetic polymorphisms  
9 of antioxidant enzymes may modulate pulmonary function and inflammatory response to O<sub>3</sub>  
10 challenge. It appears that healthy carriers of NQO1 wild type in combination with GSTM1 null  
11 genotype are more responsive to O<sub>3</sub>. Adults with GSTM1 null only genotype did not show O<sub>3</sub>  
12 hyperresponsiveness. In contrast, asthmatic children with GSTM1 null genotype (Romieu et al.,  
13 2004, [056796](#)) were reported to be more responsive to O<sub>3</sub>. However, in a controlled exposure of  
14 mild-to-moderate asthmatics (n=23; 33 ± 11 years) to 300 ppb O<sub>3</sub> for 2 hours with moderate  
15 exercise, Vagaggini et al. (2010, [387127](#)) found that six of the subjects had a NQO1<sub>wt</sub> and GSTM1  
16 null, but this genotype was not associated with the changes in lung function or inflammatory  
17 responses to O<sub>3</sub>.

18 Kim et al. (In Press, [674869](#)) also recently reported that GSTM1 genotype was not predictive  
19 of FEV<sub>1</sub> responses in young healthy adults (32 F, 27 M; 25.0 ± 0.5 year) that were roughly half  
20 GSTM1-null and half GSTM1-sufficient. Sputum neutrophil levels, measured in a subset of the  
21 subjects (13 F, 11 M), were also not significantly associated with GSTM1 genotype.

22 In a study of healthy volunteers with GSTM1 sufficient (n=19; 24 ± 3) and GSTM1 null  
23 (n=16; 25 ± 5) genotypes exposed to 400 ppb O<sub>3</sub> for 2 hours with exercise, Alexis et al. (2009,  
24 [628542](#)) found that inflammatory responses but not lung function responses to O<sub>3</sub> were dependent on  
25 genotype. At 4 hours post O<sub>3</sub> exposure, both GSTM1 genotypes had significant increases in sputum  
26 neutrophils with a tendency for a greater increase in GSTM1 sufficient than nulls. At 24 hours  
27 postexposure, sputum neutrophils had returned to baseline levels in the GSTM1 sufficient  
28 individuals. In the GSTM1 null subjects, however, sputum neutrophil levels increased from 4 hours  
29 to 24 hours and were significantly greater than both baseline levels and levels at 24 hours in the  
30 GSTM1 sufficient individuals. Since there was no FA control in the Alexis et al. (Alexis et al., 2009,  
31 [628542](#)) study, effects of the exposure other than O<sub>3</sub> itself cannot be ruled out. In general, the  
32 findings between studies are inconsistent and additional, better controlled studies are needed to  
33 clarify the influence of genetic polymorphism on O<sub>3</sub> responsiveness.

34 In a retrospective analysis of data from 541 healthy, nonsmoking, white males between the  
35 ages of 18-35 years from 15 studies conducted at the U.S. EPA Human Studies Facility in Chapel  
36 Hill, North Carolina, McDonnell et al. (2010, [383972](#)) found that increased body mass index (BMI)  
37 was found to be associated with enhanced FEV<sub>1</sub> responses. The BMI effect was of the same order of  
38 magnitude but in the opposite direction of the age effect where by FEV<sub>1</sub> responses diminish with  
39 increasing age. In a similar retrospective analysis, Bennett et al. (2007, [418827](#)) found enhanced

1 FEV<sub>1</sub> decrements following O<sub>3</sub> exposure with increasing BMI in a group of 75 healthy, nonsmoking,  
2 women (age 24 ± 4 years; BMI range 15.7 to 33.4), but not 122 healthy, nonsmoking, men (age 25 ±  
3 4 years; BMI range 19.1 to 32.9). In the women, greater O<sub>3</sub>-induced FEV<sub>1</sub> decrements were seen in  
4 overweight (BMI >25) than in normal weight (BMI from 18.5 to 25), and in normal weight than in  
5 underweight (BMI <18.5) (P trend ≤ 0.022). Higher BMI may be a risk factor for adverse pulmonary  
6 effects associated with O<sub>3</sub> exposure.

### Repeated Ozone Exposure Effects

7 Based on studies reviewed in previous O<sub>3</sub> AQCDs (U.S. EPA, 1986, [017607](#); U.S. EPA, 1996,  
8 [017831](#); U.S. EPA, 2006, [088089](#)), several conclusions can be drawn about repeated 1- to 2-h O<sub>3</sub>  
9 exposures. Repeated exposures to O<sub>3</sub> causes an enhanced (i.e., greater) pulmonary function response  
10 on the second day of exposure. The enhanced response appears to depend to some extent on the  
11 magnitude of the initial response (Horvath et al., 1981, [039221](#)). Small responses to the first O<sub>3</sub>  
12 exposure are less likely to result in an enhanced response on the second day of O<sub>3</sub> exposure  
13 (Folinsbee et al., 1994, [044189](#)). With continued daily exposures (i.e., beyond the second day) there  
14 is a substantial (or even total) attenuation of pulmonary function responses, typically on the third to  
15 fifth days of repeated O<sub>3</sub> exposure. This attenuation of responses is lost in 1 week (Kulle et al., 1982,  
16 [040668](#); Linn et al., 1982, [039646](#)) or perhaps 2 weeks (Horvath et al., 1981, [039221](#)) without O<sub>3</sub>  
17 exposure. In temporal conjunction with pulmonary function changes, symptoms induced by O<sub>3</sub> (e.g.,  
18 cough, pain on deep inspiration, and chest discomfort), are increased on the second exposure day and  
19 attenuated with repeated O<sub>3</sub> exposure thereafter (Folinsbee et al., 1980, [038880](#); Folinsbee et al.,  
20 1998, [038663](#); Foxcroft and Adams, 1986, [040463](#); Linn et al., 1982, [039646](#)). In longer-duration  
21 (4-6.6 hours), lower-concentration studies that do not cause an enhanced second-day response, the  
22 attenuation of response to O<sub>3</sub> appears to proceed more rapidly (Folinsbee et al., 1994, [044189](#)).  
23 Inflammatory markers from BALF on the day following both 2 hours (Devlin et al., 1997, [083577](#))  
24 and 4 hours (Christian et al., 1998, [029925](#); Jorres et al., 2000, [005654](#)) repeated O<sub>3</sub> exposure for  
25 4 days indicate that there is ongoing cellular damage irrespective of the attenuation of some cellular  
26 inflammatory responses of the airways, lung function and symptoms response.

#### 6.2.1.2. Epidemiology

27 Among epidemiologic studies reviewed in the 1996 and 2006 O<sub>3</sub> AQCDs, increases in ambient  
28 O<sub>3</sub> exposure were consistently associated with lung function decrements in groups with higher  
29 expected personal O<sub>3</sub> exposures and higher exertion levels, including children attending summer  
30 camps and adults exercising or working outdoors (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006,  
31 [088089](#)). An equally strong body of epidemiologic evidence demonstrated O<sub>3</sub>-associated lung  
32 function decrements in children, especially those with pre-existing respiratory disease such as  
33 asthma. These epidemiologic findings, in particular, ambient O<sub>3</sub>-associated decreases in lung  
34 function in healthy populations with increased outdoor exposures, are well-supported by findings  
35 from human controlled exposure studies. Recent epidemiologic studies contributed mixed evidence

1 of association between ambient O<sub>3</sub> exposure and lung function; however, a majority of studies  
2 conducted in asthmatic children indicated decreases in lung function in association with increases in  
3 ambient O<sub>3</sub> exposure. Newer data on children attending camps, outdoor workers, and other healthy  
4 populations were limited, and across these studies, ambient O<sub>3</sub> exposure was associated with both  
5 decreases and increases in lung function. Recent studies build upon the extant body of evidence by  
6 providing additional data to assess important lags of O<sub>3</sub> exposure associated with decrements in lung  
7 function; confounding by co-pollutants; and potential susceptibility due to corticosteroid (CS) use,  
8 genetic polymorphisms, obesity, and diet.

### **Populations with Increased Outdoor Exposures**

9 Few epidemiologic studies characterizing acute O<sub>3</sub>-related respiratory morbidity have  
10 accounted for time spent outdoors, which may be an important determinant of interindividual  
11 variability in personal O<sub>3</sub> exposure. Relative to other epidemiologic studies, studies of subjects  
12 engaged in outdoor recreation, exercise, or work may be more comparable to controlled exposure  
13 studies because of better-estimated personal O<sub>3</sub> exposures and examination of O<sub>3</sub> effects during  
14 exertion when the dose of O<sub>3</sub> reaching the lungs may be higher because of higher ventilation and  
15 inhalation of larger volumes of air. Characteristics and ambient O<sub>3</sub> concentration data from these  
16 epidemiologic studies are presented in Table 6-1. The collective body of evidence clearly  
17 demonstrates decrements in lung function in association with O<sub>3</sub> exposures during outdoor exertion  
18 or exercise (Figures 6-3 to 6-5 and Tables 6-2 to 6-4). A large number of older studies comprise a  
19 majority of the supporting evidence, whereas recent studies, which were far fewer in number,  
20 provide less compelling evidence. In addition to the consistency of associations among  
21 epidemiologic studies, the parallel findings from human controlled exposure studies indicating that  
22 lower O<sub>3</sub> exposures induce decrements in lung function when combined with exercise as compared  
23 with exposures during rest (Section 6.2.1.2), strengthen the evidence for increases in ambient O<sub>3</sub>  
24 exposure producing decrements in lung function.

**Table 6-1. Mean and upper percentile concentrations of ozone in epidemiologic studies examining lung function in populations with increased outdoor exposures**

Study	Location	Years/Season	Metric	Mean Concentration (ppb)	Middle/Upper Percentile Concentrations (ppb)
Korrick et al. (1998, <a href="#">026841</a> )	Mt. Washington, NH	1991, 1992 Warm season	Hike duration (2-12 h)	40	21-74
Thurston et al. (1997, <a href="#">077645</a> )	Connecticut River Valley, CT	1991-1993 Warm season	1-h max	83.6	Range: 20-160
Spektor et al. (1988, <a href="#">041710</a> )	Tuxedo, NY	1985 Warm season	1-h avg	NR	Range: 21-124
Spektor et al. (1988, <a href="#">040904</a> )	Fairview Lake, NJ	1984 Warm season	1-h avg <sup>a</sup>	53	Range (1-h max): 40- >100
Spektor et al. (1991, <a href="#">042612</a> )	Fairview Lake, NJ	1988 Warm season	1-h avg <sup>a</sup>	69	Range (1-h max): 40-150
Neas et al. (1999, <a href="#">003466</a> )	Philadelphia, PA	1993 Warm season	12-h avg (9:00-21:00)	57.5 (Camp 1) 55.9 (Camp 2)	IQR: 19.8 (Camp 1) IQR: 21.9 (Camp 2)
Girardot et al. (2006, <a href="#">088271</a> )	Great Smoky Mountain National Park, TN	2002-2004 Warm season	Hike duration (2-9 h)	48.1 <sup>b</sup>	Range: 25.0-74.2
Selwyn et al. (1985, <a href="#">041356</a> )	Houston, TX	1981 Warm season	15-m max	47	Range: 4-135
Thaller et al. (2008, <a href="#">195869</a> )	Galveston, TX	2002-2004 Warm season	1-h max	NR	Median: 35 Range: 19-118
Higgins et al. (1990, <a href="#">042195</a> )	San Bernardino, CA	1987 Warm season	1-h avg <sup>a</sup>	59	25-245
Avol et al. (1990, <a href="#">042366</a> )	Idyllwild, CA	1988 Warm season	1-h avg <sup>a</sup>	94	Approximate range (1-h max): 60-160 <sup>c</sup>
Burnett et al. (1990, <a href="#">670386</a> )	Lake Couchining, Ontario, CA	1983 Warm season	1-h avg <sup>a</sup>	59	Maximum: 95
Raizenne et al. (1989, <a href="#">041700</a> )	Lake Erie, Ontario, CA	1986 Warm season	1-h avg <sup>a</sup>	71	Range (1-h max): < 10-143
Brauer et al. (1996, <a href="#">080754</a> )	British Columbia, Canada	1993 Warm season	1-h max	40	Range: 13-84
Castillejos et al. (1995, <a href="#">078485</a> )	Mexico City, Mexico	1990 Warm season	1-h max	149	49-365
Romieu et al. (1998, <a href="#">086756</a> )	Mexico City, Mexico	1996 Warm season	1-h max	123	NR
Nickmilder et al. (2007, <a href="#">090710</a> )	southern Belgium	2002 Warm season	1-h max 8-h max	NR	24.5-112.7 <sup>d</sup> 18.9-81.1 <sup>d</sup>
Brunekreef et al. (1994, <a href="#">045161</a> )	Netherlands	1981 Warm season	1-h max	40	Range: 10-100
Hoek et al. (1993, <a href="#">043009</a> )	Wageningen, Netherlands	1989 Warm season	24-h avg	NR	Range: 25-120
Braun-Fahrländer et al. (1994, <a href="#">038665</a> )	southern Switzerland	1989 Warm season	1-h max	NR	Range: 20-80
Hoppe et al. (2003, <a href="#">055618</a> )	Munich, Germany	1992 Warm season	1/2-h max	High days: 65.9 Control days: 27.2	Max (high days): 86 Max (control days): 39

IQR = interquartile range, NR = not reported, Max = maximum

<sup>a</sup>1-h avg, at the time of afternoon lung function measurement.

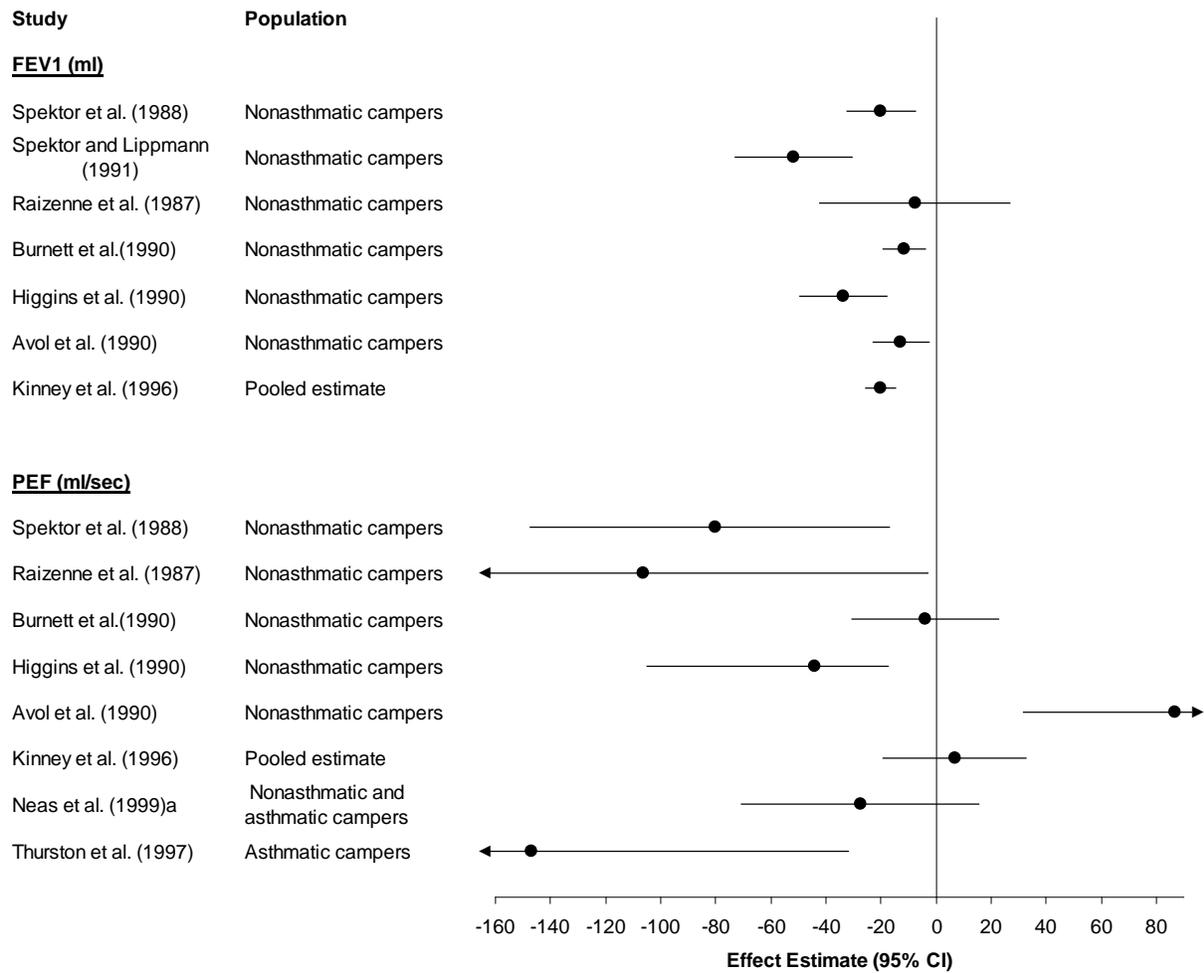
<sup>b</sup>Personal exposure estimates were derived based on time-activity diary data.

<sup>c</sup>Quantitative results not presented. Concentrations estimated from data presented in a figure.

<sup>d</sup>Concentrations 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).

1 In the 1996 O<sub>3</sub> AQCD (U.S. EPA, 1996, [017831](#)), studies of children attending summer camps  
2 were noted for their on-site measurement of ambient O<sub>3</sub> and repeated assessment of lung function  
3 over 1- to 2-week periods (Avol et al., 1990, [042366](#); Berry et al., 1991, [042377](#); Burnett et al., 1990,  
4 [670386](#); Higgins et al., 1990, [042195](#); Raizenne et al., 1987, [040903](#); Raizenne et al., 1989, [041700](#);  
5 Spektor and Lippmann, 1991, [042612](#); Spektor et al., 1988, [040904](#); Thurston et al., 1997, [077645](#)).  
6 In groups mostly comprising healthy children across heterogeneous geographic locations,

1 decrements in FEV<sub>1</sub> were consistently observed in association with ambient O<sub>3</sub> exposures averaged  
2 over the 1-8 hours preceding lung function measurement (Figure 6-3 and Table 6-2). Kinney et al.  
3 (1996, [079203](#)) corroborated this consistency in a reanalysis combining data from nonasthmatic  
4 subjects from six studies (Avol et al., 1990, [042366](#); Burnett et al., 1990, [670386](#); Higgins et al.,  
5 1990, [042195](#); Raizenne et al., 1987, [040903](#); Spektor and Lippmann, 1991, [042612](#); Spektor et al.,  
6 1988, [040904](#)). Based on uniform statistical methods, a 40-ppb increase in concurrent-hour O<sub>3</sub>  
7 concentration was associated with a -20 mL (95% CI: -25, -14) change in afternoon FEV<sub>1</sub> (Kinney et  
8 al., 1996, [079203](#)). Study-specific effect estimates ranged between a 0.76 and 48 mL decrease (per  
9 40 ppb O<sub>3</sub>) and were observed in locations with mean afternoon 1-h avg O<sub>3</sub> concentrations between  
10 53 and 123 ppb. In contrast with these previous findings, in a recent cross-sectional analysis of 72  
11 children attending 6 different camps in Belgium, children at camps with higher daily 1-h max O<sub>3</sub>  
12 concentrations did not consistently have greater decreases in intraday FEV<sub>1</sub> or FEV<sub>1</sub>/FVC  
13 (Nickmilder et al., 2007, [090710](#)). In camp studies, associations between O<sub>3</sub> exposure and peak  
14 expiratory flow (PEF) were more variable as characterized by the wider range in effect estimates and  
15 wider 95% CIs (Figure 6-4 and Table 6-3). Nonetheless, most effect estimates indicated decreases in  
16 PEF in association with ambient O<sub>3</sub> exposure, with the largest effect estimated in a group of  
17 asthmatic campers (Thurston et al., 1997, [077645](#)).



<sup>a</sup>Neas et al. (1999, [003466](#)) examined 12-h avg O<sub>3</sub> exposure (9:00 a.m. - 9:00 p.m.). All of the other studies examined O<sub>3</sub> exposure in the 1 hour preceding afternoon lung function measurement.

**Figure 6-3. Changes in FEV<sub>1</sub> (mL) or PEF (mL/sec) in association with ambient ozone exposure in studies of children attending summer camp. Effect estimates are standardized to a 40- or 30-ppb increase in 1-h or 12-h avg ozone, respectively. All effect estimates are from single pollutant models.**

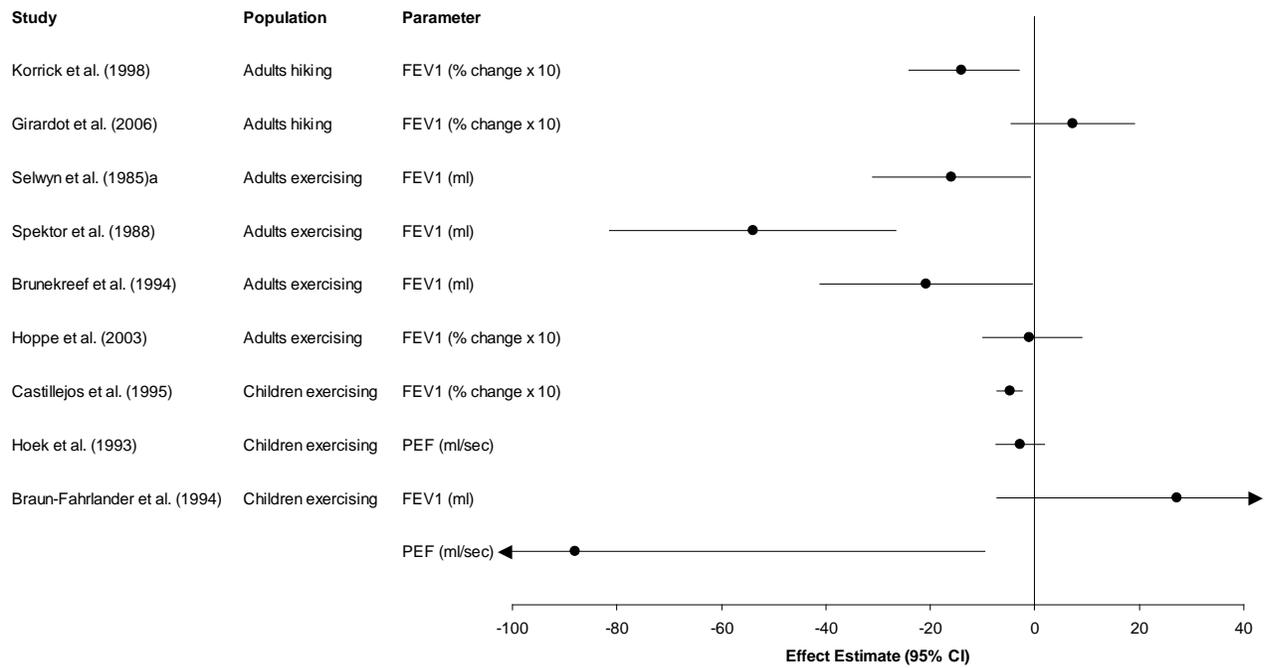
**Table 6-2. Additional characteristics and quantitative data for studies represented in Figure 6-3**

Study	Location	Population	Effect Estimate (95% CI) <sup>a</sup>
<b>FEV<sub>1</sub> (mL)</b>			
Spektor et al. (1988, <a href="#">040904</a> )	Lake Fairview, NJ	Nonasthmatic campers	-20.0 (-32.5, -7.5)
Spektor and Lippmann (1991, <a href="#">042612</a> )	Lake Fairview, NJ	Nonasthmatic campers	-51.6 (-72.8, -30.4)
Raizenne et al. (1989, <a href="#">041700</a> )	Lake Erie, Ontario, Canada	Nonasthmatic campers	-7.6 (-42.1, 26.9)
Burnett et al. (1990, <a href="#">670386</a> )	Lake Couchiching, Ontario, Canada	Nonasthmatic campers	-11.6 (-19.4, -3.8)
Higgins et al. (1990, <a href="#">042195</a> )	San Bernardino, CA	Nonasthmatic campers	-33.6 (-49.3, -17.9)
Avol et al. (1991, <a href="#">042613</a> )	Pine Springs, CA	Nonasthmatic campers	-12.8 (-23.0, -2.6)
Kinney et al. (1996, <a href="#">079203</a> )	Pooled analysis	Nonasthmatic campers	-20.0 (-25.5, -14.5)
<b>PEF (mL/sec)</b>			
Spektor et al. (1988, <a href="#">040904</a> )	Lake Fairview, NJ	Nonasthmatic campers	-80.0 (-147.3, -17.0)
Raizenne et al. (1989, <a href="#">041700</a> )	Lake Erie, Ontario, Canada	Nonasthmatic campers	-106.4 (-209.9, -2.9)
Burnett et al. (1990, <a href="#">670386</a> )	Lake Couchiching, Ontario, Canada	Nonasthmatic campers	-4.0 (-30.7, 22.7)
Higgins et al. (1990, <a href="#">042195</a> )	San Bernardino, CA	Nonasthmatic campers	-44.0 (-105.0, 17.2)
Avol et al. (1991, <a href="#">042613</a> )	Pine Springs, CA	Nonasthmatic campers	86.8 (31.9, 141.7)
Kinney et al. (1996, <a href="#">079203</a> )	Pooled analysis	Nonasthmatic campers	6.8 (-19.1, 32.7)
Neas et al. (1999, <a href="#">003466</a> )	Philadelphia, PA	Nonasthmatic and asthmatic campers	-27.5 (-70.8, 15.75)
Thurston et al. (1997, <a href="#">077645</a> )	CT River Valley, CT	Asthmatic campers	-146.7 (-261.7, -31.7)

<sup>a</sup>All effect estimates are standardized to a 40-ppb increase in 1-h avg O<sub>3</sub>, except that from Neas et al. (1999, [003466](#)), which is standardized to a 30-ppb increase in 12-h avg O<sub>3</sub>

1            Similar to the camp studies, studies of subjects exercising outdoors collectively show that low-  
2 level exposures O<sub>3</sub> (range of mean concentrations: 40-149 ppb) during short periods (10-60 minutes)  
3 of moderate to heavy exercise are associated with decreases in lung function, with stronger evidence  
4 of association observed among adults than among children (Figure 6-4 and Table 6-3). These studies  
5 were noted for the repeated examination of subjects over days with a wide range in ambient O<sub>3</sub>  
6 concentrations and assessment of O<sub>3</sub> exposures during discrete outdoor exercise periods. Further,  
7 results from these studies were consistent with those from human controlled exposure studies  
8 indicating that lower concentrations of O<sub>3</sub> exposures induced lung function decrements when  
9 combined with exercise as compared with exposures during rest. In the more limited set of studies of  
10 adult day-hikers that examined variable multihour exposures during one period of exercise, results  
11 were mixed (Girardot et al., 2006, [088271](#); Korrick et al., 1998, [026841](#)). Both Girardot et al. (2006,  
12 [088271](#)) (n = 354) and Korrick et al. (1998, [026841](#)) (n = 530) were large studies of predominantly  
13 white, healthy adults hiking in Great Smoky Mountains National Park, TN and Mt. Washington, NH,  
14 respectively. Korrick et al. (1998, [026841](#)) reported a posthike decline of 1.4% (95% CI: -2.4, -0.30)  
15 in FEV<sub>1</sub> per 30-ppb increase in 8-h avg O<sub>3</sub>. In contrast, Girardot et al. (2006, [088271](#)) found that O<sub>3</sub>  
16 exposure was associated with a posthike increase in FEV<sub>1</sub> (0.72% [95% CI: -0.46, 1.90]) per 30 ppb  
17 increase in 8-h avg O<sub>3</sub>). In Korrick et al. (1998, [026841](#)), effect estimates for O<sub>3</sub> with FVC,  
18 FEV<sub>1</sub>/FVC, FEF<sub>25-75%</sub>, and PEF were negative but associated with wide 95% CIs; however, similar  
19 associations in Girardot et al. (2006, [088271](#)) were in mixed directions. To explain discrepancies in  
20 findings between studies, Girardot et al. (2006, [088271](#)) pointed to their exclusion of 367 subjects  
21 (61%) for failure to provide at least 2 acceptable spirometry tests, compared with 31% excluded in  
22 Korrick et al. (1998, [026841](#)). Excluded subjects in Girardot et al. (2006, [088271](#)) had significantly

1 higher mean O<sub>3</sub> exposure, tended to be regular exercisers, and had small posthike increases in lung  
 2 function, which also may have contributed to weak findings for O<sub>3</sub>. Additional explanations provided  
 3 by Girardot et al. (2006, [088271](#)) included their use of a larger number of untrained technicians and  
 4 shorter mean duration of hike (5 hours versus 8 hours).



<sup>a</sup>The 95% CI was constructed using a standard error that was estimated from the p-value.

**Figure 6-4. Changes in FEV<sub>1</sub> (mL or percent change) or PEF (mL/sec) in association with ambient ozone exposures of adults and children during outdoor exercise. Effect estimates are standardized to a 40-ppb increase in ozone exposures in the range of 15 minutes to 1 hour, and a 30-ppb increase for mean ozone exposures in the range of 3 to 8 hours. All effect estimates are from single pollutant models.**

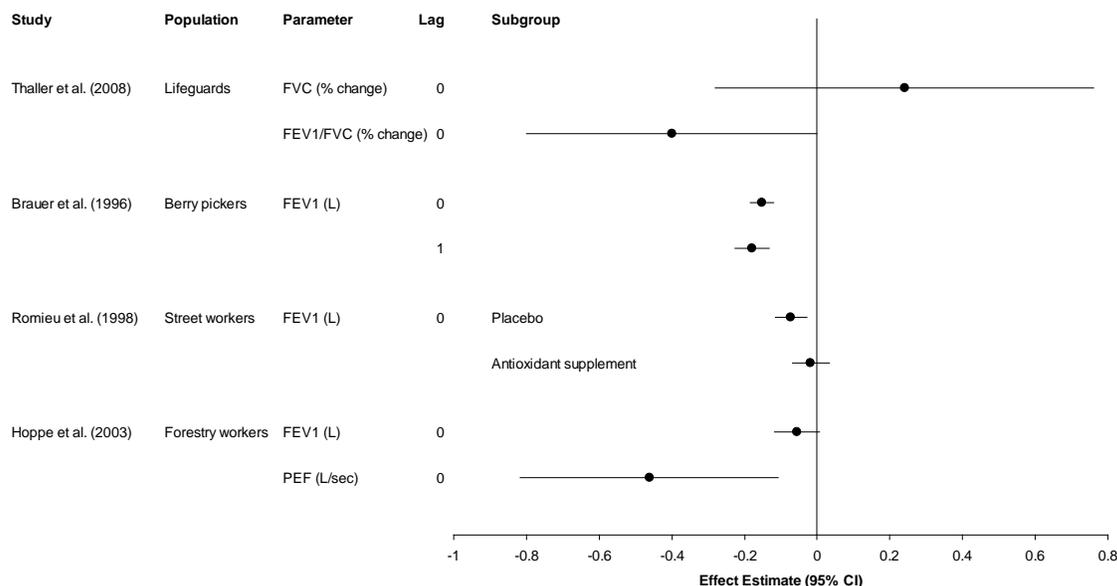
**Table 6-3. Additional characteristics and quantitative data for studies represented in Figure 6-4**

Study	Location	Population	Parameter	O <sub>3</sub> Averaging Time	Effect Estimate (95% CI) <sup>a</sup>
Korrick et al. (1996, <a href="#">026481</a> )	Mt. Washington, NH	Adult day hikers	FEV <sub>1</sub> (percent change)	8-h avg	-1.4 (-2.4, -0.30)
Girardot et al. (2006, <a href="#">088271</a> )	Great Smoky Mt, TN	Adult day hikers	FEV <sub>1</sub> (percent change)	8-h avg	0.72 (-0.46, 1.90)
Selwyn et al. (1985, <a href="#">041356</a> ) <sup>b</sup>	Houston, TX	Adults exercising	FEV <sub>1</sub> (mL)	15-m max	-16 (-31.1, -0.87) <sup>0</sup>
Spektor et al. (1962, <a href="#">014710</a> )	Tuxedo, NY	Adults exercising	FEV <sub>1</sub> (mL)	30-m avg	-54 (-84.1, -26.6)
Brunekreef et al. (1994, <a href="#">045161</a> )	Netherlands	Adults exercising	FEV <sub>1</sub> (mL)	10-m to 1-h	-20.8 (-41.2, -0.42)
Hoppe et al. (2003, <a href="#">055618</a> )	Munich, Germany	Adults exercising	FEV <sub>1</sub> (percent change)	3-h avg (8:00-11:00)	-0.01 (-0.10, 0.09)
Castillejos et al. (1995, <a href="#">078485</a> )	Mexico City, Mexico	Children exercising	FEV <sub>1</sub> (percent change)	1-h avg	-0.48 (-0.72, -0.24)
Hoek et al. (1993, <a href="#">043009</a> )	Wageningen, Netherlands	Children exercising	PEF (mL/sec)	1-h avg	-2.8 (-7.4, 1.9)
Braun-Fahrlander et al. (1994, <a href="#">038665</a> )	Switzerland	Children exercising	FEV <sub>1</sub> (mL) PEF (mL/sec)	1-h avg	27.2 (-7.2, 61.6) -88 (-166.4, -9.6)

<sup>a</sup>Effect estimates are standardized to a 40-ppb increase in O<sub>3</sub> exposures in the range of 15 minutes to 1 hour and a 30-ppb increase for mean O<sub>3</sub> exposures in the range of 3 to 8 hours.

<sup>b</sup>The 95% CI was constructed using a standard error that was estimated from the p-value.

1 Ambient O<sub>3</sub> exposure has been associated consistently with decrements in lung function  
2 among outdoor workers (Figure 6-5 and Table 6-4). In particular, Brauer et al. (1996, [080754](#)) was  
3 noted for the low ambient O<sub>3</sub> concentrations (workshift mean [SD]: 26.0 ppb [11.8]), long outdoor  
4 workshifts of the 58 berry pickers (11 hours) and a larger O<sub>3</sub>-associated decrease in afternoon FEV<sub>1</sub>  
5 (-152 mL [95% CI: -183, -121] per 40 ppb increase in 1-h max O<sub>3</sub>) compared with those observed in  
6 studies of exercising adults with higher exertion levels. Brauer et al. (1996, [080754](#)) also found that  
7 workday O<sub>3</sub> exposure was associated with a greater decrement in FEV<sub>1</sub> on the next morning  
8 (-180 mL [95% CI: -227, -133] per 40 ppb increase in 1-h max O<sub>3</sub>), indicating a delayed or persistent  
9 effect. Consistent with previous findings, a recent study of lifeguards in Galveston, TX found that O<sub>3</sub>  
10 exposure during 6-8 hour workshifts was associated with decrements in FEV<sub>1</sub>/FVC (Thaller et al.,  
11 2008, [195869](#)). In this study, 142 mostly white males, 16-27 years of age were followed for at least  
12 one summer from 2002 to 2004. Among all subjects, a 40 ppb increase in 1-h max O<sub>3</sub> was associated  
13 with a 0.4% decrease (95% CI: -0.8, 0) in afternoon FEV<sub>1</sub>/FVC. A similar magnitude of effect was  
14 estimated in a co-pollutant model that included daily max NO<sub>2</sub> and daily avg PM<sub>2.5</sub>. Ozone was not  
15 associated with either FEV<sub>1</sub> or FVC individually.



**Figure 6-5. Changes in lung function parameters in association with ambient ozone exposures among outdoor workers. Effect estimates are standardized to a 40-ppb increase for 1/2-h or 1-h max ozone and a 30-ppb increase for 8-h max ozone. All effect estimates are from single pollutant models.**

**Table 6-4. Additional characteristics and quantitative data for studies represented in Figure 6-5**

Study	Location	Population	Parameter	O <sub>3</sub> Averaging Time	Lag	Subgroup	Effect Estimate (95% CI) <sup>a</sup>
Thaller et al. (2008, <a href="#">195869</a> )	Galveston, TX	Lifeguards	FVC (percent change)	8-h max	0		0.24 (-0.28, 0.72)
			FEV <sub>1</sub> /FVC (percent change)				-0.40 (-0.80, 0)
Brauer et al. (1996, <a href="#">080754</a> )	British Columbia, Canada	Berry pickers	FEV <sub>1</sub> (mL)	1-h max	0		-152 (-183, -121)
					1		-180 (-227, -133)
Romieu et al. (1998, <a href="#">086756</a> )	Mexico City, Mexico	Street workers	FEV <sub>1</sub> (mL)	1-h max	0	Placebo	-71.6 (-113.9, -29.3)
						Antioxidant supplement	-17.6 (-68.6, 33.4)
Hoppe et al. (2003, <a href="#">055618</a> )	Munich, Germany	Forestry workers	FEV <sub>1</sub> (mL)	1/2-h max (13:00-16:00)	0		-56 (-118.4, 6.4)
			PEF (mL/sec)				-460 (-816, -107)

<sup>a</sup>Effect estimates are standardized to a 40-ppb increase for 1/2-h or 1-h max O<sub>3</sub> and a 30-ppb increase for 8-h max O<sub>3</sub>.

## Asthmatic Children

1 Studies of asthmatic children generally demonstrate that increases in ambient O<sub>3</sub> exposure are  
 2 associated with decrements in PEF and FEV<sub>1</sub> (Figures 6-6 and 6-7 and Tables 6-6 and 6-7).  
 3 Characteristics and ambient O<sub>3</sub> concentration data from these epidemiologic studies are presented in  
 4 Table 6-5. The most geographically representative data were provided by the 7-U.S. city Inner-City  
 5 Asthma Study (ICAS) of 861 children with persistent asthma and atopy (O'Connor et al., 2008,

1 [156818](#)). Using year-round data, investigators observed that a 20-ppb increase in the lag 1-5 avg of  
2 24-h avg O<sub>3</sub> was associated with decreases of 0.41 (95% CI: -1.0, 0.21) in percent predicted FEV<sub>1</sub>  
3 and of 0.22 (95% CI: -0.86, 0.43) in percent predicted PEF. Ozone was associated with larger  
4 decreases in lung function in co-pollutant models with PM<sub>2.5</sub> and NO<sub>2</sub>. Lag 1-5 avg O<sub>3</sub> also was  
5 negatively associated with morning PEF in the 1993 National Cooperative Inner City Asthma Study  
6 (NCICAS) of different children (n = 846) from the same cities plus Boston, MA (Mortimer et al.,  
7 2002, [030281](#)). Consistent with human controlled exposure studies (Section 6.2.1.2), Mortimer et al.  
8 (2002, [030281](#)) found that increasing O<sub>3</sub> exposure was associated with an increased incidence of  
9 10% declines in PEF (OR: 1.30 [95% CI: 1.04, 1.61] per 30 ppb increase in lag 1-5 of 8-h avg O<sub>3</sub>),  
10 demonstrating that O<sub>3</sub> exposure is related to clinically important changes in lung function in  
11 asthmatic children.

12 In addition to these multicity studies and the study of asthmatic children attending summer  
13 camps described earlier (Thurston et al., 1997, [077645](#)), several smaller studies conducted in the  
14 U.S., Mexico City, and Europe also found associations between ambient O<sub>3</sub> exposure and  
15 decrements in PEF among asthmatic children (Figures 6-6 and 6-7 and Tables 6-6 and 6-7).

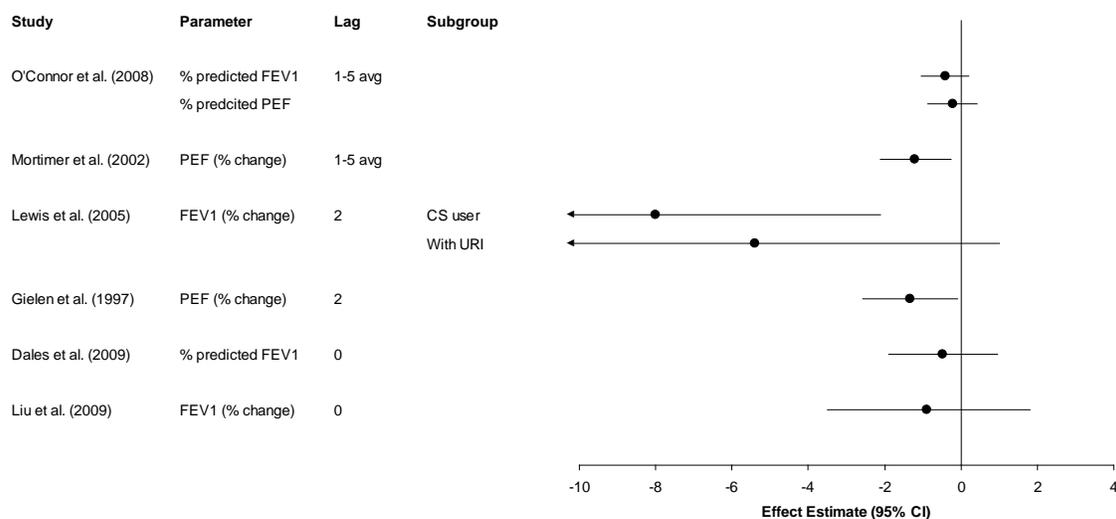
**Table 6-5. Mean and Upper Percentile Concentrations of Ozone in Epidemiologic Studies Examining Lung Function in Asthmatic Children**

Study	Location	Years/Season	Metric	Mean Concentration (ppb)	Middle/Upper Percentile Concentrations (ppb)
Mortimer et al. (2002, <a href="#">030281</a> )	8 U.S. communities (NCICAS)	1993 Warm season	8-h avg (10:00a.m.-6:00 p.m.)	48	Approximate IQR = 15 <sup>a</sup>
O'Connor et al. (2008, <a href="#">156818</a> )	7 U.S. communities (ICAS)	1998-2001 All-year	24-h avg	NR	Approximate median: 20 <sup>a</sup> Approximate range: 2-50 <sup>a</sup>
Lewis et al. (2005, <a href="#">081079</a> )	Detroit, MI	2001-2002 All-year	8-h max	Eastside: 40.4 <sup>o</sup> Westside: 41.4 <sup>b</sup>	Overall IQR: 16.0 Overall range: 14.8-92.0
Rabinovitch et al. (2004, <a href="#">096753</a> )	Denver, CO	2000-2003 Cold season	1-h max	28.2 <sup>b</sup>	Median: 30.0 Range: 0-70.0
Dales et al. (2009, <a href="#">594285</a> ) Liu et al. (2009, <a href="#">192003</a> )	Windsor, ON, Canada	2005 Cold season	24-h avg 1-h max	14.1 27.2	Median: 13.0; IQR: 8.8-17.8 Median: 27.0; IQR: 21.8-32.8
Romieu et al. (1996, <a href="#">080748</a> )	Northern Mexico City, Mexico	1991-1992 Warm and cold season	1-h max	190	Range: 40-370
Romieu et al. (1997, <a href="#">085807</a> )	Southern Mexico City, Mexico	1991-1992 Warm and cold season	1-h max	196	Range: 40-390
Romieu et al. (2002, <a href="#">034711</a> ) Romieu et al. (2004, <a href="#">056796</a> ) Romieu et al. (2006, <a href="#">090969</a> )	Mexico City, Mexico	1998-2000 All-year	8-h max 1-h max	66.2 102	Range: 11.1-142.5 Range: 12-309
Barraza-Villarreal et al. (2008, <a href="#">156254</a> ) Romieu et al. (2009, <a href="#">548788</a> )	Mexico City, Mexico	2003-2005 All-year	8-h max 1-h max	31.6 86.5	IQR: 22.0 (8-h); Range: 4.9-86.3 IQR: 48.0
Hernández-Cadena et al. (2009, <a href="#">594283</a> )	Mexico City, Mexico	2005 Warm season	24-h avg 1-h max	26.3 74.5	IQR: 17.9-35.3; Range: 9.0-62.8 IQR: 46.5-92.5; Range: 26.0-165.0
Gielen et al. (1997, <a href="#">083592</a> )	Amsterdam, Netherlands	1995 Warm season	8-h max	33.5	Range: 13.8-55.4
Hoppe et al. (2003, <a href="#">055618</a> )	Munich, Germany	1992-1995 Warm season	1/2-h max	High O <sub>3</sub> days: 65.9 Control days: 27.2	High O <sub>3</sub> days: 65.9-70.4 (range)
Wiwatanadate and Trakultivakorn (2010, <a href="#">387706</a> )	Chiang Mai, Thailand	August 2005-June 2006	24-h avg	17.5	90th percentile: 26.82 Range: 5.55-34.65
Jalaudin et al. (2000, <a href="#">011929</a> )	Sydney, Australia	February-December 1994	24-h avg	12	IQR: 8.3 Maximum: 43

NCICAS = National Cooperative Inner-City Asthma Study, IQR = interquartile range, ICAS = Inner City Asthma Study, NR = Not Reported

<sup>o</sup>Quantitative results not presented. Concentrations estimated from data presented in a figure.

<sup>b</sup>Measured at sites established by investigators.

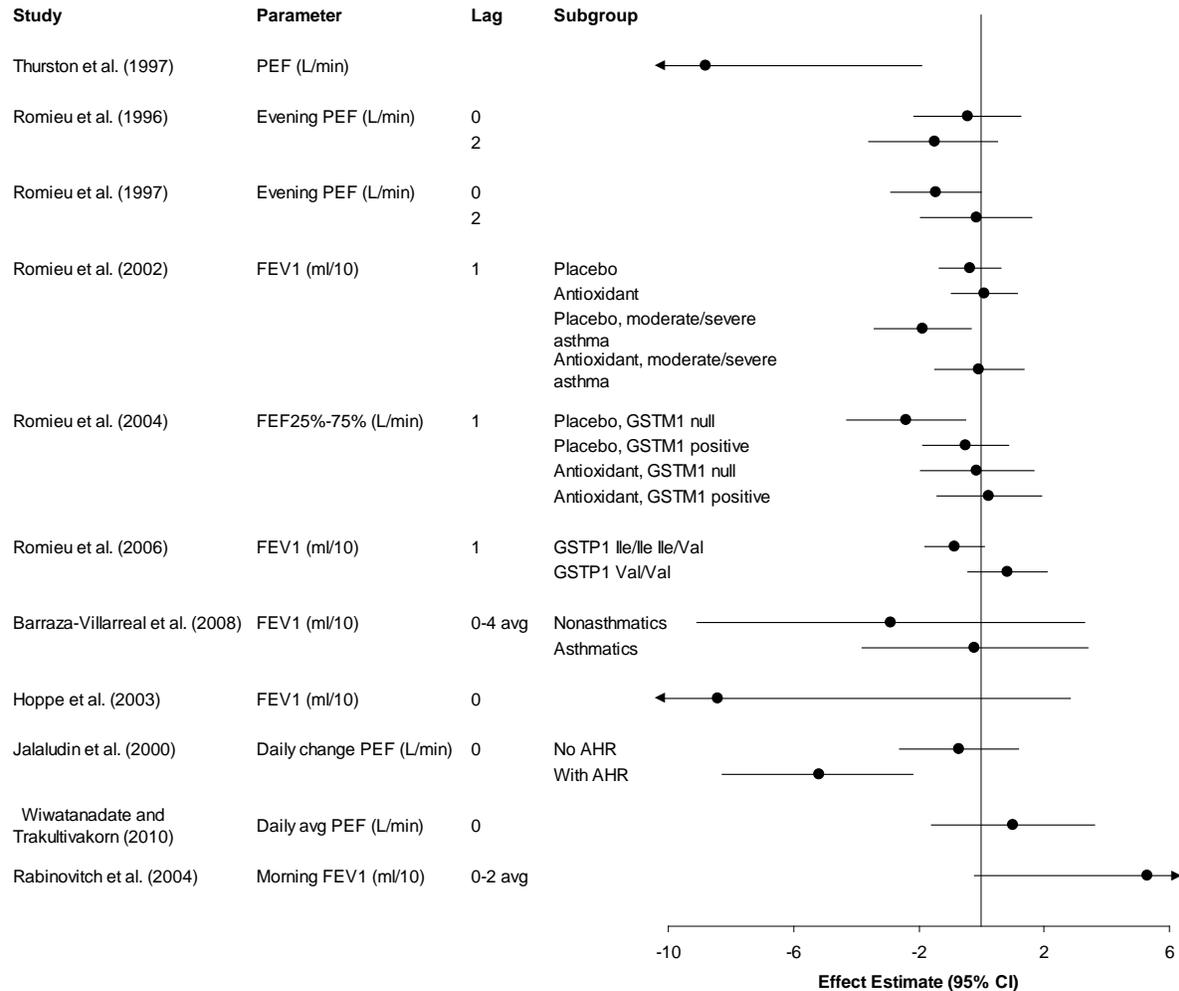


**Figure 6-6. Changes in lung function parameters (percent-predicted or %change) in association with ambient ozone exposures among asthmatic children. (CS = corticosteroid, URI = Upper respiratory infection. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg ozone, respectively. All effect estimates are from single pollutant models.**

**Table 6-6. Additional characteristics and quantitative data for studies represented in Figure 6-6**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Parameter	Subgroup	Effect Estimate (95% CI) <sup>a</sup>
O'Connor et al. (2008, <a href="#">156818</a> )	7 U.S. communities Asthmatic children	1-5 avg	24-h avg	% predicted FEV <sub>1</sub>		-0.41 (-1.03, 0.21)
				% predicted PEF		-0.22 (-0.86, 0.43)
Mortimer et al. (2002, <a href="#">030281</a> )	8 U.S. communities Asthmatic children	1-5 avg	8-h avg (10:00-18:00)	% predicted PEF		-1.2 (-2.1, -0.26)
Lewis et al. (2005, <a href="#">081079</a> )	Detroit, MI Asthmatic children	2	8-h max	percent change, lowest daily FEV <sub>1</sub>	CS user	-8.0 (-13.5, -2.1)
					With URI	-5.4 (-11.3, 1.0)
Gielen et al. (1997, <a href="#">083592</a> )	Amsterdam, Netherlands Asthmatic children	2	8-h max	percent change, PEF		-1.34 (-2.58, -0.10)
Dales et al. (2009, <a href="#">594285</a> )	Windsor, ON, Canada Asthmatic children	0	1-h max	% predicted FEV <sub>1</sub>		-0.47 (-1.67, 2.25)
Liu et al. (2009, <a href="#">192003</a> )	Windsor, ON, Canada Asthmatic children	0	24-h avg	percent change, FEV <sub>1</sub>		-0.89 (-3.5, 1.8)

<sup>a</sup>Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O<sub>3</sub>, respectively.



**Figure 6-7. Changes in lung function parameters (L/min or mL/10) in association with ambient ozone exposures among asthmatic children. [AHR = airway hyperresponsiveness. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h (or 1/2-h) max, 8-h max, and 24-h avg ozone, respectively. All effect estimates are from single pollutant models.**

**Table 6-7. Additional characteristics and quantitative data for studies represented in Figure 6-7**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Parameter	Subgroup	Effect Estimate 95% CI) <sup>a</sup>
Thurston et al. (1997, <a href="#">077645</a> )	CT River Valley, CT Asthmatic campers	0	1-h avg	PEF (L/min)		-8.8 (-15.7, -1.90)
Romieu et al. (1996, <a href="#">080748</a> )	Northern Mexico City, Mexico Asthmatic children	0 2	1-h max	Evening PEF (L/min)		-0.45 (-2.16, 1.26) -1.50 (-3.60, 0.53)
Romieu et al. (1997, <a href="#">085807</a> )	southern Mexico City, Mexico Asthmatic children	0 2	1-h max	Evening PEF (L/min)		-1.45 (-2.88, -0.02) -0.17 (-1.95, 1.62)
Romieu et al. (2002, <a href="#">034711</a> )	Mexico City, Mexico Asthmatic children Moderate/severe asthmatics	1	1-h max	FEV <sub>1</sub> (mL/10)	Placebo Antioxidant Placebo, moderate/severe asthma Antioxidant, moderate/severe asthma	-0.36 (-1.35, 0.63) 0.08 (-0.98, 1.13) -1.88 (-3.42, -0.34) -0.07 (-1.5, 1.37)
Romieu et al. (2004, <a href="#">056796</a> )	Mexico City, Mexico Asthmatic children	1	1-h max	FEF25%-75% (L/min)	Placebo, GSTM1 null Placebo, GSTM1 sufficient Supplement, GSTM1 null Supplement, GSTM1 sufficient	-2.4 (-4.3, -0.52) -0.50 (-1.86, 0.85) -0.14 (-1.95, 1.67) 0.24 (-1.43, 1.92)
Romieu et al. (2006, <a href="#">090969</a> )	Mexico City, Mexico Asthmatic children	1	1-h max	FEV <sub>1</sub> (mL/10)	GSTP1 Ile/Ile or Ile/Val GSTP1 Val/Val	-0.86 (-1.18, 0.08) 0.84 (-0.42, 2.1)
Barraza-Villarreal et al. (2008, <a href="#">156254</a> )	Mexico City, Mexico Children	1-5 avg	8-h max	FEV <sub>1</sub> (mL/10)	Nonasthmatics asthmatics	-2.9 (-9.1, 3.3) -0.22 (-3.8, 3.4)
Hoppe et al. (2003, <a href="#">055618</a> )	Munich, Germany Asthmatic children	0	1/2-h max	FEV <sub>1</sub> (mL/10)		-8.4 (-19.64, 2.84)
Jalaludin et al. (2000, <a href="#">011929</a> )	Sydney, Australia Asthmatic children	0	24-h avg	Daily change PEF (L/min)	No AHR AHR	-0.71 (-2.6, 1.17) -5.2 (-8.27, -2.18)
Wiwatanadate and Trakultivakorn (2010, <a href="#">387706</a> )	Chiang Mai, Thailand Asthmatic children	0	24-h avg	Daily avg PEF (L/min)		1.0 (-1.6, 3.6)
Rabinovitch et al. (2004, <a href="#">096753</a> )	Denver, CO Asthmatic children	0-3 avg	1-h max	Morning FEV <sub>1</sub> (mL/10)		5.3 (-0.24, 10.8)

AHR = airway hyperresponsiveness.

<sup>a</sup>Effect estimates are standardized to a 40, 30, and 20 ppb increase for 1-h (or 1/2-h) max, 8-h max, and 24-h avg O<sub>3</sub>, respectively.

1            Among the studies that examined FEV<sub>1</sub>, evidence of association with ambient O<sub>3</sub> exposure  
2 was stronger in particular subgroups of asthma severity, comorbid conditions, or antioxidant capacity  
3 (Jalaludin et al., 2000, [011929](#); Lewis et al., 2005, [081079](#); Romieu et al., 2004, [056796](#); Romieu et  
4 al., 2006, [090969](#)) than among asthmatics overall (Barraza-Villarreal et al., 2008, [156254](#); Lewis et  
5 al., 2005, [081079](#); Romieu et al., 2002, [034711](#)). Demonstrating varying susceptibilities within a  
6 group of asthmatic children, Jalaludin et al. (2000, [011929](#)) estimated a greater effect in asthmatics  
7 with airway hyperresponsiveness (AHR), and Hoppe et al. (2003, [055618](#)) found that 20% of their  
8 asthmatic subjects experienced a greater than 10% decline in FEV<sub>1</sub> in association with O<sub>3</sub> exposure,  
9 Additionally, in a group of 86 asthmatic children in Detroit, MI, ambient O<sub>3</sub> exposure was associated  
10 with decreases in lung function primarily among CS users and subjects reporting concurrent  
11 presence of symptoms related to an upper respiratory infection (URI) but not among asthmatics  
12 overall (Lewis et al., 2005, [081079](#)). In the group with a URI, 30 ppb increases in lags 1 and 2 of 8-h  
13 max O<sub>3</sub> were associated with a 6.1% decrease (95% CI: -10.4, -1.6) and a 5.4% decrease

1 (95% CI: -11.3, 0.10) in lowest daily FEV<sub>1</sub>, respectively. Ozone was associated with larger decreases  
2 in FEV<sub>1</sub> in two-pollutant models with PM<sub>10</sub> or PM<sub>2.5</sub>.

3 In human controlled exposure studies, CS treatment of asthmatics generally has not prevented  
4 O<sub>3</sub>-induced FEV<sub>1</sub> decrements (Section 6.2.1.3). In contrast, among epidemiologic studies, use of  
5 inhaled CS has shown both protective (Delfino et al., 2002, [093740](#); Mortimer et al., 2000, [013255](#))  
6 and exacerbating (Gent et al., 2003, [052885](#)) effects on respiratory symptoms. Among recent studies,  
7 effect modification on lung function responses also is mixed. In Lewis et al. (2005, [081079](#)),  
8 analyses of interactions between O<sub>3</sub> and CS use indicated stronger associations among CS users than  
9 among CS nonusers (quantitative results not reported for CS nonusers). Among the 11 (12.8%) CS  
10 users, a 30 ppb increase in lag 2 of 8-h max O<sub>3</sub> was associated with an 8.0% decrease (95% CI: -  
11 13.5, -2.1) in lowest daily FEV<sub>1</sub> and a 6.7% increase (95% CI: 0.60, 13.2) in diurnal FEV<sub>1</sub>  
12 variability. Lags 1 and 3-5 avg of 8-h max O<sub>3</sub> were estimated to have less impact as were similar lags  
13 of 24-h avg O<sub>3</sub>. Ozone exposures were estimated to produce larger changes in lung function in two-  
14 pollutant models with PM<sub>10</sub> or PM<sub>2.5</sub>. The authors purported CS use to be a proxy for greater asthma  
15 severity, based on observations that CS users had higher mean FEV<sub>1</sub> variability and lower mean  
16 daily FEV<sub>1</sub>. In contrast to Lewis et al. (2005, [081079](#)), Hernández-Cadena et al. (2009, [594283](#))  
17 observed greater O<sub>3</sub>-related decrements in post-albuterol FEV<sub>1</sub> among the 60 CS nonusers than  
18 among the 25 CS users. In two winter-only studies, consideration of CS use did not largely influence  
19 associations between ambient O<sub>3</sub> and lung function parameters (Liu et al., 2009, [192003](#);  
20 Rabinovitch et al., 2004, [096753](#)).

21 Although studies have varied in populations and season examined, recent evidence suggests  
22 that the inconsistency in effect modification by CS use may, at least in part, be explained by  
23 differences in severity of asthmatics included and definition of CS use. In Hernández-Cadena et al.  
24 (2009, [594283](#)), the group of CS nonusers included both intermittent and persistent asthmatics. In  
25 Lewis et al. (2005, [081079](#)), most moderate to severe asthmatics (91%) were included in the group  
26 of CS users (use for at least 50% of study days). Liu et al. (2009, [192003](#)) did not provide  
27 information on asthma severity; however, they defined CS use more stringently as daily use.  
28 Differences in asthma severity and definition of CS use may explain why both CS use and nonuse  
29 could serve as indicators of severe or uncontrolled asthma. Additionally, investigators did not assess  
30 adherence to reported CS regimen, and misclassification of CS use may bias findings.

31 O<sub>3</sub> is a powerful oxidant, and antioxidant capacity may influence susceptibility to ambient O<sub>3</sub>  
32 exposure (Sections 5.1.2 and 6.2.1.4). Human controlled exposure studies have demonstrated  
33 protective effects of  $\alpha$ -tocopherol (vitamin E) and ascorbate (vitamin C) on O<sub>3</sub>-induced lung function  
34 decrements (Section 6.2.1.4), and epidemiologic studies of asthmatic children conducted in  
35 Mexico City have had similar findings. In an antioxidant supplementation trial, among moderate to  
36 severe asthmatic children, ambient O<sub>3</sub> exposure was associated with a greater decrease in FEV<sub>1</sub> in  
37 the placebo group than in the supplementation group (Romieu et al., 2002, [034711](#)) (Figure 6-7 and  
38 Table 6-7). Romieu et al. (2009, [548788](#)) observed positive interactions between O<sub>3</sub> and diets higher  
39 in fruits and vegetables index (FVI) and Mediterranean pattern index (MDI). The FVI and MDI were

1 each constructed as a 4-level variable to represent increasing consumption of vitamins C and E, and  
2 the MDI additionally represented the intake of omega-3 fatty acids, which also have anti-  
3 inflammatory effects. At lag 0-4 avg O<sub>3</sub> concentrations ≥ 38 ppb, FVI was associated with an  
4 increase in FEV<sub>1</sub> (137 mL per unit increase in FVI [95% CI: 8, 266]). This protective effect of FVI  
5 was diminished at O<sub>3</sub> concentrations ≤ 25 ppb (65 mL increase in FEV<sub>1</sub> per unit increase in FVI  
6 [95% CI: -70, 200]). Similar results were obtained for MDI.

7 Antioxidant capacity also can be characterized by the activity of xenobiotic metabolizing  
8 enzymes. Ambient O<sub>3</sub> exposure has been associated with greater decreases in lung function among  
9 asthmatic GSTM1 null children, especially among those not supplemented with antioxidant vitamins  
10 (Romieu et al., 2004, [056796](#)). Human controlled exposure studies have also indicated greater  
11 susceptibility of GSTM1 null subjects, but primarily in conjunction with the NQO1 wild type  
12 genotype (Section 6.2.1.4). Effect modification by the GSTP1 variant is unclear. Romieu et al.  
13 (2006, [090969](#)) observed that asthmatic children with GSTP1 Ile/Ile or Ile/Val (associated with  
14 greater oxidative metabolism activity) had larger O<sub>3</sub>-associated decreases in FEV<sub>1</sub> (Figure 6-7 and  
15 Table 6-7). Also unexpectedly, O<sub>3</sub> exposure was associated with an increase in FEV<sub>1</sub> among  
16 asthmatics the GSTP1 Val/Val variant, which is associated with reduced antioxidant capacity.

17 Studies of asthmatic children restricted to winter months provided little evidence of an  
18 association between ambient O<sub>3</sub> exposure and changes in lung function as studies reported both  
19 positive and negative associations among various lags of O<sub>3</sub> exposure and lung function parameters  
20 (Dales et al., 2009, [594285](#); Liu et al., 2009, [192003](#); Rabinovitch et al., 2004, [096753](#)). In colder  
21 months when children remain primarily indoors, O<sub>3</sub>, which has low penetration indoors and lack of  
22 indoor sources, may have weaker effects. As noted in previous AQCDs (U.S. EPA, 1996, [017831](#);  
23 U.S. EPA, 2006, [088089](#)) and for endpoints such as respiratory hospital admissions, ED visits, and  
24 mortality, associations with O<sub>3</sub> are generally greater in the warm season.

### **Asthmatic Adults**

25 Relative to studies in asthmatic children, studies of asthmatic adults were limited in number  
26 and did not provide strong evidence of acute changes in lung function in association with ambient O<sub>3</sub>  
27 exposure. Characteristics and ambient O<sub>3</sub> concentration data from these studies are presented in  
28 Table 6-8. One exception was the recent study of 16- to 27-year-old lifeguards in Galveston, TX, that  
29 found larger O<sub>3</sub>-associated decrements in FEV<sub>1</sub>/FVC among the 16 asthmatic lifeguards (-1.6%  
30 [95% CI: -2.8, -0.4] per 40 ppb increase in 1-h max O<sub>3</sub>) than among the 126 nonasthmatic lifeguards  
31 (-0.40% [95% CI: -0.80, 0] per 40 ppb increase in 1-h max O<sub>3</sub>) (Brooks, personal communication,  
32 2010, [644155](#)). In one of the few studies that conducted personal monitoring, neither personal O<sub>3</sub>  
33 exposure nor stationary site O<sub>3</sub> concentrations was associated with PEF in a group of asthmatic  
34 children and adults (Delfino et al., 1997, [084531](#)). Khatri et al. (2009, [594282](#)) aimed to estimate  
35 personal O<sub>3</sub> exposures of 38 asthmatic and 13 healthy nonsmoking adults in Atlanta, GA using  
36 central site measurements plus time-activity data. They found atopy to be a stronger susceptibility  
37 factor than asthma (Khatri et al., 2009, [594282](#)). Investigators reported a larger decrease in percent

1 predicted FEV<sub>1</sub>/FVC per 30 ppb increase in lag 2 of 8-h max O<sub>3</sub> among the 38 atopic (asthmatic or  
 2 healthy) subjects (-12 mL [95% CI: -3, -21]) than among asthmatic subjects (-4.7 mL [95% CI: -11,  
 3 2.3]). Additionally, among asthmatics, O<sub>3</sub> was associated with an increase in FEV<sub>1</sub>. Based on  
 4 correlations observed between decreases in lung function and decreases in quality of life scores,  
 5 investigators inferred the O<sub>3</sub>-associated decreases in lung function to be clinically significant. They  
 6 further suggested that atopy may influence responses to ambient O<sub>3</sub> exposure because during the  
 7 summer, high ambient O<sub>3</sub> concentrations may increase allergenicity of pollens.

8 O<sub>3</sub> was not found to have a strong effect on the lung function of asthmatic adults in panel  
 9 studies conducted in Europe and Asia during low ambient O<sub>3</sub> periods. In a group of 11 subjects in  
 10 Rome, Italy followed for 1 month each in spring and winter, lag 0 O<sub>3</sub> was associated with a decrease  
 11 in percent predicted FEV<sub>1</sub> and FVC; however, associations with lags 0-1 and 0-2 avg O<sub>3</sub> were mostly  
 12 positive (Lagorio et al., 2006, [089800](#)). The authors attributed the lack of negative association for O<sub>3</sub>  
 13 to the stable clinical condition of asthmatics. However, this argument was weakened by observations  
 14 that NO<sub>2</sub> was consistently associated with larger decreases in FEV<sub>1</sub> and FVC. Park et al. (2005,  
 15 [088673](#)) followed asthmatics 16-75 years in age in Incheon, Korea, during a period of dust storms  
 16 when PM<sub>10</sub> concentrations fluctuated widely but O<sub>3</sub> concentrations remained relatively steady.  
 17 Whereas PM<sub>10</sub> was associated with decreases in PEF, O<sub>3</sub> was associated with increases in daily  
 18 average PEF (2.2 L/min [95% CI: -1.0, 5.5] per 30 ppb increase in 8-h max O<sub>3</sub>), suggesting that  
 19 during dust storms, PM<sub>10</sub> effects may dominate, especially because personal O<sub>3</sub> exposures are  
 20 expected to be low as a result of limited outdoor activity.

**Table 6-8. Mean and upper percentile concentrations of ozone in epidemiologic studies examining lung function in asthmatic adults**

Study	Location	Years/Season	Metric	Mean Concentration (ppb)	Middle/Upper Percentile Concentrations (ppb)
Khatri et al. (2009, <a href="#">594282</a> )	Atlanta, GA	2003, 2005, 2006 Warm season	8-h max	59 <sup>a</sup>	Range: 44-73
Thaller et al. (2008, <a href="#">195869</a> )	Galveston, TX	2002-2004 Warm season	1-h max	NR	Median: 35 Range: 19-118
Delfino et al. (1997, <a href="#">084531</a> )	Alpine, CA	1994 Warm season	12-h avg personal (8:00-20:00)	18	90th percentile: 52 Range: 0-80
Lagorio et al. (2006, <a href="#">089800</a> )	Rome, Italy	1999 Spring and winter	24-h avg	Spring: 36.2 <sup>a</sup> Winter: 8.0 <sup>b</sup>	IQR: 8.6 (Spring), 5.1 (Winter) <sup>u</sup> Overall range: 3.4-48.6 <sup>b</sup>
Park et al. (2005, <a href="#">088673</a> )	Incheon, Korea	March-June 2002	24-h avg	Dust event days: 23.6 Control days: 25.1	NR

NR = Not reported

<sup>a</sup>Personal exposure estimates were derived based on time spent in the vicinity of various O<sub>3</sub> monitors.

<sup>b</sup>Concentrations converted from µg/m<sup>3</sup> to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

## Populations Not Restricted To Asthmatics

21 Studies have examined associations between ambient O<sub>3</sub> exposure and lung function  
 22 decrements in the general population and in other potentially populations such as children and older  
 23 adults. Limited data are available in populations restricted to healthy populations. Characteristics and

1 ambient O<sub>3</sub> concentration data from these studies are presented in Table 6-9. The 2006 O<sub>3</sub> AQCD  
 2 identified children as a potentially susceptible group based on consistent evidence of association  
 3 between ambient O<sub>3</sub> exposure and decrements in FEV<sub>1</sub> and PEF (U.S. EPA, 2006, [088089](#))  
 4 (Figure 6-8 and Table 6-10). Whereas most of these studies did not distinguish between effects in  
 5 healthy and asthmatic children, Hoppe et al. (2003, [055618](#)) found larger effects in asthmatic  
 6 children. In contrast, Avol et al. (1998, [086365](#)) found that healthy children, children with asthma,  
 7 and children with wheeze had similar FEV<sub>1</sub> responses to ambient O<sub>3</sub> exposure. A recent study of 56  
 8 healthy children in Vienna, Austria did not find an association between O<sub>3</sub> and decrements in total  
 9 lung capacity; however, this study was restricted to the cold season (Neuberger et al., 2004, [093249](#)).

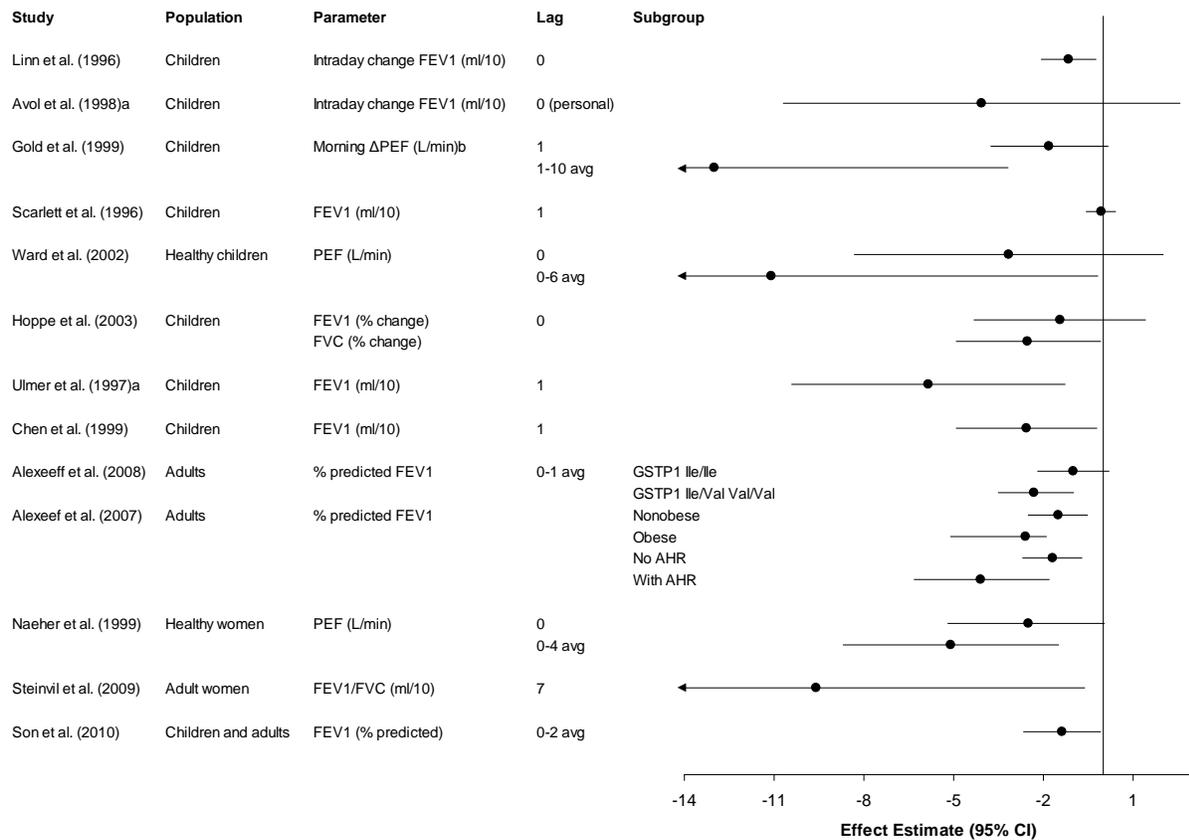
**Table 6-9. Mean and upper percentile concentrations of ozone in epidemiologic studies examining lung function in populations not restricted to asthmatic subjects**

Study	Location	Years/Season	Metric	Mean Concentration (ppb)	Middle/Upper Percentile Concentrations (ppb)
Alexeef et al. (2007, <a href="#">195862</a> ) Alexeef et al. (2008, <a href="#">195864</a> )	Greater Boston, MA	1995-2005 All-year	24-h avg	24.4 <sup>a</sup>	NR
Naeher et al. (1999, <a href="#">033568</a> )	Vinton, VA	1995-1996 Warm season	8-h max	53.7	Range: 17.0-87.6
Avol et al. (1998, <a href="#">086365</a> )	6 southern CA communities	Spring and summer	24-h avg personal	NR	Approximate range: 5-160 <sup>b</sup>
Linn et al. (1996, <a href="#">082508</a> )	Rubidoux, Upland, Torrence, CA	1992-1993, 1993-1994 Fall and spring	24-h avg	34 <sup>a</sup>	Range: 7-86 <sup>a</sup>
Gold et al. (1999, <a href="#">086919</a> )	Mexico City, Mexico	1991 Winter, spring, fall	24-h avg	52.0	IQR: 25 Range: 7.9-103
Scarlett et al. (1996, <a href="#">081158</a> )	Surrey, England	1994 Warm season	8-h max	50.7	Range: 6.8-128
Ward et al. (2002, <a href="#">025839</a> )	Birmingham and Sandwell, England	1997 Winter and summer	24-h avg	Winter median: 13.0 Summer median: 22.0	Winter range: 2-33 Summer range: 10-41
Ulmer et al. (1997, <a href="#">083625</a> )	Freudenstadt and Villingen, Germany	1994 March-October	1/2-h max	Freudenstadt median: 50.6 Villingen median: 32.1	Freudenstadt 5th-95th: 22.5-89.7 Villingen 5th-95th: 0.5-70.1
Hoppe et al. (2003, <a href="#">055618</a> )	Munich, Germany	1992-1995 Warm season	1/2-h max	High days: 65.9 Control days: 27.2	Max (high days): 86 Max (control days): 39
Steinvil et al. (2009, <a href="#">548780</a> )	Tel Aviv, Israel	2002-2007 All-year	8-h avg (10:00 a.m. – 6:00 p.m.)	41.1	IQR: 34.7-48.7 Range: 6.5-72.8
Chen et al. (1999, <a href="#">011149</a> )	3 Taiwan communities	1995-1996 May-January	1-h max	NR	Range: 19.7-110.3
Son et al. (2010, <a href="#">646655</a> )	Ulsan, Korea	2003-2007 All-year	8-h max	35.86	Median: 36.30 Range: 9.80-59.53

NR = Not Reported, IQR = interquartile range.

<sup>a</sup>Measured at sites established by investigators.

<sup>b</sup>Quantitative results not presented. Concentrations estimated from data presented in a figure.



<sup>a</sup>The 95% CI was constructed using a standard error that was estimated from the p-value.

<sup>b</sup> $\Delta$ PEF refers to the daily deviation from the mean PEF across study days.

**Figure 6-8. Changes in lung function parameters in association with ambient ozone exposures in studies not restricted to asthmatic populations. [AHR = airway hyperresponsiveness. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for a 1-h (or 1/2-h) max, 8-h max, and 24-h avg ozone exposures, respectively. All effect estimates are from single pollutant models.**

**Table 6-10. Additional characteristics and quantitative data for studies represented in Figure 6-8**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Parameter	Subgroup	Effect Estimate (95% CI) <sup>a</sup>
Linn et al. (1996, <a href="#">082508</a> )	3 southern CA communities Children	0	1-h avg	Intraday change FEV <sub>1</sub> (mL/10)		-1.16 (-2.06, -0.26)
Avol et al. (1998, <a href="#">086365</a> )	3 southern CA communities Children	0 (personal)	24-h avg	Intraday change FEV <sub>1</sub> (mL/10)		-4.08 (-10.7, 2.6) <sup>b</sup>
Gold et al. (1999, <a href="#">086919</a> )	Mexico City, Mexico Children	1 1-10 avg	24-h avg	Morning ΔPEF (L/min) <sup>c</sup>		-1.80 (-3.76, 0.16) -13.0 (-22.8, -3.2)
Scarlett et al. (1996, <a href="#">081158</a> )	Surrey, England Children	1	8-h max	FEV <sub>1</sub> (mL/10)		-0.08 (-0.57, 0.41)
Ward et al. (2002, <a href="#">025839</a> )	Birmingham and Sandwell, England Healthy children	0 0-6 avg	24-h avg	PEF (L/min)		-3.16 (-8.31, 2.0) -11.1 (-22.0, -0.18)
Hoppe et al. (2003, <a href="#">055618</a> )	Munich, Germany Children	0	1/2-h max	FEV <sub>1</sub> (percent change) FVC (percent change)		-1.4 (-4.3, 1.4) -2.5 (-4.9, -0.1)
Ulmer et al. (1997, <a href="#">083625</a> )	Freudenstadt and Villingen, Germany Children	1	1/2-h max	FEV <sub>1</sub> (mL/10)		-5.9 (-10.4, 1.3) <sup>b</sup>
Chen et al. (1999, <a href="#">011149</a> )	3 Taiwan communities Children	1	1-h max	FEV <sub>1</sub> (mL/10)		-2.56 (-4.91, -0.21)
Alexeef et al. (2008, <a href="#">195864</a> )	Greater Boston, MA Adults	0-1 avg	24-h avg	FEV <sub>1</sub> (% predicted)	GSTP1 Ile/Ile GSTP1 Ile/Val Val/Val	-1.0 (-2.2, 0.19) -2.3 (-3.5, -1.0)
Alexeef et al. (2007, <a href="#">195862</a> )	Greater Boston, MA Adults	0-1 avg	24-h avg	FEV <sub>1</sub> (% predicted)	Nonobese Obese No AHR AHR	-1.5 (-2.5, -0.52) -2.6 (-5.1, -1.9) -1.7 (-2.7, -0.73) -4.1 (-6.3, -1.8)
Naehrer et al. (1999, <a href="#">033568</a> )	Vinton, VA Healthy women	0 0-4 avg	8-h max	PEF (L/min)		-2.5 (-5.2, 0.04) -5.1 (-8.7, -1.5)
Steinvil et al. (2009, <a href="#">548780</a> )	Tel Aviv, Israel Healthy adults	7	8-h avg (10:00-18:00)	FEV <sub>1</sub> /FVC (mL/10)		-9.6 (-19.6, -0.64)
Son et al. (2010, <a href="#">646655</a> )	Ulsan, Korea Children and adults	0-2 avg	8-h max	FEV <sub>1</sub> (% predicted)		-1.36 (-2.65, -0.08)

AHR = airway hyperresponsiveness.

<sup>a</sup>Effect estimates are standardized to a 40, 30, and 20 ppb increase for 1-h (or 1/2-h) max, 8-h max, and 24-h avg O<sub>3</sub>, respectively.

<sup>b</sup>The 95% CI was constructed using a standard error that was estimated from the p-value.

<sup>c</sup>ΔPEF refers to the daily deviation from the mean PEF across study days.

1 A cross-sectional study was conducted of 2,102 children and adults living near a  
2 petrochemical plant in Ulsan, Korea (Son et al., 2010, [646655](#)). The mean percent predicted FEV<sub>1</sub>  
3 was 82.85%, indicating a large proportion of subjects with diminished lung function. Multiple O<sub>3</sub>  
4 exposure metrics, including concentrations averaged across 13 city monitors, concentrations from  
5 the nearest monitor, inverse distance-weighted concentrations, and estimates from kriging, were  
6 associated with decrements in lung function. Among single-day lags (0-2) and 2- (lag 0-1 or 1-2) and  
7 3-day (lag 0-2) avg of 8-h max O<sub>3</sub> exposure (kriged), lag 0-2 avg was associated with the largest  
8 decrements in percent predicted FEV<sub>1</sub> (-1.36 [95% CI: -2.65, -0.08] per 30 ppb increase in 8-h max  
9 O<sub>3</sub>) and FVC (-16.8 [95% CI: -20.0, -13.6]). Ozone effect estimates showed small changes in  
10 magnitude in two-pollutant models with PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, or CO. An important limitation of this  
11 study was the lack of adjustment for meteorological factors.

12 Robust findings from human controlled exposure studies demonstrate O<sub>3</sub>-induced spirometric  
13 responses in children and young adults but diminished responses in older adults (Section 6.2.1.4).  
14 While epidemiologic investigation of adults has been limited, studies find associations in healthy  
15 adults and older adults. Naehrer et al. (1999, [033568](#)) observed associations between ambient O<sub>3</sub>  
16 exposure and decreases in PEF among healthy women, ages 19-43 years. In a large cross-sectional

1 study of 2,380 healthy adults in Tel Aviv, Israel, lag 7 of 8-h avg (10:00 a.m. to 6:00 p.m.) O<sub>3</sub> was  
2 associated with a decrease in FEV<sub>1</sub>/FVC (-96 mL [95% CI: -196, -6.4] per 30 ppb increase in O<sub>3</sub>);  
3 however, overall, the study provided weak evidence for an effect of O<sub>3</sub>, as associations of other lags  
4 of exposure (single day lags 0-7 and 0-6 avg) with FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC were positive  
5 (Steinvil et al., 2009, [548780](#)). Whereas Hoppe et al. (2003, [055618](#)) did not find ambient O<sub>3</sub>  
6 exposure-associated decreases in lung function among elderly subjects, findings from the Normative  
7 Aging Study demonstrated that ambient O<sub>3</sub> exposure was associated with decrements in FEV<sub>1</sub> and  
8 FVC among 900 mostly white, healthy men (mean [SD] age = 68.9 [7.2] years) from the Greater  
9 Boston, MA area (Alexeeff et al., 2008, [195864](#)). This study in the Greater Boston area conducted  
10 spirometry once every 3 years for 10 years in, a large proportion of whom were middle-aged or  
11 elderly. Among all subjects, a 20 ppb increase in lag 0-1 avg of 24-h avg O<sub>3</sub> was associated with a  
12 1.7% decrease (95% CI: -2.6, -0.72) in FEV<sub>1</sub>, which was the largest decrement observed among all  
13 lags of O<sub>3</sub> exposure (1- to 7-day avg) examined (Alexeeff et al., 2008, [195864](#)). Additionally,  
14 consistent with findings from human controlled exposure studies (Section 6.2.1.4), larger effects  
15 were estimated in specific groups, namely, obese adults, adults with AHR, and adults with the  
16 GSTP1 Ile/Val or Val/Val variant (Alexeeff et al., 2007, [195862](#); Alexeeff et al., 2008, [195864](#))  
17 (Figure 6-8 and Table 6-10). Larger O<sub>3</sub>-related decrements in FEV<sub>1</sub> and FVC were also observed in  
18 subjects with long GT dinucleotide repeats in the promoter region of the antioxidant enzyme heme  
19 oxygenase-1 (Alexeeff et al., 2008, [195864](#)), which has been associated with reduced inducibility  
20 (Hiltermann et al., 1998, [086158](#)). The largest O<sub>3</sub>-related percent decreases in lung function were  
21 observed in the group of obese subjects with AHR (-5.3% FEV<sub>1</sub> [95% CI: -8.3, -2.4] per 20 ppb  
22 increase in lag 0-1 avg of 24-h avg O<sub>3</sub>).

### **Lag Structure in Ambient Ozone Exposure-associated Lung Function Decrements**

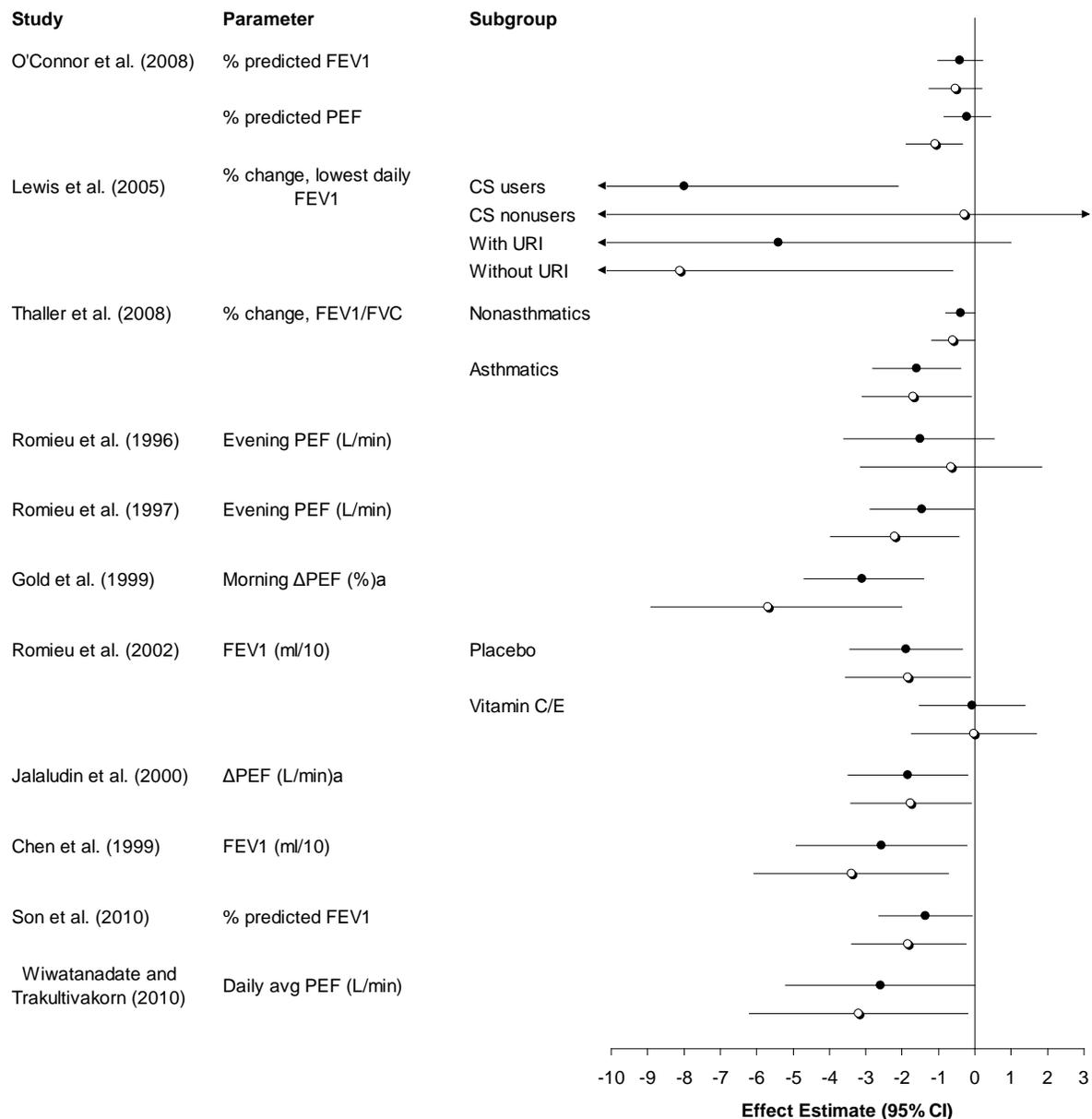
23 Controlled human exposure studies demonstrate decreases in lung function within 2 hours to 2  
24 days of O<sub>3</sub> exposure, depending on the exposure regimen, with an attenuation of effect after 3-5 days  
25 after a daily exposure regimen. Consistent with these findings, studies of subjects engaged in  
26 outdoor recreation, exercise, or work indicate decreases in lung function in association with O<sub>3</sub>  
27 exposures over the duration of activity. Among the few studies of subjects with increased outdoor  
28 exposures that examined other lags of O<sub>3</sub> exposure, some found no persistence of effects (Hoppe et  
29 al., 2003, [055618](#); Spektor et al., 1991, [042383](#)), whereas others found that the effects of O<sub>3</sub>  
30 exposure carried over to the next day (Brauer et al., 1996, [080754](#); Spektor et al., 1988, [041710](#)).

31 Collectively, epidemiologic studies in other populations have examined associations with  
32 single-day O<sub>3</sub> concentrations lagged from 0 to 7 days as well concentrations averaged over  
33 2-10 days. Some studies have found decreases in lung function associated with same-day or  
34 previous-day O<sub>3</sub> exposures (Alexeeff et al., 2008, [195864](#); Chen et al., 1999, [011149](#); Jalaludin et al.,  
35 2000, [011929](#); Lewis et al., 2005, [081079](#); Romieu et al., 1996, [080748](#); Romieu et al., 1997,  
36 [085807](#); Ross et al., 2002, [042749](#); Son et al., 2010, [646655](#)). Relatively fewer epidemiologic studies

1 have found associations with longer lags of ambient O<sub>3</sub> exposures (5-7 days) (Hernández-Cadena et  
2 al., 2009, [594283](#); Steinvil et al., 2009, [548780](#); Wiwatanadate and Trakultivakorn, 2010, [387706](#)).  
3 Additionally, in many studies, multiday averages of O<sub>3</sub> exposure (2-10 days) were associated  
4 with decreases in lung function (Alexeeff et al., 2007, [195862](#); Barraza-Villarreal et al., 2008,  
5 [156254](#); Gold et al., 1999, [086919](#); Liu et al., 2009, [192003](#); Mortimer et al., 2002, [030281](#); Naeher  
6 et al., 1999, [033568](#); O'Connor et al., 2008, [156818](#); Son et al., 2010, [646655](#); Ward et al., 2002,  
7 [025839](#)), indicating that exposures accumulated over several days may be important or may be  
8 subject to less measurement error. Collectively, among studies that examined a range of single-day  
9 lags and multiday averages, evidence did not overwhelmingly point to stronger immediate, delayed,  
10 or cumulative effects of O<sub>3</sub> exposure on lung function. Some studies indicated stronger effects of  
11 multiday O<sub>3</sub> exposures (Gold et al., 1999, [086919](#); Mortimer et al., 2002, [030281](#); Naeher et al.,  
12 1999, [033568](#); Ward et al., 2002, [025839](#)), whereas many others did not find a consistent trend  
13 (Alexeeff et al., 2008, [195864](#); Lagorio et al., 2006, [089800](#); Lewis et al., 2005, [081079](#); Liu et al.,  
14 2009, [192003](#); Son et al., 2010, [646655](#); Steinvil et al., 2009, [548780](#); Wiwatanadate and  
15 Trakultivakorn, 2010, [387706](#)).

### **Summary of Epidemiologic Studies of Lung Function**

16 The cumulative body of epidemiologic evidence strongly supports associations between  
17 ambient O<sub>3</sub> exposure and decrements in lung function among children, in particular, those with  
18 asthma and those with increased outdoor exposures. Consistent with findings from human controlled  
19 exposure studies, epidemiologic evidence demonstrates ambient O<sub>3</sub>-associated decrements in lung  
20 function in adults exercising or working outdoors. Although recent epidemiologic studies contributed  
21 mixed results, most studies of asthmatic children indicated negative associations between O<sub>3</sub>  
22 exposure and decrements in lung function (Figures 6-6 and 6-7 and Tables 6-6 and 6-7). Whereas  
23 previous evidence was weak, new evidence indicates that O<sub>3</sub> exposure may be associated with  
24 decrements in lung function in older adults. Effect modification by any individual susceptibility  
25 factor was examined only in one to two studies; however, O<sub>3</sub>-associated lung function decrements  
26 were increased with obesity, reduced activity of antioxidant enzymes, AHR, or concurrent URI. High  
27 dietary antioxidant intake was found to decrease susceptibility to O<sub>3</sub>-associated decreases in lung  
28 function. A small proportion of studies of lung function have evaluated confounding by  
29 co-pollutants; however, in studies that provided quantitative (Figure 6-9 and Table 6-11) or graphical  
30 results (Dales et al., 2009, [594285](#); Liu et al., 2009, [192003](#)) of co-pollutant modeling, most O<sub>3</sub>  
31 effect estimates did not change considerably in magnitude when adjusted for PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, or  
32 SO<sub>2</sub>. Ambient O<sub>3</sub> exposures accumulated over several days are associated with decreases in lung  
33 function; however, in epidemiologic studies, there is uncertainty around the relative effects of  
34 immediate, delayed, or cumulative O<sub>3</sub> exposures.



<sup>a</sup>ΔPEF refers to the daily deviation from the mean PEF across study days.

**Figure 6-9. Comparison of ozone-lung function effect estimates in single- and co-pollutant models.** CS = corticosteroid, URI = Upper respiratory infection. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg ozone, respectively. Effect estimates depicted as black circles are from single pollutant models, and effect estimates depicted as open circles are from co-pollutant models.

**Table 6-11. Additional characteristics and quantitative data for studies presented in Figure 6-9**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Parameter	Subgroup	O <sub>3</sub> Effect Estimate in Single-pollutant Model (95% CI) <sup>a</sup>	O <sub>3</sub> Effect Estimate in Co-pollutant Model (95% CI) <sup>a</sup>
O'Connor et al. (2008, <a href="#">156818</a> )	7 U.S. communities Asthmatic children	1-5 avg	24-h avg	% predicted FEV <sub>1</sub>		-0.41 (-1.03, 0.21)	-0.54 (-1.27, 0.19) with PM <sub>2.5</sub> , NO <sub>2</sub>
Lewis et al. (2005, <a href="#">081079</a> )	Detroit, MI Asthmatic children	2	8-h max	percent change, lowest daily FEV <sub>1</sub>	CS user With URI	-8.0 (-13.5, -2.1) -5.4 (-11.3, 1.0)	-0.3 (-16.0, 18.0) with PM <sub>2.5</sub> -8.1 (-15.0, -0.60)
Thaller et al. (2008, <a href="#">195869</a> )	Galveston, TX Outdoor workers	0	1-h max	percent change, FEV <sub>1</sub> /FVC	Nonasthmatic Asthmatic	-0.4 (-0.8, 0) -1.6 (-2.8, -0.4)	-0.6 (-1.2, 0) with PM <sub>2.5</sub> , NO <sub>2</sub> -1.7 (-3.1, -0.1)
Romieu et al. (1996, <a href="#">080748</a> )	Mexico City, Mexico Asthmatic children	0	1-h max	Evening PEF (L/min)		-1.50 (-3.60, 0.53)	-0.66 (-3.16, 1.85) with PM <sub>2.5</sub>
Romieu et al. (1997, <a href="#">085807</a> )	Mexico City, Mexico Asthmatic children	0	1-h max	Evening PEF (L/min)		-1.45 (-2.88, -0.02)	-2.20 (-3.96, -0.44) with PM <sub>10</sub>
Gold et al. (1999, <a href="#">086919</a> )	Mexico City, Mexico Children	1-10 avg	24-h avg	Morning ΔPEF (%) <sup>b</sup>		-3.1 (-4.7, -1.4)	-5.7 (-8.9, -2.0) with PM <sub>2.5</sub>
Romieu et al. (2002, <a href="#">034711</a> )	Mexico City, Mexico Asthmatic children	1	1-h max	FEV <sub>1</sub> (mL/10)	Placebo Vitamin C/E	1.88 (-3.43, -0.34) -0.07 (-1.52, 1.37)	-1.84 (-3.55, -0.13) with PM <sub>10</sub> , NO <sub>2</sub> -0.02 (-1.73, 1.69)
Jalaudin et al. (2000, <a href="#">011929</a> )	Sydney, Australia Children with wheeze	0	24-h avg	ΔPEF <sup>b</sup>		-1.84 (-3.48, -0.19)	-1.76 (-3.42, -0.11) with PM <sub>10</sub> , NO <sub>2</sub>
Chen et al. (1999, <a href="#">011149</a> )	3 Taiwan communities	1	1-h max	FEV <sub>1</sub> (mL/10)		-2.56 (-4.91, -0.21)	-3.40 (-6.07, -0.73) with NO <sub>2</sub>
Son et al. (2010, <a href="#">646655</a> )	Incheon, Korea Children and adults	0-2 avg	8-h max	% predicted FEV <sub>1</sub>		-1.36 (-2.65, -0.08)	-1.83 (-3.4, -0.25) with PM <sub>10</sub>
Wiwatanadate and Trakultivakom (2010, <a href="#">387706</a> )	Chiang Mai, Thailand Asthmatic children	5	24-h avg	Daily avg PEF (L/min)		-2.6 (-5.2, 0)	-3.2 (-6.2, -0.2) with SO <sub>2</sub>

<sup>a</sup>Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O<sub>3</sub>, respectively.

<sup>b</sup>ΔPEF refers to the daily deviation from the mean PEF across sampling days.

<sup>c</sup>Effect estimate is based on a multi-pollutant model of the joint effects of an increase in O<sub>3</sub> and PM<sub>2.5</sub>.

### 6.2.1.3. Toxicology

1           The 2006 O<sub>3</sub> AQCD found that pulmonary function decrements occur in a number of species  
2 with acute exposures (≤ 1 week), ranging from 0.25 to 0.4 ppm O<sub>3</sub> (U.S. EPA, 2006, [088089](#)).  
3 Information published more recently adds to the evidence of ventilation defects induced by acute or  
4 subchronic exposure. Rats exposed to 0.5 ppm O<sub>3</sub> for 2 or 6 days, either continuously or  
5 alternately, were analyzed by magnetic resonance imaging (MRI). Although the lung capacity of  
6 the animals was unaffected by O<sub>3</sub> exposure, ventilation defects were evident, based on delayed and  
7 incomplete or heterogeneous lung filling. This effect increased with the duration of exposure, and  
8 was more prevalent and severe in animals exposed alternately (12 h/day) as opposed to  
9 continuously (22 h/day). Among rats exposed over six days for 12 h/day, 85% exhibited ventilation

1 defects. The authors suggest that the delayed filling of lung lobes or segments is likely a result of an  
2 increase in airway resistance brought about by narrowing of the peripheral small airways  
3 (Crémillieux et al., 2008, [180454](#)). Lung resistance and elastance were unaffected in allergen  
4 sensitized mice exposed solely to 0.5 ppm O<sub>3</sub> once a week for 4 weeks (Farraj et al., 2010, [380846](#)).  
5 However, co-exposure to O<sub>3</sub> and diesel exhaust particles increased lung resistance. Long-term  
6 exposure to O<sub>3</sub> during development may ultimately affect pulmonary function by altering lung  
7 morphology (see Chapter 7).

## 6.2.2. Airway Hyperresponsiveness

8 Airway hyperresponsiveness refers to a condition in which the conducting airways undergo  
9 enhanced bronchoconstriction in response to a variety of stimuli. Airway responsiveness is typically  
10 quantified by measuring changes in pulmonary function (e.g., FEV<sub>1</sub> or specific airway resistance)  
11 following the inhalation of an aerosolized specific (allergen) or nonspecific (e.g., methacholine)  
12 bronchoconstricting agent or another stimulus such as exercise or cold air. Asthmatics are generally  
13 more sensitive to bronchoconstricting agents than nonasthmatics, and the use of an airway challenge  
14 to inhaled bronchoconstricting agents is a diagnostic test in asthma. Standards for airway  
15 responsiveness testing have been developed for the clinical laboratory (American Thoracic Society.,  
16 2000, [090799](#)), although variation in methodology for administering the bronchoconstricting agent  
17 may affect the results (Cockcroft et al., 2005, [090805](#)). There is a wide range of airway  
18 responsiveness in nonasthmatic people, and responsiveness is influenced by wide range of factors,  
19 including cigarette smoke, pollutants, respiratory infections, occupational exposures, and respiratory  
20 irritants. Since the 2006 O<sub>3</sub> AQCD, no epidemiology studies have examined airway responsiveness  
21 as a biological endpoint.

### 6.2.2.1. Controlled Human Exposures

22 Beyond its direct effect on lung function, O<sub>3</sub> exposure causes an increase in airway  
23 responsiveness in human subjects as indicated by a reduction in the concentration of methacholine  
24 required to produce a given reduction in FEV<sub>1</sub> or increase in sRaw. Increased airway responsiveness  
25 is an important consequence of exposure to ambient O<sub>3</sub>, because the airways are then predisposed to  
26 narrowing upon inhalation of a variety of ambient stimuli including specific allergens, SO<sub>2</sub>, and cold  
27 air.

28 O<sub>3</sub> exposure of asthmatic subjects, who characteristically have increased airway  
29 responsiveness at baseline, can cause further increases in responsiveness (Kreit et al., 1989, [041817](#)).  
30 Similar relative changes in airway responsiveness are seen in asthmatics and health controls exposed  
31 to O<sub>3</sub> despite their markedly different baseline airway responsiveness. Several studies (Jorres et al.,  
32 1996, [078122](#); Kehrl et al., 1999, [022101](#); Molfino et al., 1991, [042379](#)) have been published  
33 suggesting an increase in specific (i.e., allergen-induced) airway reactivity. An important aspect of

1 increased airway responsiveness after O<sub>3</sub> exposure is that this may represent a plausible link between  
2 ambient O<sub>3</sub> exposure and increased hospital admissions for asthma.

3 Changes in airway responsiveness after O<sub>3</sub> exposure appear to resolve more slowly than  
4 changes in FEV<sub>1</sub> or respiratory symptoms (Folinsbee and Hazucha, 2000, [001701](#)). Furthermore, in  
5 studies of repeated exposure to O<sub>3</sub>, changes in airway responsiveness tend to be somewhat less  
6 susceptible to attenuation with consecutive exposures than changes in FEV<sub>1</sub> (Dimeo et al., 1981,  
7 [039662](#); Folinsbee et al., 1994, [044189](#); Gong et al., 1997, [082696](#); Kulle et al., 1982, [040668](#)).  
8 Increases in airway responsiveness do not appear to be strongly associated with decrements in lung  
9 function or increases in symptoms (Aris et al., 1995, [075945](#)).

10 Since the 2006 O<sub>3</sub> AQCD, no controlled human exposure studies have been conducted to  
11 examine the mechanistic aspects of O<sub>3</sub>-induced airway hyperresponsiveness. The mechanism of  
12 O<sub>3</sub>-induced increases in airway responsiveness is poorly understood, but it appears to be associated  
13 with a number of cellular and biochemical changes in airway tissue. Although inflammation could  
14 play a role in the increase in airway responsiveness, cyclooxygenase inhibitors have not been  
15 effective at blocking the O<sub>3</sub>-induced influx of PMNs into BALF (Hazucha et al., 1996, [043923](#); Ying  
16 et al., 1990, [042334](#)). Therefore, O<sub>3</sub>-induced airway responsiveness may not be due to the presence  
17 of PMNs in the airway or to the release of arachidonic acid metabolites. Rather, it seems likely that  
18 the mechanism for this response is multifactorial as discussed in detail below.

#### 6.2.2.2. Toxicology

19 In addition to studies with human subjects, a number of species, including nonhuman  
20 primates, dogs, cats, rabbits, and rodents, have been used to examine the effect of O<sub>3</sub> exposure on  
21 airway hyperresponsiveness. With a few exceptions, commonly used animal models have been  
22 guinea pigs, rats, or mice acutely exposed to high O<sub>3</sub> concentrations (1-3 ppm) to induce airway  
23 hyperresponsiveness. These high dose models are helpful for determining underlying mechanisms of  
24 general airway hyperresponsiveness, but have questionable relevance for extrapolation to potential  
25 airway responses in humans exposed to ambient levels of O<sub>3</sub>.

26 A limited number of studies have observed airway hyperresponsiveness in rodents and guinea  
27 pigs after exposure to less than 0.3 ppm O<sub>3</sub>. As previously reported in the 2006 O<sub>3</sub> AQCD, one study  
28 demonstrated that a very low concentration of O<sub>3</sub> (0.05 ppm) induced airway hyperresponsiveness in  
29 certain strains of rats suggesting a genetic component (Depuydt et al., 1999, [011995](#)). More recently,  
30 Chhabra and colleagues (2010, [677665](#)) demonstrated that exposure of OVA-sensitized guinea pigs  
31 to 0.12 ppm for 2 h/d for 4 weeks produced specific airway hyperresponsiveness to an inhaled OVA  
32 challenge. Interestingly, dietary supplementation of the guinea pigs with vitamins C and E  
33 ameliorated a portion of the airway hyperresponsiveness as well as indices of inflammation and  
34 oxidative stress in this study. Larsen and colleagues did an O<sub>3</sub> concentration-response study in mice  
35 sensitized by 10 daily inhalation treatments with an OVA aerosol (Larsen et al., 2010, [628560](#)).  
36 Although airway responsiveness to methacholine was increased in non-sensitized animals exposed to  
37 a single 3-h exposure to 0.5, but not 0.1 or 0.25, ppm O<sub>3</sub>, airway hyperresponsiveness was observed

1 after exposure to 0.1 and 0.25 ppm O<sub>3</sub> in OVA-sensitized mice. Shore and colleagues (Johnston et  
2 al., 2005, [596394](#)) have also demonstrated O<sub>3</sub>-induced airway hyperresponsiveness in mice after  
3 exposure to 0.3 ppm O<sub>3</sub> for 3 hours. Adaptation to this effect was observed in mice that were  
4 exposed to the same concentration of O<sub>3</sub> for 72 hours and showed no evidence of airway  
5 hyperresponsiveness. Thus, recent toxicological studies have demonstrated that O<sub>3</sub>-induced airway  
6 hyperresponsiveness occurs in monkeys, guinea pigs, and mice after either acute or repeated  
7 exposure to relevant concentrations of O<sub>3</sub>.

8 The mechanisms by which O<sub>3</sub> enhances the airway responsiveness to either specific (e.g.,  
9 OVA) or non-specific (e.g., methacholine) bronchoprovocation are not clear and appear to be  
10 associated with complex cellular and biochemical changes in the conducting airways. Considerable  
11 research effort has been directed towards exploring the causes of O<sub>3</sub>-induced airway  
12 hyperresponsiveness, but the majority of such studies have been conducted at high concentrations of  
13 O<sub>3</sub>. It is clear that inflammation plays a key role in O<sub>3</sub>-induced airway hyperresponsiveness, although  
14 the precise mediators and cells that are involved have not been identified at relevant concentrations  
15 of O<sub>3</sub>. Because inflammation is likely to play a role in O<sub>3</sub>-induced airway hyperresponsiveness, the  
16 mechanism for this response may be multifactorial, involving the presence of cytokines, prostanoids,  
17 or neuropeptides; activation of macrophages, eosinophils, or mast cells; and epithelial damage that  
18 increases direct access of mediators to the smooth muscle or receptors in the airways that are  
19 responsible for reflex bronchoconstriction. Johnston et al. (2005, [596394](#)) demonstrated that airway  
20 hyperresponsiveness occurred in both wild type and IL-6 knockout mice exposed to 0.3 ppm O<sub>3</sub>  
21 despite reduction in markers of lung injury and inflammation in O<sub>3</sub>-exposed IL-6 knockout mice.  
22 This same group of investigators has demonstrated the involvement of natural killer T cells, obesity,  
23 CXCR2, leptin, and IL-17 in O<sub>3</sub>-induced airway hyperresponsiveness albeit at exposure  
24 concentrations of 1-2 ppm O<sub>3</sub> (Garantziotis et al., 2010, [624947](#); Johnston et al., 2005, [596393](#); Lu et  
25 al., 2006, [597955](#); Pichavant et al., 2008, [596409](#); Shore et al., 2003, [057302](#); Voynow et al., 2009,  
26 [194311](#); Williams et al., 2007, [597545](#)) have been proposed for airway hyperresponsiveness induced  
27 by single exposures to O<sub>3</sub> at 1-3 ppm. Thus, a number of potential mediators and cells may play a  
28 role in O<sub>3</sub>-induced airway hyperresponsiveness, but mechanistic studies are needed at more relevant  
29 concentrations of O<sub>3</sub>.

30 In order to evaluate the ability of O<sub>3</sub> to enhance specific and non-specific airway  
31 responsiveness, it is important to understand the role of adaptation in ozone's effects. Several studies  
32 have clearly demonstrated that some adverse effects caused by acute exposure are absent after  
33 repeated exposures to O<sub>3</sub>. The ability of the pulmonary system to adapt to repeated insults to O<sub>3</sub> is  
34 complex, however, and experimental findings for adaptation to O<sub>3</sub>-induced airway  
35 hyperresponsiveness are inconsistent. As described above, airway hyperresponsiveness was observed  
36 in mice after a 3-h exposure but not in mice exposed continuously for 72 hours to 0.3 ppm (Johnston  
37 et al., 2005, [596394](#)). However, the Chhabra study demonstrated O<sub>3</sub>-induced airway  
38 hyperresponsiveness in guinea pigs exposed for 2 h/day for 10 days (Chhabra et al., 2010, [677665](#)).  
39 Besides the obvious species disparity, these studies differ in that the mice were exposed continuously

1 for 72 hours, whereas the guinea pigs were exposed intermittently over 10 days, suggesting that  
2 adaptation might be lost with periods of rest in between O<sub>3</sub> exposures. This type of reasoning is the  
3 basis for the episodic exposure protocol used in the infant rhesus monkey studies (Plopper et al.,  
4 2007, [596412](#)).

### 6.2.3. Pulmonary Inflammation, Injury and Oxidative Stress

#### 6.2.3.1. Controlled Human Exposures

5 In addition to physiological pulmonary responses, respiratory symptoms, and airway  
6 hyperresponsiveness, O<sub>3</sub> exposure has been shown to result in epithelial permeability and respiratory  
7 tract inflammation. As reported in studies reviewed in the 1996 and 2006 O<sub>3</sub> AQCDs (U.S. EPA,  
8 1996, [017831](#); U.S. EPA, 2006, [088089](#)), acute O<sub>3</sub> exposure initiates an acute inflammatory response  
9 throughout the respiratory tract which may persist for at least 18-24 hours postexposure. A meta-  
10 analysis of 21 studies (Mudway and Kelly, 2004, [057299](#)) showed that PMN influx in healthy  
11 subjects is significantly associated (statistically) with total O<sub>3</sub> dose (i.e., the product of O<sub>3</sub>  
12 concentration, exposure duration, and V<sub>E</sub>).

13 The presence of neutrophils (PMNs) in the lung has long been accepted as a hallmark of  
14 inflammation and is an important indicator that O<sub>3</sub> causes inflammation in the lungs. Neutrophilic  
15 inflammation of tissues indicates activation of the innate immune system and requires a complex  
16 series of events which are normally followed by processes that clear the evidence of acute  
17 inflammation. Inflammatory effects have been assessed in vivo by lavage (proximal airway and  
18 bronchoalveolar), bronchial biopsy, and more recently, induced sputum. A single acute exposure  
19 (1-4 hours) of humans to moderate concentrations of O<sub>3</sub> (0.2-0.6 ppm) while exercising at moderate  
20 to heavy levels results in a number of cellular and biochemical changes in the lung, including an  
21 inflammatory response characterized by increased numbers of PMNs, increased permeability of the  
22 epithelial lining of the respiratory tract, cell damage, and production of proinflammatory cytokines  
23 and prostaglandins (U.S. EPA, 2006, [088089](#)). These changes also occur in humans exposed to 80  
24 and 100 ppb O<sub>3</sub> for 6-8 hours (Alexis et al., 2010, [628538](#); Devlin et al., 1991, [040359](#); Peden et al.,  
25 1997, [085842](#)). Soluble mediators of inflammation such as the cytokines (e.g., IL-6, IL-8) and  
26 arachidonic acid metabolites (e.g., prostaglandin [PG]E<sub>2</sub>, PGF<sub>2α</sub>, thromboxane, and leukotrienes  
27 [LTs] such as LTB<sub>4</sub>) have been measured in the BALF of humans exposed to O<sub>3</sub>. In addition to their  
28 role in inflammation, many of these compounds have bronchoconstrictive properties and may be  
29 involved in increased airway responsiveness following O<sub>3</sub> exposure. The possible relationship  
30 between repetitive bouts of acute inflammation in humans caused by O<sub>3</sub> and the development of  
31 chronic respiratory disease is unknown.

32 Studies reviewed in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) reported that inflammatory  
33 responses do not appear to be correlated with lung function responses in either asthmatic or healthy  
34 subjects (Balmes et al., 1996, [080830](#); Balmes et al., 1997, [086092](#); Devlin et al., 1991, [040359](#);

1 Holz et al., 1999, [058731](#)). However, Vagaggini et al. (2010, [387127](#)) recently reported a significant  
2 ( $r=0.61$ ,  $p=0.015$ ) correlation between changes in FEV<sub>1</sub> and changes in sputum neutrophils in mild-  
3 to-moderate asthmatics ( $n=23$ ;  $33 \pm 11$  years) exposed to 300 ppb O<sub>3</sub> for 2 hours with moderate  
4 exercise. Significant inflammatory responses to O<sub>3</sub> exposures that did not elicit significant  
5 spirometric responses have also been observed (Holz et al., 2005, [077170](#); McBride et al., 1994,  
6 [043912](#)).

7 The time course of the inflammatory response to O<sub>3</sub> in humans has not been fully  
8 characterized. Different markers exhibit peak responses at different times. Studies in which lavages  
9 were performed 1 hour after O<sub>3</sub> exposure (1 hour at 0.4 ppm or 4 hours at 0.2 ppm) have  
10 demonstrated that the inflammatory responses are quickly initiated (Devlin et al., 1996, [042840](#);  
11 Schelegle et al., 1991, [042491](#); Torres et al., 1997, [084265](#)). Inflammatory mediators and cytokines  
12 such as IL-8, IL-6, and PGE<sub>2</sub> are greater at 1 hours than at 18 hours post-O<sub>3</sub> exposure (Devlin et al.,  
13 1996, [042840](#); Torres et al., 1997, [084265](#)). However, IL-8 still remain elevated at 18 hours post-O<sub>3</sub>  
14 (4 hours at 0.2 ppm O<sub>3</sub> versus FA) in healthy subjects (Balmes et al., 1996, [080830](#)). Schelegle et al.  
15 (1991, [042491](#)) found increased PMNs in the “proximal airway” lavage at 1, 6, and 24 hours after O<sub>3</sub>  
16 exposure (4 hours at 0.2 ppm O<sub>3</sub>), with a peak response at 6 hours. Although, at 18-24 hours after O<sub>3</sub>  
17 exposure, PMNs remain elevated relative to 1 hour postexposure (Schelegle et al., 1991, [042491](#);  
18 Torres et al., 1997, [084265](#)).

19 Alexis et al. (2010, [628538](#)) recently reported that a 6.6-h exposure with moderate exercise to  
20 80 ppb O<sub>3</sub> caused an increased sputum neutrophil levels at 18 hours postexposure in young healthy  
21 adults ( $n=15$ ;  $24 \pm 1$  years). In a prior study, Alexis et al. (2009, [628542](#)) found genotype effects on  
22 inflammatory responses but not lung function responses to a 2 h-exposure to 400 ppb O<sub>3</sub>. At 4 hours  
23 post O<sub>3</sub> exposure, both GSTM1 genotypes had significant increases in sputum neutrophils with a  
24 tendency for a greater increase in GSTM1-sufficient than null individuals. At 24 hours postexposure,  
25 neutrophils had returned to baseline levels in the GSTM1-sufficient individuals. In the GSTM1-null  
26 subjects, however, neutrophil levels increased further from 4 hours to 24 hours and were  
27 significantly greater than both baseline levels and 24-h levels in GSTM1-sufficient individuals.  
28 Alexis et al. (2009, [628542](#)) found that GSTM1-sufficient individuals ( $n=19$ ;  $24 \pm 3$  years) had a  
29 decrease in macrophage levels at 4-24 hours postexposure to 400 ppb O<sub>3</sub> for 2 hours with exercise.  
30 Effects of the exposure apart from O<sub>3</sub> can not be ruled out in the Alexis et al. (2009, [628542](#); 2010,  
31 [628538](#)) studies, however, since no FA exposure was conducted.

32 Kim et al. (In Press, [674869](#)) has more recently shown a significant ( $p < 0.001$ ) increase in  
33 sputum neutrophil levels following a 6.6-h exposure to 60 ppb O<sub>3</sub> relative to FA in young healthy  
34 adults (13 F, 11 M;  $25.0 \pm 0.5$  years). There was no significant effect of GSTM1 genotype (half  
35 GSTM1-null) on the inflammatory responses observed in these individuals. Previously,  
36 inflammatory responses had only been evaluated down to a level of 80 ppb.

37 Inflammatory responses to O<sub>3</sub> exposure have also been studied in asthmatic subjects (Basha et  
38 al., 1994, [075950](#); Peden et al., 1997, [085842](#); Scannell et al., 1996, [080755](#)). In these studies,  
39 asthmatics showed significantly more neutrophils in the BALF (18 hours postexposure) than did

1 similarly exposed healthy individuals. In one of these studies (Peden et al., 1997, [085842](#)), which  
2 included only allergic asthmatics who tested positive for *Dematophagoides farinae* antigen, there  
3 was an eosinophilic inflammation (twofold increase), as well as neutrophilic inflammation (threefold  
4 increase). In a study of subjects with intermittent asthma exposed to 0.4 ppm O<sub>3</sub> for 2 hours,  
5 increases in eosinophil cationic protein, neutrophil elastase and IL-8 were found to be significantly  
6 increased 16 hours postexposure and comparable in induced sputum and BALF (Hiltermann et al.,  
7 1999, [013196](#)). Scannell et al. (1996, [080755](#)) also reported that IL-8 tends to be higher in the BALF  
8 of asthmatics compared to nonasthmatics following O<sub>3</sub> exposure, suggesting a possible mediator for  
9 the significantly increased neutrophilic inflammation in those subjects. Bosson et al. (2003, [051687](#))  
10 found significantly greater epithelial expression of IL-5, IL-8, granulocyte-macrophage colony-  
11 stimulating factor (GM-CSF) and epithelial cell-derived neutrophil-activating peptide 78 (ENA-78)  
12 in asthmatics compared to healthy subjects following exposure to 0.2 ppm O<sub>3</sub> for 2 hours. In  
13 contrast, Stenfors et al. (2002, [030473](#)) did not detect a difference in the O<sub>3</sub>-induced increases in  
14 neutrophil numbers between 15 mild asthmatic and 15 healthy subjects by bronchial wash at the 6  
15 hours postexposure time point. However, the asthmatics were on average 5 years older than the  
16 healthy subjects in this study, and it is not yet known how age affects inflammatory responses. It is  
17 also possible that the time course of neutrophil influx differs between healthy and asthmatic  
18 individuals.

19 Vagaggini et al. (2002, [035191](#)) investigated the effect of prior allergen challenge on responses  
20 in mild asthmatics exposed for 2 hours to 0.27 ppm O<sub>3</sub> or filtered air. At 6 hours postexposure,  
21 eosinophil numbers in induced sputum were found to be significantly greater after O<sub>3</sub> than after air  
22 exposures. Studies such as this suggest that the time course of eosinophil and neutrophil influx  
23 following O<sub>3</sub> exposure can occur at levels detectable within the airway lumen by as early as 6 hours.  
24 They also suggest that the previous or concurrent activation of proinflammatory pathways within the  
25 airway epithelium may enhance the inflammatory effects of O<sub>3</sub>. For example, in an in vitro study of  
26 primary human nasal epithelial cells and BEAS-2B cell line, cytokine production induced by  
27 rhinovirus infection was enhanced synergistically by concurrent exposure to O<sub>3</sub> at 0.2 ppm for 3  
28 hours (Spannhake et al., 2002, [030637](#)).

29 Markers from BALF following both 2 hours (Devlin et al., 1997, [083577](#)) and 4 hours  
30 (Christian et al., 1998, [029925](#); Jorres et al., 2000, [005654](#)) repeated O<sub>3</sub> exposures (up to 5 days)  
31 indicate that there is ongoing cellular damage irrespective of the attenuation of some cellular  
32 inflammatory responses of the airways, pulmonary function, and symptom responses. Devlin et al.  
33 (1997, [083577](#)) found that several indicators of inflammation (e.g., PMN, IL-6, PGE<sub>2</sub>, fibronectin)  
34 were attenuated after 5 days of exposure (i.e., values were not different from FA). However, other  
35 markers (LDH, IL-8, total protein, epithelial cells) did not show attenuation, suggesting that tissue  
36 damage probably continues to occur during repeated exposure. Christian et al. (1998, [029925](#))  
37 showed decreased numbers of neutrophils and a decrease in IL-6 levels in healthy adults after 4 days  
38 of exposure versus the single exposure to 0.2 ppm O<sub>3</sub> for 4 hours. Jörres et al. (2000, [005654](#)) also  
39 found both functional and BALF cellular responses to O<sub>3</sub> were abolished at 24 hours postexposure

1 following the fourth exposure day. However, levels of total protein, IL-6, IL-8, reduced glutathione  
2 and ortho-tyrosine were still increased significantly. In addition, visual scores (bronchoscopy) for  
3 bronchitis and erythema and the numbers of neutrophils in bronchial mucosal biopsies were  
4 increased. Results indicate that, despite an attention of some markers of inflammation in BALF and  
5 pulmonary function decrements, inflammation within the airways persists following repeated  
6 exposure to O<sub>3</sub>. The continued presence of cellular injury markers indicates a persistent effect that  
7 may not necessarily be recognized due to the attenuation of spirometric and symptom responses.

8 A number of studies show that O<sub>3</sub> exposures increases epithelial cell permeability through  
9 direct (technetium-99m labeled diethylene triamine pentaacetic acid, <sup>99m</sup>Tc-DTPA, clearance) and  
10 indirect (e.g., increased BALF albumin, protein) techniques. Kehrl et al. (1987, [040824](#)) showed  
11 increased <sup>99m</sup>Tc-DTPA clearance in healthy young adults at 75 minutes postexposure to 0.4 ppm O<sub>3</sub>  
12 for 2 hours. Foster and Stetkiewicz (1996, [079920](#)) have shown that increased <sup>99m</sup>Tc-DTPA clearance  
13 persists for at least 18-20 hours post-O<sub>3</sub> exposure (130 minutes to average O<sub>3</sub> concentration of  
14 0.24 ppm), and the effect is greater at the lung apices than at the base. Increased BALF protein,  
15 suggesting O<sub>3</sub>-induced changes in epithelial permeability, have also been reported at 1 hour and  
16 18 hours postexposure (Balmes et al., 1996, [080830](#); Devlin et al., 1997, [083577](#)). Meta-analysis of  
17 results from 21 publications (Mudway and Kelly, 2004, [057299](#)), showed that increased BALF  
18 protein is associated with total inhaled O<sub>3</sub> dose (i.e., the product of O<sub>3</sub> concentration, exposure  
19 duration, and V<sub>E</sub>). Changes in permeability associated with acute inflammation may provide  
20 increased access of inhaled antigens, particles, and other inhaled substances deposited on lung  
21 surfaces to the smooth muscle, interstitial cells, and the blood.

### 6.2.3.2. Epidemiology

22 In the 2006 O<sub>3</sub> AQCD, epidemiologic evidence of O<sub>3</sub>-associated changes in biological markers  
23 of airway inflammation was limited to observations of increases in upper airway nasal lavage levels  
24 of inflammatory cell counts, eosinophilic cationic protein, and myeloperoxidases (U.S. EPA, 2006,  
25 [088089](#)). As a consequence of advances in less invasive methods to collect biological samples  
26 repeatedly from subjects in the field, the number of recent studies assessing ambient O<sub>3</sub>-related  
27 changes in lower airway inflammation and oxidative stress has increased dramatically. Although  
28 most biomarkers were not specific to the lung, most studies collected exhaled breath, exhaled breath  
29 condensate (EBC), nasal lavage fluid, or induced sputum with the aim of monitoring inflammatory  
30 responses in airways, as opposed to monitoring systemic responses in blood. These recent studies  
31 form a larger base to establish coherence with findings from human experimental and animal  
32 toxicological studies that have measured similar endpoints and provide further biological plausibility  
33 for associations of ambient O<sub>3</sub> with respiratory symptoms and lung function. These endpoints also  
34 allow assessment of potential O<sub>3</sub>-related acute respiratory morbidity in populations that are less  
35 likely to experience increases in respiratory symptoms, including healthy populations and groups  
36 with increased outdoor exposures.

1           Despite the strengths of biomarker studies, several limitations are recognized that may limit  
2 the interpretations of associations between ambient O<sub>3</sub> exposure and changes in biomarker levels.  
3 For example, the clinical relevance of the observed magnitudes of changes has not been well  
4 characterized (Duramad et al., 2007, [625792](#); Murugan et al., 2009, [625839](#)). The inadequate  
5 understanding of the changes in biomarker levels in relation to other endpoints of respiratory  
6 morbidity may provide an explanation for the mixed results observed in studies that evaluate  
7 multiple biomarkers in addition to lung function or respiratory symptoms. The lack of standardized  
8 methodology for collection, low sensitivity and specificity of many assay methods, and poor  
9 characterization of subject factors that contribute to inter-individual variability, including asthma  
10 severity and recent medication use, are sources of uncertainty that may contribute to the  
11 inconsistency of findings among studies.

12           In recent studies, the biomarker most frequently measured was exhaled nitric oxide (eNO),  
13 likely related to its ease of collection in the field and automated measurement. NO acts as a signaling  
14 molecule in numerous biological processes; however, studies pointed to observations of inducible  
15 nitric oxide synthase activation and NO production by proinflammatory cytokines, macrophages,  
16 neutrophils, and epithelial cells in the lung (Barnes and Liew, 1995, [083814](#)) to support analysis of  
17 eNO as an indicator of airway inflammation. Further support is provided by observations of higher  
18 eNO in asthmatics, especially in those with poorly controlled asthma (Jones et al., 2001, [625816](#);  
19 Kharitonov and Barnes, 2000, [625817](#)). Other biological media analyzed included EBC, induced  
20 sputum, and nasal lavage fluid, all of which are hypothesized to contain aerosolized particles and/or  
21 cells from fluid lining the lower and upper airways (Balbi et al., 2007, [625784](#); Howarth et al., 2005,  
22 [625805](#); Hunt, 2002, [625808](#)). These fluids contain cytokines, cells, and markers of oxidative stress  
23 that mediate inflammatory responses underlying asthma pathogenesis and exacerbation. Ozone has  
24 been demonstrated to increase formation of reactive oxygen species (ROS) and oxidation products in  
25 airways (Section 5.1.2) ((Frampton et al., 1999, [040757](#); Mudway and Kelly, 2000, [010452](#)), and  
26 oxidative stress has been linked to asthma by regulating expression of cytokines and activity of  
27 inflammatory cells in airways (Heidenfelder et al., 2009, [190026](#)). Recent studies examined  
28 8-isoprostane, which is a prostaglandin F<sub>2a</sub>-like compound produced by ROS via the nonenzymatic  
29 peroxidation of arachidonic acid in membrane phospholipids (Morrow et al., 1990, [625835](#)). EBC  
30 8-isoprostane levels are consistently higher in asthmatics than in nonasthmatics and increase upon  
31 asthma exacerbation (Baraldi et al., 2003, [625802](#)). Studies also measured thiobarbituric acid  
32 reactive substances (TBARS) to represent oxidative stress. TBARS are derived from oxidative  
33 degradation of lipids and sugars (Janero, 1990, [625809](#)).

34           Table 6-12 presents the characteristics and ambient O<sub>3</sub> concentration data from recent studies  
35 assessing associations between O<sub>3</sub> exposure and biological markers of airway inflammation and  
36 oxidative stress. Many recent studies reported positive associations between short-term ambient O<sub>3</sub>  
37 exposure and increases in airway inflammation and oxidative stress, in particular, studies of  
38 asthmatic children in Mexico City (Figures 6-10 and 6-11 and Tables 6-13 and 6-14). Further, diet  
39 and antioxidant intake were identified as potential susceptibility factors.

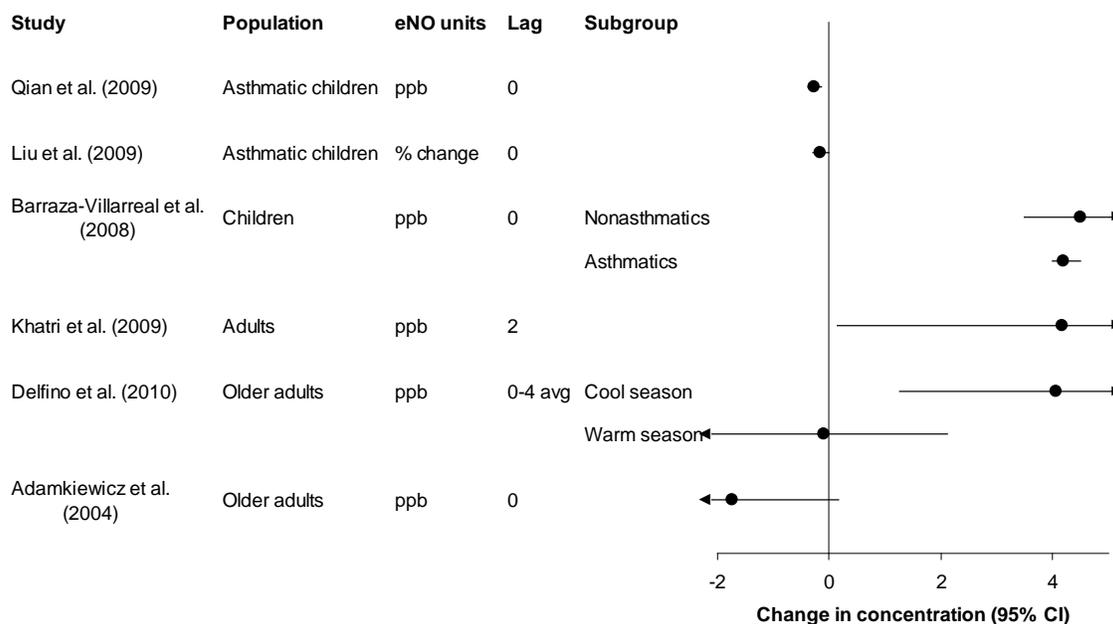
**Table 6-12. Mean and upper percentile ozone concentrations in studies examining biological markers of airway inflammation and oxidative stress**

Study	Location	Years	Metrics	Mean Concentration (ppb)	Middle/Upper Percentile Concentrations (ppb)
Qian et al. (2009, <a href="#">548793</a> )	6 U.S. communities (SOCS)	1997-1999 All-year	8-h max	33.6	1.6-91.5
Khatri et al. (2009, <a href="#">594282</a> )	Atlanta, GA	2003, 2005, 2006 Warm season	8-h max	59 <sup>a</sup>	Range: 44-73
Ferdinands et al. (2008, <a href="#">156433</a> )	Atlanta, GA	2004 Warm season	1-h max	71	Median: 61 IQR: 54-67
Adamkiewicz et al. (2007, <a href="#">187925</a> )	Steubenville, OH	2000 Cold season	24-h avg 1-h max	15.3 19.8	Maximum: 32.2 Maximum: 61.6
Delfino et al. (2010, <a href="#">647222</a> )	Los Angeles, CA	2005-2007 All-year	24-h avg	Warm season: 33.3 Cool season: 20.6	Range: 8.04-76.4 (warm season), 6.17-44.9 (cool season)
Liu et al. (2009, <a href="#">192003</a> )	Windsor, ON, Canada	2005 Cold season	24-h avg 1-h max	14.1 27.2	Median: 13.0; IQR: 8.8-17.8 Median: 27.0; IQR: 21.8-32.8
Sienra-Monge et al. (2004, <a href="#">196422</a> )	Mexico City, Mexico	1999-2000 All-year	8-h max	66.2	Range: 11.1-142.5
Barraza-Villarreal et al. (2008, <a href="#">156254</a> )	Mexico City, Mexico	2003-2005 All-year	8-h max 1-h max	31.6 86.5	IQR: 22.0 (8-h); Range: 4.9-86.3 IQR: 48.0; Range: NR
Romieu et al. (2008, <a href="#">179908</a> )	Mexico City, Mexico	2004 All-year	8-h max	31.1	Median: 31.4 Range: 9.8-60.7
Chimenti et al. (2009, <a href="#">418828</a> )	Sicily, Italy	NR All-year	8-h avg (07:00-15:00)	Fall: 32.7 (week), 35.1 (race) <sup>o</sup> Winter: 37.0 (week), 30.8 (race) <sup>b</sup> Summer: 51.2 (week), 46.1 (race) <sup>b</sup>	NR
Rodriguez et al. (2007, <a href="#">092842</a> )	Perth, Australia	1996-2001 All-year	24-h avg 1-h max	28 33	Range: 9-74 Range: 12-95

IQR = interquartile range , NR = Not Reported.

<sup>a</sup>Personal exposure estimates were derived based on time spent in the vicinity of various O<sub>3</sub> monitors.

<sup>b</sup>Concentrations converted from µg/m<sup>3</sup> to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).



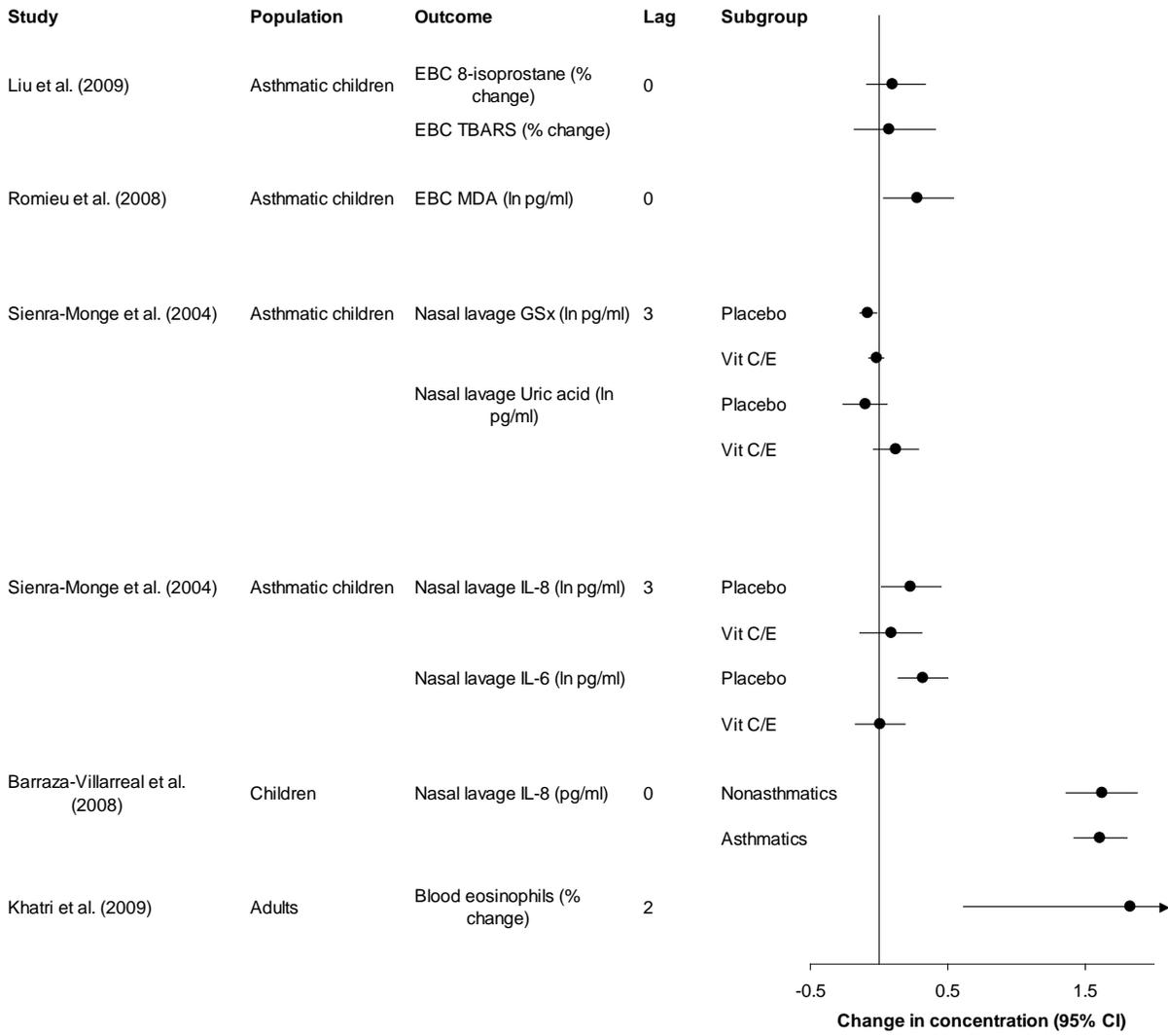
**Figure 6-10. Associations of ambient ozone exposure with changes in concentrations of exhaled nitric oxide (eNO).**

All results are from single-pollutant models. Effect estimates were standardized to a 30- or 20-ppb increase for 8-h max or 24-h avg ozone, respectively.

**Table 6-13. Additional characteristics and quantitative data for studies presented in Figure 6-10**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	eNO Units	Subgroup	Effect Estimate (95% CI) <sup>a</sup>
Qian et al. (2009, <a href="#">548793</a> )	6 U.S. communities Asthmatic children	0	8-h max	ppb		-0.27 (-0.39, -0.15)
Liu et al. (2009, <a href="#">192003</a> )	Windsor, ON, Canada Asthmatic children	0	24-h avg	percent change		-0.17 (-0.30, -0.01)
Barraza-Villarreal et al. (2008, <a href="#">156254</a> )	Mexico City, Mexico Asthmatic children	0	8-h max	ppb	Nonasthmatics	4.5 (3.5, 5.9)
					Asthmatics	4.2 (4.0, 4.5)
Khatri et al. (2009, <a href="#">594282</a> )	Atlanta, GA	2	8-h max	ppb		4.17 (0.14, 8.2)
Delfino et al. (2010, <a href="#">647222</a> )	Los Angeles, CA	0-4 avg	24-h avg	ppb	Cool season	4.06 (1.25, 6.87)
					Warm season	-0.10 (-2.31, 2.11)
Adamkiewicz et al. (2007, <a href="#">187925</a> )	Steubenville, Ohio	0	24-h avg	ppb		-1.74 (-3.64, 0.17)

<sup>a</sup>Effect estimates were standardized to a 30- or 20-ppb increase for 8-h max or 24-h avg O<sub>3</sub>, respectively.



**Figure 6-11. Associations of ambient ozone exposure with biological markers of airway oxidative stress and airway inflammation. EBC = exhaled breath condensate, TBARS = thiobarbituric acid reactive substances, MDA = malondialdehyde, GSx = glutathione, IL-8 = interleukin 8, IL-6 = interleukin 6, Vit C/E = group supplemented with vitamins C and E. Effect estimates were standardized to a 30- or 20-ppb increase for 8-h max or 24-h avg ozone, respectively.**

**Table 6-14. Additional characteristics and quantitative data for studies presented in Figure 6-11**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Outcome	Subgroup	Effect estimate (95% CI) <sup>a</sup>
Liu et al. (2009, <a href="#">192003</a> )	Windsor, ON, Canada Asthmatic children	0	24-h avg	EBC 8-isoprostane (percent change) EBC TBARS (percent change)		0.10 (-0.09, 0.34) 0.07 (-0.18, 0.41)
Romieu et al. (2008, <a href="#">179908</a> )	Mexico City, Mexico Asthmatic children	0	8-h max	EBC MDA (ln pg/mL)		0.28 (0.03, 0.54)
Sierra-Monge et al. (2004, <a href="#">196422</a> )	Mexico City, Mexico Asthmatic children	3	8-h max	Nasal lavage GSx (ln pg/mL)		
				Nasal lavage Uric acid (ln pg/mL)	Placebo	-0.08 (-0.14, -0.02)
					Vit C/E	-0.02 (-0.07, 0.03)
					Placebo	-0.10 (-0.26, 0.06)
					Vit C/E	0.12 (-0.04, 0.29)
Nasal lavage IL-8 (ln pg/mL)	Placebo	0.23 (0.02, 0.45)				
	Vit C/E	0.09 (-0.14, 0.31)				
	Placebo	0.32 (0.14, 0.50)				
	Vit C/E	0.01 (-0.17, 0.19)				
Barraza-Villarreal et al. (2008, <a href="#">156254</a> )	Mexico City, Mexico Children	0	8-h max	Nasal lavage IL-8 (pg/mL)	Nonasthmatics Asthmatics	1.62 (1.36, 1.88) 1.61 (1.42, 1.80)
Khatri et al. (2009, <a href="#">594282</a> )	Atlanta, GA Adults	2	8-h max	Blood eosinophils (percent change)		1.83 (0.62, 4.28)

EBC = exhaled breath condensate, TBARS = thiobarbituric acid reactive substances, MDA = malondialdehyde, GSx = glutathione, IL-8 = interleukin 8, IL-6 = interleukin 6, Vit C/E = group supplemented with vitamins C and E.

<sup>a</sup>Effect estimates were standardized to a 30- or 20-ppb increase for 8-h max or 24-h avg O<sub>3</sub>, respectively.

## Asthmatic Subjects

1 Among asthmatics, evidence of association between O<sub>3</sub> and eNO was inconsistent, with  
2 studies reporting positive and negative associations. In the multicity (Boston, MA; New York, NY;  
3 Denver, CO; Philadelphia, PA; San Francisco, CA; and Madison, WI) salmeterol (β-2 adrenergic  
4 agonist) trial of 119 persistent asthmatics, 12-65 years of age, increases in O<sub>3</sub> exposure were  
5 associated with statistically significant decreases in eNO (Qian et al., 2009, [548793](#)) eNO was  
6 measured every 2-4 weeks over a 16-week period between February 1997 and January 1999 and  
7 related to 8-h max O<sub>3</sub> exposures (single-day lags 0 to 4 days and 0-4 day avg). Among all subjects,  
8 increases in lag 0 and 0-4 avg O<sub>3</sub> were associated with the largest decreases in eNO (-0.27 ppb [95%  
9 CI: -0.39, -0.15] per 30 ppb increase in lag 0 of 8-h max O<sub>3</sub>). Subgroup analyses did not reveal  
10 strong heterogeneity in response among salmeterol, CS, or placebo groups. Associations of NO<sub>2</sub> and  
11 PM<sub>10</sub> with eNO were positive and statistically significant in all three treatment groups, suggesting  
12 that the counterintuitive findings for O<sub>3</sub> were not simply due to the reduction of inflammatory  
13 responses by medication use. The authors suggested that at higher O<sub>3</sub> exposures, O<sub>3</sub> may rapidly  
14 react with NO in airways to form reactive nitrogen species such as peroxyxynitrite. In the cross-  
15 sectional study of adults in Atlanta, GA, Khatri et al. (2009, [594282](#)) observed that a 30-ppb increase  
16 in lag 1 of 8-h max O<sub>3</sub> was associated with a 4.17-ppb increase in eNO (95% CI: 0.14, 8.2) among  
17 asthmatics. Consistent with eNO results, O<sub>3</sub> was also positively associated with blood eosinophils,  
18 which are believed to be the main effector cells that initiate and sustain inflammation in asthma and

1 allergy (Schmekel et al., 2001, [625849](#)). In one of the few studies to compare effects between  
2 asthmatics and nonasthmatics, Barraza-Villarreal et al. (2008, [156254](#)) found that O<sub>3</sub> may increase  
3 eNO in both asthmatic and healthy children. Among asthmatics, a 30-ppb increase in lag 0 of 8-h  
4 max O<sub>3</sub> was associated with a 1.45-ppb increase (95% CI: 1.39, 1.50) in eNO, and the association  
5 remained statistically significant in a co-pollutant model with PM<sub>2.5</sub>. A slightly larger effect was  
6 estimated for nonasthmatics.

7 Similar to other studies restricted to winter months, Liu et al. (2009, [192003](#)) (described in  
8 Section 6.2.1.2) reported a negative association between O<sub>3</sub> and eNO. Results for EBC levels of  
9 TBARS and 8-isoprostane also did not provide strong evidence of O<sub>3</sub> effects on airway oxidative  
10 stress. SO<sub>2</sub>, NO<sub>2</sub>, and PM<sub>2.5</sub> had larger, positive estimated effects on all three biomarkers, suggesting  
11 that in the winter when O<sub>3</sub> concentrations are low, other more dominant pollutants may have stronger  
12 effects on respiratory health endpoints.

13 Several studies of asthmatic children in Mexico City demonstrated associations between acute  
14 changes in ambient O<sub>3</sub> and changes in an array of proinflammatory and oxidative stress mediators  
15 (Barraza-Villarreal et al., 2008, [156254](#); Romieu et al., 2008, [179908](#); Romieu et al., 2009, [548788](#);  
16 Sienna-Monge et al., 2004, [196422](#)). By also examining differences in responses by antioxidant  
17 intake, these studies, as a whole, provided strong evidence that inhaled O<sub>3</sub> may be an important  
18 source of ROS in airways and/or may increase airway inflammation via oxidative stress-mediated  
19 mechanisms. All of these studies measured nasal lavage levels of the cytokine IL-8. Although IL-8 is  
20 not believed to be a key mediator of the asthmatic response, higher IL-8 levels have been described  
21 in asthmatics. Further, observations of increased IL-8 expression as a consequence of increased  
22 expression of other proinflammatory cytokines by secondary reaction products suggest that IL-8 may  
23 be a nonspecific downstream indicator of systemic oxidative stress and inflammation (Section 5.1.2).  
24 Other markers analyzed in these studies included eNO, TBARS, EBC pH, and IL-6, which have  
25 shown stronger relationships with asthma and airway inflammation. For example, EBC pH, which  
26 reflects the proton-buffering capacity of ammonium in airways, is consistently lower in asthmatics,  
27 decreases upon acute asthma exacerbation, and is negatively correlated with airway levels of  
28 proinflammatory cytokines (Carpagnano et al., 2005, [625789](#); Hunt et al., 2000, [002173](#); Kostikas et  
29 al., 2002, [625821](#)).

30 Romieu et al. (2008, [179908](#)) analyzed malondialdehyde (MDA, a TBARS) in EBC samples  
31 collected biweekly between January and October 2004. A 30-ppb increase in lag 0 of 8-h max O<sub>3</sub>  
32 was associated with a 0.29 nmol (95% CI: 0.03, 0.54) increase in log-transformed MDA. Similar  
33 results were reported for lag 1 and 2-day cumulative exposure, and associations were robust to the  
34 addition of PM<sub>2.5</sub> into models. Approximately 25% of EBC samples had nondetectable levels of  
35 MDA, and the random assignment of concentrations between 0 and 4.1 nmol may have contributed  
36 random measurement error to the estimated O<sub>3</sub> effects. Because MDA represents less than 1% of  
37 lipid peroxides and is present at low concentrations, its reliability as a marker of oxidative stress in  
38 vivo has been questioned. However, the authors pointed to their observations of statistically  
39 significant associations of EBC MDA levels with FEV<sub>1</sub>, FVC, and nasal lavage IL-8 levels to

1 support its analysis as a biologically-relevant indicator of airway inflammation. They also used  
2 recent observations of increases in exhaled MDA during acute asthma exacerbation in children  
3 (Corradi et al., 2003, [625790](#)) to assert that their findings were evidence for O<sub>3</sub>-associated increased  
4 respiratory morbidity.

5 As with eNO, Barraza-Villarreal et al. (2008, [156254](#)) observed that O<sub>3</sub> was associated with  
6 similar changes in nasal lavage IL-8 and EBC pH among asthmatic and nonasthmatic children.  
7 Among asthmatics, a 30-ppb increase in lag 0 of 8-h max O<sub>3</sub> was associated with a 1.61 pg/mL  
8 increase (95% CI: 1.42, 1.80) in IL-8, and a 0.10-unit decrease (95% CI: -0.18, -0.01) in EBC pH,  
9 and results remained statistically significant in co-pollutant models with PM<sub>2.5</sub>. In the same cohort of  
10 asthmatic and nonasthmatic children, a diet high in FVI was found to protect against O<sub>3</sub>-related  
11 increases in nasal lavage IL-8 (Romieu et al., 2009, [548788](#)). At high ambient O<sub>3</sub> levels (≥ 38 ppb, 8-  
12 h max), a 1-unit increase in FVI was associated with a 0.219 decrease (95% CI: -0.38, -0.05) in the  
13 natural log of IL-8, suggesting that a diet rich in antioxidants may protect against O<sub>3</sub>-stimulated  
14 nasal inflammation by scavenging ROS. The protective effect was diminished by about 49% at O<sub>3</sub>  
15 levels of 25 ppb or lower.

16 That high levels of antioxidants may protect against O<sub>3</sub>-associated airway inflammation was  
17 also observed by Sienna-Monge et al. (2004, [196422](#)). For 12 weeks, 59 asthmatics received a daily  
18 vitamin C and E supplement, and 58 received a placebo. At baseline, 6 weeks, and 12 weeks,  
19 investigators measured nasal lavage levels of IL-6, IL-8, uric acid, and total glutathione. While the  
20 roles of these markers in the inflammatory cascade of asthma are not well characterized, they have  
21 been shown to be induced by experimental O<sub>3</sub> exposure (Jorres et al., 2000, [005654](#); Mudway et al.,  
22 1999, [001270](#)). IL-6 is involved in recruitment of inflammatory cells to sites of tissue damage. Uric  
23 acid and glutathione are ROS scavengers that are present in the RTLF and are observed to be  
24 consumed in the initial phase of antioxidant defense against inhaled O<sub>3</sub> (Section 5.1.2). Consistent  
25 with findings from human clinical and animal studies (Section 5.1.2), the results in the placebo  
26 group from Sienna-Monge et al. (2004, [196422](#)) indicate that ambient O<sub>3</sub> exposure may initiate an  
27 antioxidant response, as indicated by decreases in nasal lavage levels of uric acid and glutathione  
28 (Figure 6-11 and Table 6-14). However, despite decreases in the levels of endogenous antioxidants,  
29 O<sub>3</sub> was positively associated with increases in the inflammatory cytokines, IL-6 and IL-8 (Figure 6-  
30 11 and Table 6-14). Results in the vitamin C/E supplementation group indicated that augmenting the  
31 circulating levels of antioxidants may confer some protection against O<sub>3</sub>-associated inflammation in  
32 nasal passages. Per a 30-ppb increase in 3-day 8-h max O<sub>3</sub>, a smaller increase in IL-6 was observed  
33 in the vitamin C/E group (0.03 ln pg/mL [95% CI: -0.28, 0.33]) than in the placebo group (0.43 ln  
34 pg/mL [95% CI: 0.16, 0.71]). These observations were supported by other findings in the same  
35 cohort that O<sub>3</sub>-associated increases in respiratory symptoms were higher in subjects with reduced  
36 activity in oxidative metabolism genes (Romieu et al., 2006, [090969](#)) (Section 6.2.3.1). In Sienna-  
37 Monge et al. (2004, [196422](#)), O<sub>3</sub> was associated with increases in uric acid in the placebo group  
38 across O<sub>3</sub> lags but decreases in glutathione in both the placebo and supplementation group.  
39 Therefore, the results do not clearly delineate the interactions among inhaled O<sub>3</sub>, endogenous

1 antioxidants, and dietary supplementations of antioxidants. It is also unclear what may be the  
2 optimal levels of vitamins C and E to confer protection against O<sub>3</sub>-associated respiratory effects.  
3 Whereas this study found that supplementation of vitamin-deficient subjects to increase vitamin C  
4 and E levels to five times above the recommended daily allowance may confer protection, the results  
5 from Romieu et al. (2009, [548788](#)) suggested that antioxidant intake from usual diets may be  
6 sufficient.

### **Populations not Restricted to Asthmatic Subjects**

7 Although limited in number and sample sizes, consistent with the collective body of evidence,  
8 recent studies of subjects engaged in outdoor activities mostly supported a positive association  
9 between O<sub>3</sub> exposure and airway inflammation. The exception was a well-designed panel study in  
10 which 16 adolescent long-distance runners in Atlanta, GA, were followed before and after exercise  
11 for 10 days in August 2004 (Ferdinands et al., 2008, [156433](#)). Effect estimates for lags 0, 1, and 2 of  
12 1-h max O<sub>3</sub> with EBC pH were positive, indicating O<sub>3</sub>-associated decreases in airway inflammation.  
13 In a cross-sectional study of children at camps in south Belgium, although O<sub>3</sub> was not associated  
14 with lung function, an association was found for eNO. Children at camps with 1-h max O<sub>3</sub>  
15 concentrations above 85.2 ppb had greater increases in intraday eNO compared with children at  
16 camps with O<sub>3</sub> concentrations below 51 ppb. A benchmark dose analysis indicated that the threshold  
17 for an O<sub>3</sub>-induced increase of 4.3 ppb eNO (indicating increased airway inflammation) was 68.6 ppb  
18 for the 1-h max and 56.3 ppb for the 8-hr max O<sub>3</sub>. Among 9 adult male runners in Sicily, Italy  
19 examined 3 days before and 20 hours after 3 races in fall, winter, and summer, weekly average O<sub>3</sub>  
20 concentrations (8-h avg, 7:00-15:00) were positively correlated with apoptosis of airway cells  
21 (Spearman's  $r = 0.76$ ,  $p < 0.0005$ ) and bronchial epithelial cell differential counts (Spearman's  $r =$   
22  $0.467$ ,  $p < 0.05$ ) but not with neutrophil or macrophage cell counts or levels of the proinflammatory  
23 cytokines TNF- $\alpha$  and IL-8 (Chimenti et al., 2009, [418828](#)). These limited data from Chimenti et al.  
24 (2009, [418828](#)) suggested that O<sub>3</sub> exposure during exercise may increase airway epithelial injury and  
25 activate anti-inflammatory mechanisms such as apoptosis; however, studies with a larger number of  
26 subjects and repeated measures are needed to strengthen the evidence.

27 Panel studies examining O<sub>3</sub>-associated changes in eNO in elderly subjects produced  
28 contrasting findings. Both studies were similar in that outdoor O<sub>3</sub> was monitored by investigators in  
29 the vicinity of subjects' residences and cool season-specific results were presented. However, several  
30 differences were noteworthy, including geographic location, inclusion of healthy subjects, and  
31 examination of multiday average exposures. Delfino et al. (2010, [647222](#)) followed 60 elderly  
32 subjects with coronary artery disease in the Los Angeles, CA area for two 6-week periods, one in the  
33 warm season and one in the cool season, although the exact months were not specified. Multiday  
34 averages of O<sub>3</sub> (3- to 9-day) were associated with statistically significant increases in eNO, with  
35 effect estimates increasing with increasing number of averaging days. Additionally, in contrast to  
36 most other studies, a strong positive effect was estimated for the cooler season (4.06 ppb [95% CI:  
37 1.25, 6.87]) per 20-ppb increase in 5-day avg O<sub>3</sub>), whereas no association was observed for the warm

1 season (-0.01 ppb [95% CI: -2.31, 2.11]). Despite the unusual findings, they were similar to findings  
2 from another study of Los Angeles area adult asthmatics conducted between October and November,  
3 in which O<sub>3</sub> was associated with a decrease in indoor activity (Eiswerth et al., 2005, [196443](#)).  
4 Adamkiewicz et al. (2004, [087925](#)) did not find a positive association and eNO in a mixed group of  
5 older adults (ages 54-91 years) comprising healthy subjects and those with asthma or COPD. The  
6 study was conducted in Steubenville, OH between September and December, and as was observed in  
7 most other studies conducted during colder months, O<sub>3</sub> (concurrent 1 hour and 24 hours preceding  
8 eNO collection) was associated with decreases (statistically nonsignificant) in eNO. Associations  
9 with other O<sub>3</sub> exposure lags were not examined. The authors attributed the negative associations to  
10 weak, but negative correlations of O<sub>3</sub> with NO and PM<sub>2.5</sub>, which were associated with small,  
11 statistically significant increases in eNO.

### **Summary of Epidemiologic Studies of Pulmonary Inflammation and Oxidative Stress**

12 Many recent studies reported positive associations between short-term ambient O<sub>3</sub> exposure  
13 and increases in airway inflammation and oxidative stress, in particular, studies of asthmatic children  
14 in Mexico City. Further, diets high in antioxidant vitamin content and antioxidant vitamin  
15 supplementation were identified as factors that may protect against O<sub>3</sub>-associated increases in airway  
16 inflammation. Limited evidence suggested that ambient O<sub>3</sub> exposure may increase airway  
17 inflammation in subjects with increased outdoor exposures and older adults. In the few studies that  
18 evaluated co-pollutant models, O<sub>3</sub> effect estimates showed small changes in magnitude but little  
19 change in statistical significance (Barraza-Villarreal et al., 2008, [156254](#); Liu et al., 2009, [192003](#);  
20 Romieu et al., 2008, [179908](#)).

21 Several recent studies simultaneously assessed associations of O<sub>3</sub> with lung function and  
22 biological markers of airway inflammation. In most cases, the results differed among endpoints, and  
23 whether evaluated at the same or different lags of O<sub>3</sub> exposure, associations were generally stronger  
24 for biological markers of airway inflammation than for lung function (Barraza-Villarreal et al., 2008,  
25 [156254](#); Escamilla-Nuñez et al., 2008, [594284](#); Nickmilder et al., 2007, [090710](#)). These findings are  
26 consistent with those from human controlled exposure studies that indicate a lack of correlation  
27 between inflammatory and spirometric responses induced by O<sub>3</sub> exposure. Studies have suggested  
28 that O<sub>3</sub>-related respiratory morbidity may occur via multiple mechanisms with varying time courses  
29 of action, and the examination of a limited number of O<sub>3</sub> exposure lags in these aforementioned  
30 studies may explain some of the inconsistencies in associations of O<sub>3</sub> with different respiratory  
31 health endpoints.

32 Collectively, studies examined associations with single-day O<sub>3</sub> concentrations lagged from 0 to  
33 5 days, as well concentrations averaged over 2 to 9 days. Lag 0 O<sub>3</sub> exposure was most frequently  
34 examined and consistently associated with increased airway inflammation and oxidative stress.  
35 However, among studies that examined single- and multi-day lags, multiday average O<sub>3</sub> exposures  
36 were associated with greater increases in airway inflammation and oxidative stress (Delfino et al.,

1 2010, [647222](#); Liu et al., 2009, [192003](#); Sienra-Monge et al., 2004, [196422](#)). Human controlled  
2 exposure studies have similarly found that several indicators of airway inflammation remain elevated  
3 following exposures to O<sub>3</sub> repeated over multiple days (Section 6.2.3.1).

### 6.2.3.3. Toxicology

4 The 2006 O<sub>3</sub> AQCD states that the “extensive human clinical and animal toxicological  
5 evidence, together with the limited available epidemiologic evidence, is clearly indicative of a causal  
6 role for O<sub>3</sub> in inflammatory responses in the airways.” Numerous recent in vitro and in vivo studies  
7 add to these observations of O<sub>3</sub>-induced inflammation and injury, and provide new information  
8 regarding the underlying mechanisms (Aibo et al., 2010, [378559](#); Carey et al., 2007, [195752](#);  
9 Castagna et al., 2009, [596372](#); Cho et al., 2007, [596373](#); Dahl et al., 2007, [196986](#); Damera et al.,  
10 2009, [596375](#); Fakhrzadeh et al., 2008, [596380](#); Farraj et al., 2010, [380846](#); Garantziotis et al., 2010,  
11 [624947](#); Han et al., 2008, [596387](#); Hicks et al., 2010, [624932](#); Huffman et al., 2006, [596388](#); Inoue  
12 et al., 2008, [197803](#); Jang et al., 2005, [195638](#); Janic et al., 2005, [483658](#); Johnston et al., 2005,  
13 [596393](#); Johnston et al., 2005, [596394](#); Johnston et al., 2006, [097439](#); Johnston et al., 2007, [596392](#);  
14 Kenyon et al., 2006, [596396](#); Kooter et al., 2007, [596397](#); Manzer et al., 2006, [596404](#); Oslund et al.,  
15 2008, [195654](#); Oslund et al., 2009, [201539](#); Oyarzún et al., 2005, [596407](#); Plopper et al., 2006,  
16 [596410](#); Servais et al., 2005, [195667](#); Vancza et al., 2009, [596419](#); Voynow et al., 2009, [194311](#);  
17 Wagner et al., 2007, [596420](#); Wang et al., 2007, [596421](#); Yoon et al., 2007, [596422](#)).

18 The similarities of non-human primates to humans make them attractive models in which to  
19 study the pulmonary response to O<sub>3</sub>. A single 6 h exposure of adult male Cynomolgus monkeys to  
20 1 ppm O<sub>3</sub> induced significant increases in inflammatory and injury markers, including BAL  
21 neutrophils, total protein, alkaline phosphatase, IL-6, IL-8, and G-CSF (Hicks et al., 2010, [624932](#)).  
22 Gene expression analysis confirmed the increases in IL-8, which has been previously observed in  
23 O<sub>3</sub>-induced pulmonary injury in rhesus monkeys (Chang MM-J; Wu et al., 1998, [011983](#)). Anti-  
24 inflammatory IL-10 was also elevated, but fold changes in IL-10 and G-CSF were relatively low and  
25 highly variable. The single exposure also caused necrosis and sloughing of the epithelial lining of the  
26 most distal portions of the terminal bronchioles and the respiratory bronchioles. Bronchiolitis,  
27 alveolitis, parenchymal and centriacinar inflammation were also observed. A second exposure  
28 protocol (two exposures with a 2-week inter-exposure interval) resulted in similar inflammatory  
29 responses, with the exception of total protein and alkaline phosphatase levels which were attenuated,  
30 indicating some adaptation with respect to injury.

31 Exposure of adult BALB/c mice to 0.01 ppm O<sub>3</sub> for 4 hours increased BAL levels of  
32 keratinocyte chemoattractant (KC; IL-8 homologue) (~ sixfold), IL-6 (~12-fold), and TNF- $\alpha$  (~  
33 twofold) (Damera et al., 2010, [380255](#)). Additionally, O<sub>3</sub> increased BAL neutrophils by 21% without  
34 changes in other cell types. A trend of increased neutrophils with increased O<sub>3</sub> concentration  
35 (0.12-2 ppm) was observed in BALB/c mice exposed for 3 hours (Jang et al., 2005, [195638](#)).  
36 Although alterations in the epithelium of the airways were not evident in 129J mice after 4 hours of  
37 exposure to 0.2 ppm O<sub>3</sub> (Plopper et al., 2006, [596410](#)), detachment of the bronchiolar epithelium

1 was observed in SD rats after 5 days or 60 days of exposure to 0.25 ppm O<sub>3</sub> (Oyarzún et al., 2005,  
2 [596407](#)). Subacute (65 hours) exposure to 0.3 ppm O<sub>3</sub> induced pulmonary inflammation and  
3 enhanced vascular permeability in mixed strain mice (129/Ola and C57BL/6) (Inoue et al., 2008,  
4 [197803](#)). Three hours or 72 hours of exposure to 0.3 ppm O<sub>3</sub> resulted in similar levels of IL-6  
5 expression in the lungs of C57BL/6 mice (Johnston et al., 2005, [596394](#)), along with increases in  
6 BAL protein, sTNFR1, and sTNFR2. Increased neutrophils were observed only after the 72-h  
7 exposure, and neither exposure resulted in detectable levels of IL-6 or KC protein. Levels of BAL  
8 protein, sTNFR1, and sTNFR2 were higher in the 72-h exposure group than in the 3-h exposure  
9 group. In another study, the same subacute (72 hours) exposure protocol elicited increases in BALF  
10 protein, IP-10, sTNFR1, macrophages, neutrophils, and IL-6, IL-1 $\alpha$ , and IL-1 $\beta$  expression (Johnston  
11 et al., 2007, [596392](#)). Yoon et al. (2007, [596422](#)) exposed C57BL/6J mice continuously to 0.3 ppm  
12 O<sub>3</sub> for 6, 24, 48, or 72 hours, and observed elevated levels of KC, MIP-2, metalloproteinases, and  
13 inflammatory cells in the lungs at various time points.

14 After exposing adult C57BL mice to 0.5 ppm O<sub>3</sub> for 3 hours, Han et al. (2008, [596387](#))  
15 observed early (5 hours postexposure) increases in BAL TNF- $\alpha$  and IL-1 $\beta$ , which diminished by  
16 24 hours postexposure. Total BAL protein was elevated at 24 hours, but there were only minimal or  
17 negligible changes in LDH, total cells, or PMNs. Ozone increased BAL mucin levels (with statistical  
18 significance by 24 hours postexposure), and significantly elevated surfactant protein D at both time  
19 points. Prior intratracheal (IT) exposure to multiwall carbon nanotubes enhanced most of these  
20 effects, but the majority of responses to the combined exposure were not greater than those to  
21 nanotubes alone. Ozone exposure did not induce markers of oxidative stress in lung tissue, BAL, or  
22 serum. Consistent with this study, Aibo et al. (2010, [378559](#)) did not detect changes in BAL  
23 inflammatory cell numbers in the same mouse strain after a 6-h exposure to 0.25 or 0.5 ppm. The  
24 majority of inflammatory cytokines (pulmonary or circulating) were not significantly changed (as  
25 assessed 9 hours post O<sub>3</sub> exposure).

26 In a study examining age, strain, and gender as factors for susceptibility to O<sub>3</sub> in mice,  
27 increased BAL neutrophils were observed in four strains of neonates 24 hours after exposure to  
28 0.8 ppm O<sub>3</sub> for 5 hours (Vancza et al., 2009, [596419](#)). Three of these strains also exhibited increased  
29 BAL protein, although the two endpoints were not necessarily consistently correlated in a given  
30 strain. Inflammation and injury were observed in adult mice as well. A study assessing NQO1 as a  
31 susceptibility factor was conducted by Voynow et al. (2009, [194311](#)). Specific effects of this gene on  
32 O<sub>3</sub> responses are discussed in Chapter 8; only ozone's effects in wild type C57BL/6 mice are  
33 described here. Exposure to 1 ppm for 3 hours increased BAL total cells, neutrophils, and KC; these  
34 responses were greatest at 24 hours postexposure. F<sub>2</sub>-isoprostane (8-isoprostane), a marker of  
35 oxidative stress, was also elevated by O<sub>3</sub>, peaking at 48 hours postexposure.

36 Atopic asthma appears to be a risk factor for more severe O<sub>3</sub> induced airway inflammation in  
37 humans (Balmes et al., 1997, [086092](#); Scannell et al., 1996, [080755](#)), and allergic animal models are  
38 often used to investigate the effects of O<sub>3</sub> on this susceptible population. Farraj et al. (2010, [380846](#))  
39 exposed allergen-sensitized adult male BALB/c mice to 0.5 ppm O<sub>3</sub> for 5 hours once per week for

1 4 weeks. Ovalbumin-sensitized mice exposed to O<sub>3</sub> had significantly increased BAL eosinophils by  
2 85% and neutrophils by 103% relative to OVA sensitized mice exposed to air, but these changes  
3 were not evident upon histopathologic evaluation of the lung, and no O<sub>3</sub> induced lesions were  
4 evident in the nasal passages. Ozone increased BAL levels of N-acetyl-glucosaminidase (NAG; a  
5 marker of injury) and protein. DEP co-exposure (2.0 mg/m<sup>3</sup>, nose only) inhibited these responses.  
6 Wagner et al. (2007, [596420](#)) exposed the relatively O<sub>3</sub>-resistant Brown Norway rat strain to 1 ppm  
7 O<sub>3</sub> after sensitizing and challenging with OVA. Rats were exposed for 2 days, and airway  
8 inflammation was assessed one day later. Filtered air for controls contained less than 0.02 ppm O<sub>3</sub>.  
9 Histopathology indicated O<sub>3</sub> induced site-specific lung lesions in the centriacinar regions,  
10 characterized by wall thickening partly due to inflammatory cells influx. BAL neutrophils were  
11 elevated by O<sub>3</sub> in allergic rats, and modestly increased in non-allergic animals (not significant). A  
12 slight (but not significant) increase in macrophages was observed, but eosinophil numbers were not  
13 affected by O<sub>3</sub>. Soluble mediators of inflammation (Cys-LT, MCP-1, and IL-6) were elevated by O<sub>3</sub>  
14 in allergic animals but not non-allergic rats. Treatment with γT, which neutralizes oxidized lipid  
15 radicals and protects lipids and proteins from nitrosative damage, did not alter the morphologic  
16 character or severity of the centriacinar lesions caused by O<sub>3</sub>, nor did it reduce neutrophil influx. It  
17 did, however, significantly reduce O<sub>3</sub>-induced soluble inflammatory mediators in allergic rats.

### **Mechanisms of Injury**

18 Since O<sub>3</sub> has been well established as a causative agent of airway inflammation and injury, the  
19 majority of recent research has focused on the underlying mechanisms. A brief description of some  
20 of the recent contributions to this area of research is provided here; more detailed descriptions of the  
21 mechanisms behind O<sub>3</sub>-mediated injury and inflammation can be found in the mode of action  
22 chapter (Chapter 5). There are several signaling pathways responsive to changes in oxidation status,  
23 which tend to be influenced at different levels in different host backgrounds. The molecular  
24 mechanisms of TNF receptor-mediated lung injury induced by O<sub>3</sub> and associated signaling pathways  
25 (NF-κB, MAPK/AP-1) have been examined (Cho et al., 2007, [596373](#); Fakhrzadeh et al., 2008,  
26 [596380](#)), along with the changes in gene expression which characterize O<sub>3</sub>-induced stress and  
27 inflammation (Wang et al., 2007, [596421](#)). Other contributors to injury and inflammation include the  
28 IL-1 and neurokinin receptors (Johnston et al., 2007, [596392](#); Oslund et al., 2008, [195654](#)),  
29 calcitonin gene-related peptide receptor activation (Oslund et al., 2009, [201539](#)), CXCR2, a receptor  
30 for neutrophil chemokines (Johnston et al., 2005, [596393](#)), and NQO1 (Voynow et al., 2009,  
31 [194311](#)), an enzyme involved in oxidative stress. Studies indicate a role for oxidative stress in  
32 mediating inflammation (Jang et al., 2005, [195638](#); Wagner et al., 2007, [596420](#)). Protective roles  
33 have been identified for nitric oxide synthase (Kenyon et al., 2006, [596396](#)), metallothionein (Inoue  
34 et al., 2008, [197803](#)), matrix metalloproteinases (Yoon et al., 2007, [596422](#)), Clara cell secretory  
35 protein (Plopper et al., 2006, [596410](#)), and the recognition of oxidized lipids by alveolar  
36 macrophages (Dahl et al., 2007, [196986](#)).

## 6.2.4. Respiratory Symptoms and Medication Use

### 6.2.4.1. Epidemiology

1           In epidemiologic studies, respiratory symptom data are typically collected by having subjects  
2 or parents record symptoms such as wheeze, cough, and shortness of breath and medication use in a  
3 diary without direct supervision by study staff. Several limitations of symptom reports are well-  
4 recognized: recall error if not recorded daily, differences among subjects in the interpretation of  
5 symptoms, biased reporting between asthmatic and healthy participants and between known high and  
6 low pollution days, and occurrence in a smaller percent of the population compared with changes in  
7 lung function and mediators of airway inflammation. Nonetheless, symptom diaries remain a  
8 convenient and useful tool to collect individual-level data from a large number of subjects and allow  
9 the modeling associations of daily changes in O<sub>3</sub> exposure with daily changes in respiratory  
10 morbidity. Furthermore, they represent an overt clinical effect and may have greater impact on  
11 subjects' activities. Importantly, most of the limitations described above are sources of random  
12 measurement error that can bias effect estimates to the null or increase the uncertainty around effect  
13 estimates.

14           Table 6-15 presents the characteristics and ambient O<sub>3</sub> concentration data from studies  
15 assessing associations between O<sub>3</sub> exposure and respiratory symptoms and medication use. Most  
16 studies have been conducted in asthmatics, and the collective body of epidemiologic evidence  
17 strongly supports associations between acute increases in ambient O<sub>3</sub> exposure and increases in  
18 respiratory symptoms in children with asthma (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#))  
19 (Figures 6-12 and Tables 6-16). Evidence also indicated that O<sub>3</sub> exposure is likely to be associated  
20 with increased use of asthma medication (Figure 6-13 and Table 6-17). The effect of O<sub>3</sub> exposure on  
21 respiratory symptoms in subjects with other pre-existing diseases and in healthy children is not  
22 clearly indicated (Figure 6-14 and Table 6-18).

**Table 6-15. Mean and upper percentile ozone concentrations in studies examining respiratory symptoms, asthma medication use, and activity levels**

Study	Location	Years/Season	Metrics	Mean Concentration (ppb)	Middle/Upper Percentile Concentrations (ppb)
Mortimer et al. (2002, <a href="#">030281</a> )	8 U.S. communities: (NCICAS)	1993 Warm season	8-h avg (10:00 a.m. to 6:00 p.m.)	48	Approximate IQR = 15 <sup>a</sup>
O'Connor et al. (2008, <a href="#">156818</a> )	7 U.S. communities: (ICAS)	1998-2001 All-year	24-h avg	NR	Approximate median: 20 <sup>a</sup> Approximate range: 2-50 <sup>a</sup>
Schildcrout et al. (2006, <a href="#">089812</a> )	8 U.S. communities (CAMP)	1993-1995 Warm season	1-h max	NR	Range in medians: 43.5-65.8 Range in 10th-90th: 23.3-53.3
Apte et al. (2008, <a href="#">195865</a> )	Multiple U.S. cities	1994-1998 All-year	24-h avg Workday avg (8:00 a.m. - 5:00 p.m.)	25.5 36.6	Range: 2.5-67.3 Range: 2.5-107.1
Gent et al. (2003, <a href="#">052885</a> )	CT, southern MA	2001 Warm season	1-h avg 8-h avg	58.6 51.3	Range: 27.1-125.5 Range: 21.4-99.6
Thurston et al. (1997, <a href="#">077645</a> )	Connecticut River Valley, CT	1991-1993 Warm season	1-h max	83.6	Range: 20-160
Triche et al. (2006, <a href="#">093274</a> )	southwestern VA	1995-1996 Warm season	8-h max	54.5	Range: 23.5-87.6
Khatri et al. (2009, <a href="#">594282</a> )	Atlanta, GA	2003, 2005, 2006 Warm season	8-h max	59 <sup>b</sup>	Range: 44-73 <sup>b</sup>
Ross et al. (2002, <a href="#">042749</a> )	Moline, Illinois	1994 April-October	8-h avg	41.5	Range: 8.9-78.3
Rabinovitch et al. (2004, <a href="#">096753</a> )	Denver, CO	2000-2003 Cold season	1-h max	28.2 <sup>c</sup>	Median: 30.0 <sup>c</sup> Range: 0-70.0 <sup>c</sup>
Mann et al. (2010, <a href="#">635827</a> )	Fresno/Clovia, California	2000-2005 All-year	8-h max	NR	Median: 49.4 Range: 3.7-120.0
Linn et al. (1996, <a href="#">082508</a> )	Rubidoux, Upland, Torrence, CA	1992-1993, 1993-1994 Fall and spring	24-h avg	34 <sup>b</sup>	Range: 7-86 <sup>b</sup>
Ostro et al. (2001, <a href="#">016702</a> )	Los Angeles, CA	1993 Warm season	1-h max	Los Angeles: 59.5 Pasadena: 95.8	Range: 10-130 Range: 10-220
Delfino et al. (2003, <a href="#">050460</a> )	Los Angeles, CA	1999-2000 Cold season	1-h max 8-h max	25.4 17.1	Range: 4-52 Range: 3-37
Eiswerth et al. (2005, <a href="#">196443</a> )	Los Angeles, CA	1983 Cold season	1-h max	NR	NR
Romieu et al. (1996, <a href="#">080748</a> )	northern Mexico City, Mexico	1991-1992 Warm and cold season	1-h max	190	Range: 40-370
Romieu et al. (1997, <a href="#">085807</a> )	southern Mexico City, Mexico	1991-1992 Warm and cold season	1-h max	196	Range: 40-390
Gold et al. (1999, <a href="#">086919</a> )	Mexico City, Mexico	1991 Winter, spring, fall	24-h avg	52.0	IQR: 25 Range: 7.9-103
Romieu et al. (2006, <a href="#">090969</a> )	Mexico City, Mexico	1998-2000 All-year	8-h max 1-h max	66.2 102	Range: 11.1-142.5 Range: 12-309
Escamilla-Nunez et al. (2008, <a href="#">594284</a> )	Mexico City, Mexico	2003-2005 All-year	8-h max 1-h max	31.6 86.5	IQR: 22.0 (8-h); Range: 4.9-86.3 IQR:48.0; Range: NR
Gielen et al. (1997, <a href="#">083592</a> )	Amsterdam, Netherlands	1995 Warm season	8-h max	33.5	Range: 13.8-55.4
Hoek and Brunekreef (1995, <a href="#">046184</a> )	Deurne and Enkhuizen, Netherlands	1989 March-July	1-h max	Deurne: 57 Enkhuizen: 59	Range: 22-107 Range: 4-114
Just et al. (2002, <a href="#">035429</a> )	Paris, France	1996 April-June	8-h avg	29.5	5-61
Feo Brito et al. (2007, <a href="#">093259</a> )	Ciudad Real and Puertollano, Spain	2000-2001 Warm season	1-h max	65.9 (Ciudad Real) <sup>d</sup> 56.8 (Puertollano) <sup>d</sup>	Range: 45.4-101.5 <sup>d</sup> (Ciudad Real), 11.2-70.5 <sup>d</sup> (Puertollano)
Park et al. (2005, <a href="#">088673</a> )	Incheon, Korea	March-June 2002	24-h avg	Dust event days: 23.6 Control days: 25.1	NR
Moon et al. (2009, <a href="#">190297</a> )	4 cities, South Korea	April-May, 2003 Warm season	24-h avg	NR	NR

Study	Location	Years/Season	Metrics	Mean Concentration (ppb)	Middle/Upper Percentile Concentrations (ppb)
Jalaludin et al. (2004, <a href="#">056595</a> )	Sydney, Australia	1993 All-year	1-h max	26	IQR = 13.7 Maximum: 91
Rodriguez et al. (2007, <a href="#">092842</a> )	Perth, Australia	1996-2001 All-year	24-h avg 1-h max	28 33	Range: 9-74 Range: 12-95

NCICAS = National Cooperative Inner-City Asthma Study, IQR = interquartile range, ICAS = Inner City Asthma Study, NR = Not Reported, CAMP = Childhood Asthma Management Program

<sup>a</sup>Quantitative results not presented. Concentrations estimated from data presented in a figure.

<sup>b</sup>Personal exposure estimates were derived based on time spent in the vicinity of various O<sub>3</sub> monitors.

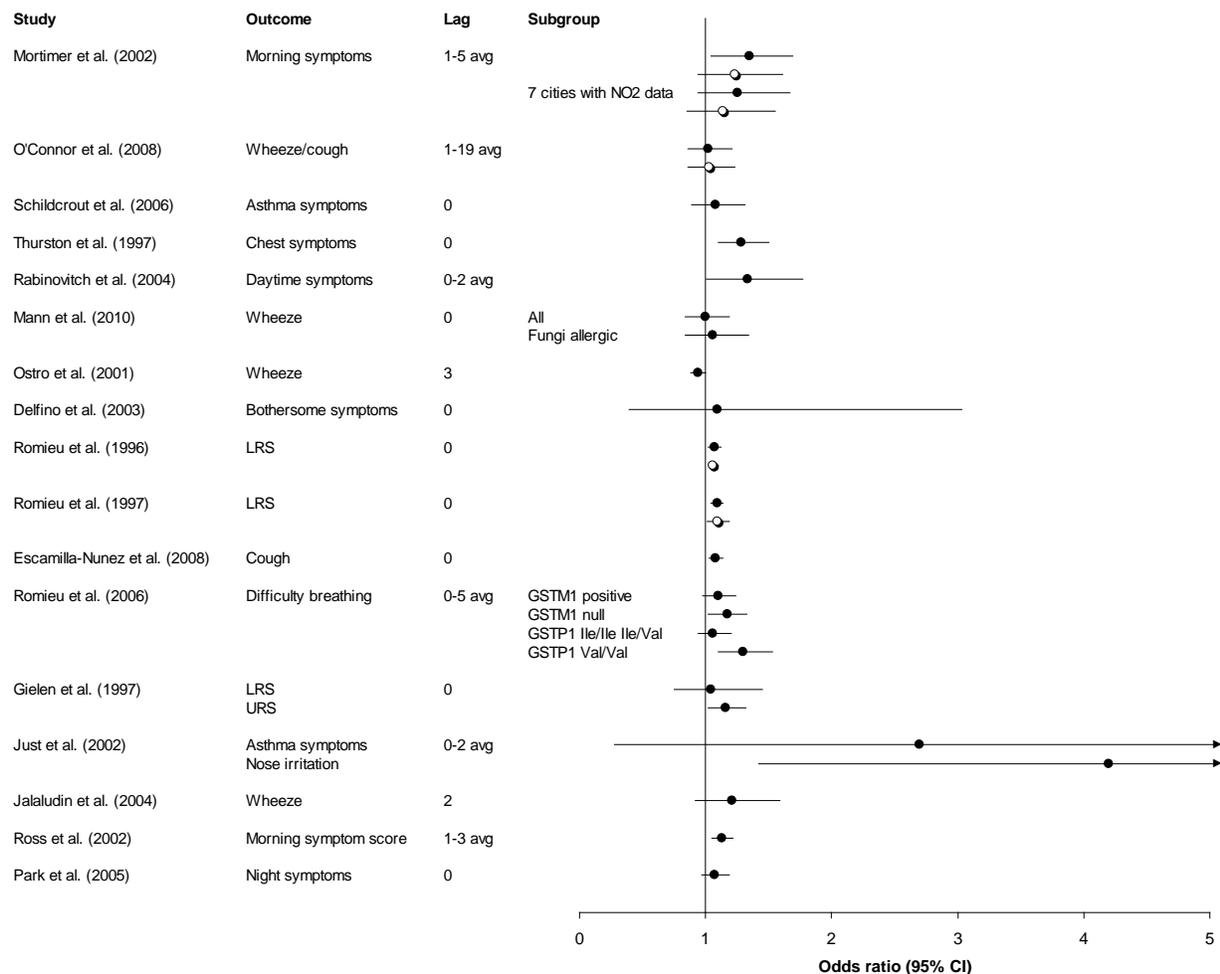
<sup>c</sup>Measured at sites established by investigators.

<sup>d</sup>Concentrations converted from µg/m<sup>3</sup> to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

## Asthmatic Subjects

1 The strong body of evidence demonstrating associations between ambient O<sub>3</sub> exposure and  
2 respiratory symptoms among asthmatic children and adults mostly comprises several single-region  
3 or single-city studies (Figure 6-12 and Table 6-16). In contrast, U.S. multicity studies provided  
4 mixed evidence of O<sub>3</sub>-associated increases in respiratory symptoms among asthmatic children  
5 (Mortimer et al., 2002, [030281](#); O'Connor et al., 2008, [156818](#); Schildcrout et al., 2006, [089812](#)). In  
6 particular, NCICAS (Mortimer et al., 2000, [013255](#); Mortimer et al., 2002, [030281](#)) and ICAS  
7 (O'Connor et al., 2008, [156818](#)) of different children from mostly the same cities produced  
8 contrasting findings. In the NCICAS cohort, lag 1-4 avg O<sub>3</sub> was positively associated with morning  
9 asthma symptoms (OR: 1.35 [95% CI: 1.04, 1.69] per 30-ppb increase in 8-h avg O<sub>3</sub>) (Mortimer et  
10 al., 2002, [030281](#)). Ozone effect estimates decreased slightly in magnitude in two-pollutant models  
11 with SO<sub>2</sub> (OR: 1.23 [95% CI: 0.94, 1.61]) or NO<sub>2</sub> (OR: 1.14 [95% CI: 0.85, 1.59]). In the ICAS  
12 cohort (described in section 6.2.1.2), associations of 19-day avg O<sub>3</sub> with wheeze and nighttime  
13 asthma were positive and negative, respectively (O'Connor et al., 2008, [156818](#)). NCICAS was  
14 conducted during the warm season, and symptom data were collected daily (Mortimer et al., 2000,  
15 [013255](#); Mortimer et al., 2002, [030281](#)), whereas in ICAS, every 2 months, parents reported the  
16 number of days with respiratory symptoms over the previous 2 weeks (O'Connor et al., 2008,  
17 [156818](#)). Because of the two-week symptom reporting period, ICAS investigators were precluded  
18 from examining associations with single-day and shorter-duration O<sub>3</sub> exposure periods.

19 Evidence of O<sub>3</sub>-associated respiratory symptoms was also weak in another recent U.S.  
20 multicity study (Albuquerque, NM; Baltimore, MD; Boston, MA; Denver, CO; San Diego, CA;  
21 Seattle, WA; St. Louis, MO; and Toronto, Canada) of 990 asthmatic children (Schildcrout et al.,  
22 2006, [089812](#)). In this study, symptom data were collected daily and analyses were restricted to high  
23 O<sub>3</sub> periods between May and September. In meta-analyses that combined city-specific estimates, a  
24 40-ppb increase in daily lag 0 of 1-h max O<sub>3</sub> was associated with any asthma symptom with an OR  
25 (95% CI) of 1.08 (0.89, 1.31). Odds ratios for lags 1 and 2 and the 3-day sum of O<sub>3</sub> were near 1.0.  
26 Because O<sub>3</sub> analyses were restricted to summer months, the median follow-up of subjects was  
27 2 months, and data were available from an average of 12 subjects per day per city, the study may  
28 have lacked sufficient power to perform city-specific analyses stratified by season, which the authors  
29 suggested may have been necessary to discern O<sub>3</sub>-related effects.



**Figure 6-12. Associations of ambient ozone exposure with respiratory symptoms in asthmatic subjects.** All studies are of asthmatic children except for Ross et al. (2002, [042749](#)) which includes asthmatic children and adults and Park et al. (2005, [088673](#)) which includes asthmatic adults. LRS = lower respiratory symptoms, URS = upper respiratory symptoms. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max (or 8-h avg), and 24-h avg ozone, respectively. Effect estimates depicted as black circles are from single-pollutant models, and effect estimates depicted as open circles are from co-pollutant models.

**Table 6-16. Additional characteristics and quantitative data for studies presented in Figure 6-12**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Outcome	Subgroup	Odds Ratio (95% CI) <sup>a</sup>
Mortimer et al. (2002, <a href="#">030281</a> )	8 U.S. communities Asthmatic children	1-4 avg	8-h avg (10:00-18:00)	Morning symptoms	All 8 cities 7 cities with NO <sub>2</sub> data	1.35 (1.04, 1.69) 1.23 (0.94, 1.61) with SO <sub>2</sub> 1.25 (0.94, 1.67) 1.14 (0.85, 1.55) with NO <sub>2</sub>
O'Connor et al. (2008, <a href="#">156818</a> )	7 U.S. communities Asthmatic children	1-19 avg	24-h avg	Wheeze/cough		1.02 (0.86, 1.21) 1.03 (0.86, 1.21) with PM <sub>2.5</sub> , NO <sub>2</sub>
Schildcrout et al. (2006, <a href="#">089812</a> )	8 U.S. communities Asthmatic children	0	1-h max	Asthma symptoms		1.08 (0.89, 1.31)
Thurston et al. (1997, <a href="#">077645</a> )	CT River Valley, CT Asthmatic campers	0	1-h max	Chest symptoms		1.28 (1.1, 1.5)
Rabinovitch et al. (2004, <a href="#">096753</a> )	Denver, CO Asthmatic children	0-2 avg	1-h max	Daytime symptoms		1.34 (1.01, 1.77)
Mann et al. (2010, <a href="#">635827</a> )	Fresno/Clovia, California Asthmatic children	0	8-h max	Wheeze	All Fungi allergic	1.00 (0.84, 1.19) 1.06 (0.84, 1.34)
Ostro et al. (2001, <a href="#">016702</a> )	Los Angeles, CA Asthmatic children	3	1-h max	Wheeze		0.94 (0.88, 1.00)
Delfino et al. (2003, <a href="#">050460</a> )	Los Angeles, CA Asthmatic children	0	1-h max	Symptoms bothersome/ interfering with activity		1.09 (1.04, 1.14)
Romieu et al. (1996, <a href="#">080748</a> )	northern Mexico City, Mexico Asthmatic children	0	1-h max	LRS		1.07 (1.02, 1.12) 1.06 (1.02, 1.10) with PM <sub>2.5</sub>
Romieu et al. (1997, <a href="#">085807</a> )	southern Mexico City, Mexico Asthmatic children	0	1-h max	LRS		1.09 (1.04, 1.14) 1.09 (1.01, 1.19) with PM <sub>2.5</sub>
Escamilla-Nunez et al. (2008, <a href="#">594284</a> )	Mexico City, Mexico Asthmatic children	0	1-h max	Wheeze		1.08 (1.03, 1.14)
Romieu et al. (2006, <a href="#">090969</a> )	Mexico City, Mexico Asthmatic children	0-5 avg	1-h max	Difficulty breathing	GSTM1 sufficient GSTM1 null GSTP1 Ile/Ile Ile/Val GSTP1 Val/Val	1.10 (0.98, 1.24) 1.17 (1.02, 1.33) 1.06 (0.94, 1.20) 1.30 (1.10, 1.53)
Gielen et al. (1997, <a href="#">083592</a> )	Amsterdam, Netherlands Asthmatic children	0	8-h max	LRS URS		1.04 (0.75, 1.45) 1.16 (1.02, 1.32)
Just et al. (2002, <a href="#">035429</a> )	Paris, France Asthmatic children	0-2 avg	8-h avg	Asthma symptoms Nose irritation		2.7 (0.28, 25.8) 4.2 (1.42, 12.4)
Jalaludin et al. (2004, <a href="#">056595</a> )	Sydney, Australia Asthmatic children	2	1-h max	Wheeze		1.21 (0.92, 1.59)
Ross et al. (2002, <a href="#">042749</a> )	Moline, Illinois Asthmatic children and adults	1-3 avg	8-h avg	Morning symptoms		1.13 (1.05, 1.22)
Park et al. (2005, <a href="#">088673</a> )	Incheon, Korea Asthmatic adults	0	24-h avg	Night symptoms		1.07 (0.97, 1.19)

LRS = Lower respiratory symptoms, URS = Upper respiratory symptoms.

<sup>a</sup>Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max (or 8-h avg), and 24-h avg O<sub>3</sub>, respectively.

1 Previous O<sub>3</sub> AQCDs acknowledged uncertainty regarding confounding by airborne allergens  
2 or increased susceptibility of atopic asthmatics as few studies considered allergen exposures or  
3 allergic sensitization of subjects (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)). A growing  
4 body of studies aimed to address this gap in knowledge, although results were mixed. Mortimer et al.  
5 (2000, [013255](#)) found that although O<sub>3</sub> was associated with greater decrements in PEF and incidence  
6 of asthma symptoms among nonatopic asthmatics, associations were stronger among asthmatics with  
7 higher residential exposures to cat or cockroach allergen. In a recent study of asthmatic children in

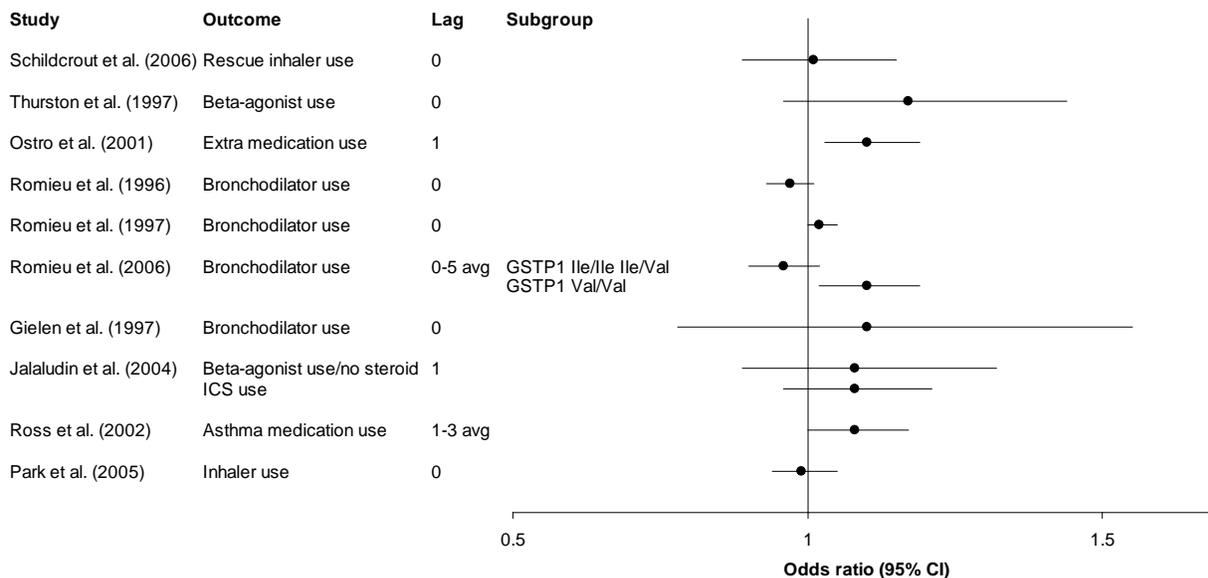
1 Fresno, CA, most associations of single- and multiday lags of O<sub>3</sub> exposure (0-14 days) with wheeze  
2 were near or below 1.0 (Mann et al., 2010, [635827](#)). The estimated effects did not differ between  
3 fungi allergic and fungi nonallergic subjects (ascertained by skin prick test), although the odds ratio  
4 was larger among cat nonallergic subjects than among cat allergic. In this study, many subjects were  
5 allergic to multiple allergens; however, associations were not compared between subjects with any  
6 versus no allergic sensitization. Feo Brito et al. (2007, [093259](#)) followed a group of 137 pollen-  
7 allergic asthmatics residing in two cities in central Spain during 1 pollen season (May-June 2000 or  
8 2001). In the industrial Puertollano, a 40-ppb increase in lag 3 of 1-h max O<sub>3</sub> was associated with a  
9 14.3% increase (95% CI: 3.6, 26.0) in the number of subjects reporting symptoms, adjusting only for  
10 time trend. A smaller, statistically nonsignificant effect estimate was obtained for pollen. Conversely,  
11 in the less industrialized and less polluted Ciudad Real, pollen significantly contributed to increased  
12 incidence of respiratory symptoms, whereas O<sub>3</sub> did not. While co-pollutant modeling was not  
13 conducted, in both locations, O<sub>3</sub> and pollen concentrations were weakly correlated, indicating that  
14 the findings for O<sub>3</sub> were not likely confounded by pollen. Rather, the results suggested that O<sub>3</sub> and  
15 pollen may have independent effects that vary between locations, depending on the mix of airborne  
16 pollutants.

17 Several studies conducted in multiple cohorts of asthmatic children in Mexico City, Mexico  
18 demonstrated O<sub>3</sub>-associated increases in respiratory symptoms (Escamilla-Nuñez et al., 2008,  
19 [594284](#); Romieu et al., 1996, [080748](#); Romieu et al., 1997, [085807](#); Romieu et al., 2006, [090969](#)).  
20 Recent studies expanded on earlier evidence by providing new information to assess important lags  
21 of O<sub>3</sub> exposure and factors that may contribute to heterogeneity in symptom responses to ambient O<sub>3</sub>  
22 exposure. For example, Romieu et al. (2006, [090969](#)) and Escamilla-Nunez et al. (2008, [594284](#))  
23 found that the magnitudes of association of ambient O<sub>3</sub> exposure with respiratory symptoms and  
24 medication use increased with increasing averaging days of O<sub>3</sub> exposure. Combined evidence from  
25 Romieu et al. (1996, [080748](#)) and Romieu et al. (1997, [085807](#)) indicated that among single-day lags  
26 of exposure, lag 0 O<sub>3</sub> had the greatest estimated effect on respiratory symptoms. Additionally,  
27 although the interaction between O<sub>3</sub> and season was not statistically significant, Escamilla-Nunez et  
28 al. (2008, [594284](#)) estimated larger effects during the warm season (May-September).

29 Although Romieu et al. (2006, [090969](#)) did not observe differences in associations between O<sub>3</sub>  
30 and lung function by GST polymorphisms (Section 6.2.1.2), they did observe effect modification for  
31 respiratory symptoms. Compared with GSTM1 sufficient subjects and GSTP1 Ile/Ile or Ile/Val  
32 subjects, respectively, larger effects were estimated for GSTM1 null subjects and for GSTP1 Val/Val  
33 subjects (Figure 6-12 and Table 6-16). Ozone had the greatest estimated effect on difficulty breathing  
34 in asthmatics who were both GSTM1 null and GSTP1 Val/Val (OR: 1.49 [95% CI: 1.14, 1.93]).  
35 These results add to the body of epidemiologic evidence that deficiencies in oxidant metabolism may  
36 increase susceptibility to O<sub>3</sub>-related respiratory morbidity and also are consistent with findings from  
37 human controlled exposure studies indicating increased responsiveness to O<sub>3</sub> among GSTM1 null  
38 subjects (Section 6.2.1.4). As was discussed in Section 6.2.1.2, compared with the GSTM1 genotype,  
39 evidence for susceptibility related to GSTP1 polymorphisms is less certain. Romieu et al. (2006,

1 [090969](#)) found that the GSTP1 Val/Val variant was associated with a lesser O<sub>3</sub>-associated decrement  
2 in lung function but greater risk of respiratory symptoms. Whereas some studies have reported  
3 greater risk of asthma among GSTP1 Ile/Ile or Ile/Val subjects (Hemmingsen et al., 2001, [670827](#);  
4 Mapp et al., 2002, [670826](#)), others have reported greater risk among GSTP1 Val/Val subjects (Tamer  
5 et al., 2004, [199914](#)). In Romieu et al. (2006, [090969](#)), GSTP1 Ile/Ile was associated with greater  
6 severity of asthma, and Lee et al. (2004, [090971](#)) also reported greater risk of air pollution-  
7 associated asthma among GSTP1 Ile/Ile subjects.

8         The 2006 O<sub>3</sub> AQCD concluded that ambient O<sub>3</sub> was likely associated with increased asthma  
9 medication use (U.S. EPA, 2006, [088089](#)). Although evidence in recent studies was mixed (Park et  
10 al., 2005, [088673](#); Romieu et al., 2006, [090969](#); Schildcrout et al., 2006, [089812](#)), the overall body  
11 of evidence supports the previous conclusion (Figure 6-13 and Table 6-17). The effects are estimated  
12 with greater uncertainty as indicated by the wide 95% CIs. The wide 95% CIs have been attributed to  
13 a smaller number of study subjects reporting medication use and the low frequency of use over the  
14 study period. Within most studies, findings were similar for respiratory symptoms and asthma  
15 medication use. For example, Romieu et al. (2006, [090969](#)) and Escamilla-Nunez et al. (2008,  
16 [594284](#)) observed positive, statistically significant associations of O<sub>3</sub> with both respiratory  
17 symptoms and bronchodilator use. Schildcrout et al. (2006, [089812](#)) and Park et al. (2005, [088673](#)),  
18 did not observe a positive association for either respiratory symptoms or rescue inhaler use. In  
19 contrast, Romieu et al. (1996, [080748](#)) and Rabinovitch et al. (2004, [096753](#)) observed that O<sub>3</sub> was  
20 positively associated with daytime respiratory symptoms but not with bronchodilator use.



**Figure 6-13. Associations of ambient ozone exposure with asthma medication use.** [All studies are of asthmatic children except for Ross et al. (2002, [042749](#)) which included asthmatic children and adults and Park et al. (2005, [088673](#)) which included asthmatic adults. ICS = corticosteroid use. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max (or 8-h avg), and 24-h avg ozone, respectively. All effect estimates are from single pollutant models.]

**Table 6-17. Additional characteristics and quantitative data for studies presented in Figure 6-13.**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Outcome	Subgroup	Odds Ratio (95% CI) <sup>a</sup>
Schildcrout et al. (2006, <a href="#">089812</a> )	8 U.S. communities Asthmatic children	0	1-h max	Rescue inhaler use		1.01 (0.89, 1.15)
Thurston et al. (1997, <a href="#">077645</a> )	CT River Valley, CT Asthmatic campers	0	1-h max	Beta-agonist use		1.17 (0.96, 1.44)
Ostro et al. (2001, <a href="#">016702</a> )	Los Angeles, CA Asthmatic children	1	1-h max	Extra medication use		1.10 (1.03, 1.19)
Romieu et al. (1996, <a href="#">080748</a> )	northern Mexico City, Mexico Asthmatic children	0	1-h max	Bronchodilator use		0.97 (0.93, 1.01)
Romieu et al. (1997, <a href="#">085807</a> )	southern Mexico City, Mexico Asthmatic children	0	1-h max	Bronchodilator use		1.02 (1.00, 1.05)
Romieu et al. (2006, <a href="#">090969</a> )	Mexico City, Mexico Asthmatic children	0-5 avg	1-h max	Bronchodilator use	GSTP1 Ile/Ile/Val/Val GSTP1 Val/Val	0.96 (0.90, 1.02) 1.10 (1.02, 1.19)
Gielen et al. (1997, <a href="#">083592</a> )	Amsterdam, Netherlands Asthmatic children	0	8-h max	Bronchodilator use		1.10 (0.78, 1.55)
Jalaludin et al. (2004, <a href="#">056595</a> )	Sydney, Australia Asthmatic children	1	1-h max	Beta-agonist use/no steroid ICS use		1.08 (0.89, 1.32) 1.08 (0.96, 1.21)
Ross et al. (2002, <a href="#">042749</a> )	Moline, Illinois Asthmatic children and adults	1-3 avg	8-h avg	Asthma medication use		1.08 (1.00, 1.17)
Park et al. (2005, <a href="#">088673</a> )	Incheon, Korea Asthmatic adults	0	24-h avg	Inhaler use		0.99 (0.94, 1.05)

ICS= Inhaled corticosteroid use.

<sup>a</sup>Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max (or 8-h avg), and 24-h avg O<sub>3</sub>, respectively.

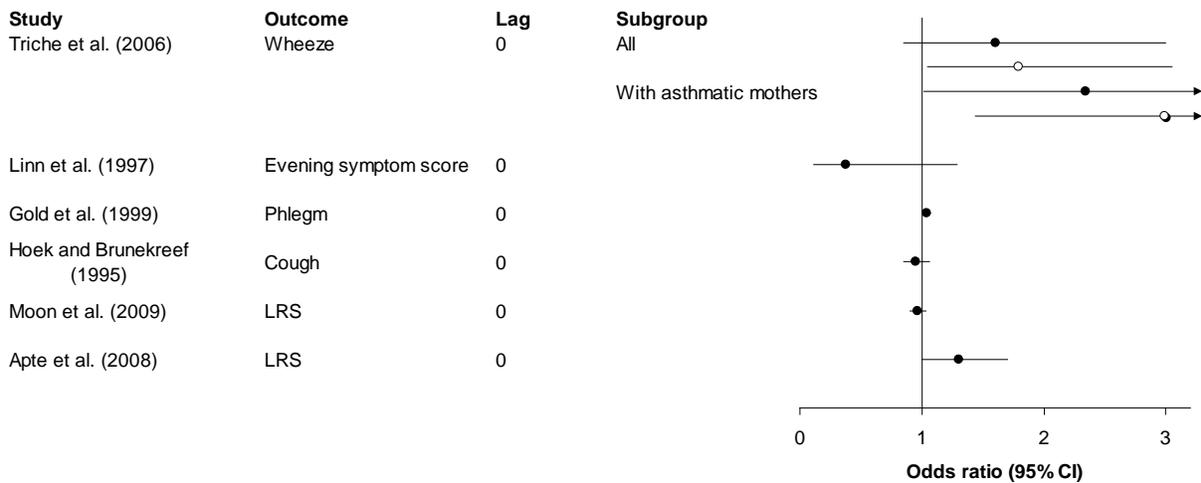
1 While investigation is limited, studies have indicated that O<sub>3</sub> exposure may be associated with  
2 diminished activity level in asthmatics (Delfino et al., 2003, [050460](#); Eiswerth et al., 2005, [196443](#);  
3 Khatri et al., 2009, [594282](#); O'Connor et al., 2008, [156818](#)). In a panel study of asthmatics in  
4 Los Angeles CA, Delfino et al. (2003, [050460](#)) found that a 40-ppb increase in 1-h max O<sub>3</sub> was  
5 associated with symptoms that interfered with daily activity with an OR (95% CI) of 7.41 (1.18,  
6 43.2). In a cross-sectional study of asthmatic adults in Atlanta, GA (described in Section 6.2.1.2),  
7 Khatri et al. (2009, [594282](#)) observed that a 30-ppb increase in lag 2 of 8-h max O<sub>3</sub> was associated  
8 with a 0.69-point decrease (95% CI: -1.28, -0.11) in the Juniper quality of life score, which  
9 incorporates indices for symptoms, mood, and activity limitations (7-point scale). Eiswerth et al.  
10 (2005, [196443](#)) examined the activities of 64 asthmatics (age 16 years and older) in Los Angeles, CA  
11 in fall of 1983. A 40-ppb increase in 1-h max O<sub>3</sub> was associated with a 0.24% (95% CI: 0.08, 0.40%)  
12 lower probability of participation in indoor activities. The associations with outdoor activities were  
13 positive but statistically nonsignificant. Although the authors acknowledged that their findings were  
14 unexpected and may have been influenced by lack of control for potential confounders, they  
15 interpreted the decrease in indoor activities as rest replacing chores. Collectively, these findings  
16 highlight the potentially broader impact of O<sub>3</sub> exposure on quality of life among asthmatics.

17 Several studies have reported positive associations between long lags of O<sub>3</sub> exposure (14-day  
18 and 30-day distributed lags or 19-day avg) and school absenteeism among asthmatic children (Chen  
19 et al., 2000, [011931](#); Gilliland et al., 2001, [013232](#); O'Connor et al., 2008, [156818](#)). Whereas Chen et  
20 al. (2000, [011931](#)) and O'Connor et al. (2008, [156818](#)) examined absences for any reason, Gilliland  
21 et al. (2001, [013232](#)) found associations with absences for respiratory causes. Despite this evidence,

1 several limitations have been noted, including the uncertain biological relevance of long lag periods  
2 of O<sub>3</sub> exposure and the potential for residual seasonal confounding when examining long lag periods  
3 of exposure.

### Populations not Restricted to Asthmatic Subjects

4 Aside from subjects with increased outdoor exposures, the collective body of epidemiologic  
5 evidence has been mixed regarding associations between acute O<sub>3</sub> exposure on respiratory symptoms  
6 in healthy subjects (Figure 6-14 and Table 6-18). The strongest effects were estimated in a subgroup  
7 of infants with asthmatic mothers (Triche et al., 2006, [093274](#)). Triche et al. (2006, [093274](#))  
8 followed 691 infants in southwestern VA followed for 83 days between June and August of 1995  
9 and/or 1996 and found that a 20-ppb increase in lag 0 of 24-h avg O<sub>3</sub> was associated with odds ratios  
10 (95% CI) of 2.34 (1.02, 5.37) for wheeze and of 3.63 (1.81, 7.28) for difficulty breathing among the  
11 61 infants with asthmatic mothers. In analyses that included all subjects, the estimated effects were  
12 smaller and statistically nonsignificant. Odds ratios increased in magnitude in co-pollutant models  
13 that included PM<sub>2.5</sub> or PM<sub>10-2.5</sub>. While these results suggested that children with asthmatic mothers  
14 may be at greater risk of O<sub>3</sub>-related respiratory morbidity, the authors acknowledged that mothers  
15 with asthma may be more likely to report symptoms in their children and that transient wheeze in  
16 infants and may not predict respiratory morbidity later in life. Gold et al. (1999, [086919](#)) reported an  
17 association between ambient O<sub>3</sub> exposure and phlegm in children in Mexico, City; however, they  
18 acknowledged being unable to distinguish between the effects of O<sub>3</sub> and PM<sub>2.5</sub> exposure. Several  
19 other studies of school-aged children reported null or negative associations between ambient O<sub>3</sub>  
20 exposure and respiratory symptoms (Hoek and Brunekreef, 1995, [046184](#); Moon et al., 2009,  
21 [190297](#); Rodriguez et al., 2007, [092842](#)). In a large study of 696 children (ages <13 years) in 4  
22 regions in South Korea, Moon et al. (2009, [190297](#)) observed a positive association with LRS  
23 (cough, phlegm, or wheeze) in the region of Jeju island (OR: 1.08 [95% CI: 0.96, 1.21] per 30 ppb  
24 increase in lag 0 8-h avg O<sub>3</sub>); however, the odds ratios were lower close to 1.0 in other cities and  
25 analyses with other symptoms. In a cross-sectional study of 4,200 adult workers from 100 office  
26 buildings across the U.S., O<sub>3</sub> was positively associated with building-related URS (nasal congestion  
27 or sore throat) and LRS (wheeze, shortness of breath, or chest tightness) (Apte et al., 2008, [195865](#)).  
28 Investigators suggested that the findings may have been attributable to formaldehyde and organic  
29 acids produced from O<sub>3</sub>-initiated reactions within buildings; however, additional data on indoor  
30 levels of volatile organic compounds, indoor O<sub>3</sub>, and infiltration rates would likely be required to  
31 characterize the relationship between ambient O<sub>3</sub> concentrations and building-related symptoms.



**Figure 6-14. Associations of ambient ozone exposure with respiratory symptoms in studies not restricted to asthmatic populations. LRS = lower respiratory symptoms. Effect estimates are standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg ozone, respectively. Effect estimates depicted as black circles are from single-pollutant models, and effect estimates depicted as open circles are from co-pollutant models.**

**Table 6-18. Additional characteristics and quantitative data for studies presented in Figure 6-14.**

Study	Location/ Population	O <sub>3</sub> Lag	O <sub>3</sub> Averaging Time	Outcome	Subgroup	Odds Ratio (95% CI) <sup>a</sup>
Triche et al. (2006, <a href="#">093274</a> )	southwestern VA Infants	0	8-h max	Wheeze	All subjects	1.60 (0.85, 3.0)
					With asthmatic mothers	1.79 (1.05, 3.05) 2.34 (1.02, 5.37) 2.99 (1.44, 6.23) with PM <sub>2.5</sub>
Linn et al. (1996, <a href="#">082508</a> )	3 southern CA communities Children	0	24-h avg	Evening symptom score		0.38 (0.11, 1.29)
Gold et al. (1999, <a href="#">086919</a> )	Mexico City, Mexico Children	1	24-h avg	Phlegm		1.04 (1.00, 1.07)
Hoek and Brunekreef (1995, <a href="#">046184</a> )	Deurne and Enkhuizen, Netherlands Children	0	1-h max	Cough		0.95 (0.85, 1.06)
Moon et al. (2009, <a href="#">190297</a> )	4 cities, South Korea Children	0	24-h avg	LRS		0.96 (0.90, 1.03)
Apte et al. (2008, <a href="#">195865</a> )	Multiple U.S. cities Office building workers	0	24-h avg	LRS		1.30 (1.00, 1.70)

LRS = Lower respiratory symptoms

<sup>a</sup>Effect estimates were standardized to a 40-, 30-, and 20-ppb increase for 1-h max, 8-h max, and 24-h avg O<sub>3</sub>, respectively.

### 6.2.4.2. Summary of Epidemiologic Studies of Respiratory Symptoms and Asthma Medication Use

- 1 With a majority of investigation focused on asthmatic subjects, most studies find that short-
- 2 term ambient O<sub>3</sub> exposure is positively associated with respiratory symptoms and asthma medication

1 use. While evidence for effects on school absenteeism is less compelling, there is some evidence that  
2 short-term O<sub>3</sub> exposure is associated with reduced activity levels among asthmatics. Although  
3 studies were limited in number, O<sub>3</sub> was positively associated with respiratory symptoms in infants  
4 with family history of asthma and office building workers (Apte et al., 2008, [195865](#); Triche et al.,  
5 2006, [093274](#)).

6 Collectively, studies examined associations with single-day O<sub>3</sub> concentrations lagged from 0 to  
7 5 days as well concentrations averaged over 2 to 19 days. While lag 0 O<sub>3</sub> exposures were  
8 consistently associated with respiratory symptoms, several studies that examined a range of exposure  
9 lags found larger effect estimates for multiday averages (3-day to 6-day) of O<sub>3</sub> exposure (Escamilla-  
10 Nuñez et al., 2008, [594284](#); Just et al., 2002, [035429](#); Mortimer et al., 2002, [030281](#); Rabinovitch et  
11 al., 2004, [096753](#); Romieu et al., 2006, [090969](#); Ross et al., 2002, [042749](#)). These findings for  
12 multiday average of O<sub>3</sub> exposure indicate that exposures accumulated over several days may be  
13 important or may be subject to less measurement error. In the limited analysis of confounding by  
14 co-pollutants, O<sub>3</sub> effect estimates showed small changes in magnitude but little change in statistical  
15 significance (Escamilla-Nuñez et al., 2008, [594284](#); O'Connor et al., 2008, [156818](#); Triche et al.,  
16 2006, [093274](#)).

17 Several recent studies concurrently examined associations of ambient O<sub>3</sub> exposure with  
18 respiratory symptoms and lung function and reported conflicting associations whether evaluated at  
19 the same or different lag of exposure. Associations were generally stronger for respiratory symptoms  
20 than for lung function (Khatri et al., 2009, [594282](#); Rabinovitch et al., 2004, [096753](#); Romieu et al.,  
21 2006, [090969](#)). These findings suggest that O<sub>3</sub>-associated respiratory morbidity may occur via  
22 multiple mechanisms with varying time courses of action, and the examination of a limited number  
23 of exposure lags in these aforementioned studies may explain some of the inconsistencies in  
24 associations of O<sub>3</sub> exposure with different respiratory health endpoints.

### 6.2.5. Lung Host Defenses

25 The mammalian respiratory tract has a number of closely integrated defense mechanisms that,  
26 when functioning normally, provide protection from the adverse effects of a wide variety of inhaled  
27 particles and microbes. For simplicity, these interrelated defenses can be divided into two major  
28 parts: (1) nonspecific (transport and phagocytosis) and (2) specific (immunologic) defense  
29 mechanisms. A variety of sensitive and reliable methods have been used to assess the effects of O<sub>3</sub>  
30 on these components of the lung's defense system to provide a better understanding of the health  
31 effects associated with the inhalation of this pollutant. The previous O<sub>3</sub> AQCD (U.S. EPA, 2006,  
32 [088089](#)) states that animal toxicological studies provide extensive evidence that acute O<sub>3</sub> exposures  
33 as low as 0.08 to 0.5 ppm can cause increases in susceptibility to infectious diseases due to  
34 modulation of lung host defenses. This section discusses the various components of host defenses,  
35 such as the mucociliary escalator, the phagocytic and regulatory role of the alveolar macrophages  
36 (AMs), the adaptive immune system, and integrated mechanisms that are studied by investigating the  
37 host's response to experimental pulmonary infections.

### 6.2.5.1. Mucociliary Clearance

1 The mucociliary system is one of the lung's primary defense mechanisms. It protects the  
2 conducting airways by trapping and quickly removing material that has been deposited or is being  
3 cleared from the alveolar region by migrating alveolar macrophages. Ciliary movement directs  
4 particles trapped on the overlying mucous layer toward the pharynx, where the mucus is swallowed  
5 or expectorated.

6 The effectiveness of mucociliary clearance can be determined by measuring such biological  
7 activities as the rate of transport of deposited particles; the frequency of ciliary beating; structural  
8 integrity of the ciliated cells; and the size, number, and distribution of mucus-secreting cells. Once  
9 this defense mechanism has been altered, a buildup of both viable and nonviable inhaled substances  
10 can occur on the epithelium and may jeopardize the health of the host, depending on the nature of the  
11 uncleared substance. Impaired mucociliary clearance can result in an unwanted accumulation of  
12 cellular secretions, increased infections, chronic bronchitis, and complications associated with  
13 chronic obstructive pulmonary disease. A number of previous studies with various animal species  
14 have examined the effect of O<sub>3</sub> exposure on mucociliary clearance and reported morphological  
15 damage to the cells of the tracheobronchial tree from acute and sub-chronic exposure to 0.20 up to  
16 1.0 ppm of O<sub>3</sub>. The cilia were either completely absent or had become noticeably shorter or blunt.  
17 After placing these animals in a clean-air environment, the structurally damaged cilia regenerated  
18 and appeared normal (U.S. EPA, 1986, [017607](#)). Based on such morphological observations, related  
19 effects such as ciliostasis, increased mucus secretions, and a slowing of mucociliary transport rates  
20 might be expected. However, no measurable changes in ciliary beating activity have been reported  
21 due to O<sub>3</sub> exposure alone. Essentially no data are available on the effects of prolonged exposure to  
22 O<sub>3</sub> on ciliary functional activity or on mucociliary transport rates measured in the intact animal. In  
23 general, functional studies of mucociliary transport have observed a delay in particle clearance soon  
24 after acute exposure. Decreased clearance is more evident at higher doses (1 ppm), and there is some  
25 evidence of tolerance/adaptation for these effects (U.S. EPA, 1986, [017607](#)). However, no recent  
26 studies have evaluated the effects of O<sub>3</sub> on mucociliary clearance.

### 6.2.5.2. Alveolobronchiolar Transport Mechanism

27 In addition to the transport of particles deposited on the mucous surface layer of the  
28 conducting airways, particles deposited in the deep lung may be removed either up the respiratory  
29 tract or through interstitial pathways to the lymphatic system. The pivotal mechanism of  
30 alveolobronchiolar transport involves the movement of alveolar macrophages (AMs) with  
31 phagocytized particles to the bottom of the mucociliary escalator. Failure of the AMs to phagocytize  
32 and sequester the deposited particles from the vulnerable respiratory membrane can lead to particle  
33 entry into the interstitial spaces. Once lodged in the interstitium, particle removal is more difficult  
34 and, depending on the toxic or infectious nature of the particle, its interstitial location may allow the  
35 particle to set up a focus for pathologic processes. Although some studies show reduced early

1 (tracheobronchial) clearance after O<sub>3</sub> exposure, late (alveolar) clearance of deposited material is  
2 accelerated, presumably due to macrophage influx (which in itself can be damaging due to proteases  
3 and oxidative reactions in these cells). In an important older study investigating the effects of longer  
4 term O<sub>3</sub> exposure on alveolobronchiolar clearance, rats were exposed to an urban pattern of O<sub>3</sub>  
5 (continuous 0.06 ppm, 7 days/week with a slow rise to a peak of 0.25 ppm and subsequent decrease  
6 to 0.06 ppm over a 9 h period for 5 days/week) for 6 weeks and were exposed 3 days later to  
7 chrysotile asbestos, which can cause pulmonary fibrosis and neoplasia (Pinkerton et al., 1989,  
8 [042102](#)). After 30 days, the lungs of the O<sub>3</sub>-exposed animals had twice the number and mass of  
9 asbestos fibers as the air-exposed rats. New evaluations of O<sub>3</sub> effects on alveolar clearance have not  
10 been performed.

### 6.2.5.3. Alveolar Macrophages

11 Within the gaseous exchange region of the lung, the first line of defense against  
12 microorganisms and nonviable particles that reach the alveolar surface is the AM. This resident  
13 phagocyte is responsible for a variety of activities, including the detoxification and removal of  
14 inhaled particles, maintenance of pulmonary sterility, and interaction with lymphocytes for  
15 immunologic protection. Under normal conditions, AMs seek out particles deposited on the alveolar  
16 surface and ingest them, thereby sequestering the particles from the vulnerable respiratory  
17 membrane. To adequately fulfill their defense function, the AMs must maintain active mobility, a  
18 high degree of phagocytic activity, and an optimally functioning biochemical and enzyme system. As  
19 discussed in previous AQCDs, short periods of O<sub>3</sub> exposure can cause a reduction in the number of  
20 free AMs available for pulmonary defense, and these AMs are more fragile, less phagocytic, and  
21 have decreased lysosomal enzyme activities. In results from earlier work in rabbits, a 2 h exposure to  
22 0.1 ppm O<sub>3</sub> inhibited phagocytosis and a 3 h exposure to 0.25 ppm decreased lysosomal enzyme  
23 activities (Driscoll et al., 1987, [040803](#); Hurst et al., 1970, [015591](#)). Effects on in vitro viability of  
24 AM were observed at 0.06 ppm (Weissbecker et al., 1969, [015806](#)). A few recent studies have  
25 evaluated ozone's effects on macrophage function. At 1 and 24 h after a 4 h exposure of marine toads  
26 (*Bufo marinus*) to 0.8 ppm O<sub>3</sub>, macrophages exhibited reduced in vitro capacity to phagocytize  
27 fluorescent polystyrene microspheres. However, this effect did not persist at 48 h postexposure and  
28 exposure did not affect yields of pulmonary macrophages (Dohm et al., 2005, [180452](#)). In another  
29 study, in vitro exposure to 0.03 ppm O<sub>3</sub> for five minutes significantly decreased macrophage-like cell  
30 mobility in response to pathogen-related chemotactic stimulation (Klestadt et al., 2005, [130425](#)).  
31 Additionally, O<sub>3</sub> mediated oxidation of surfactant proteins reduced their ability to enhance  
32 phagocytosis of both gram-positive and gram-negative bacteria by macrophages (Mikerov et al.,  
33 2008, [596405](#)). A single controlled human exposure study reviewed in the 1996 O<sub>3</sub> AQCD found  
34 decrements in the ability of alveolar macrophages to phagocytize microorganisms upon exposure to  
35 0.08 to 0.1 ppm O<sub>3</sub> for 6.6 h during moderate exercise (Devlin et al., 1991, [040359](#)).

36 Collectively, these studies demonstrate that O<sub>3</sub> can affect multiple steps or aspects required for  
37 proper macrophage function.

## 6.2.5.4. Infection and Adaptive Immunity

### ***General Effects on the Immune System***

1 The effects of O<sub>3</sub> on the immune system are complex and dependent on the exposure regimen  
2 and the observation period. It appears that the T-cell-dependent functions of the immune system are  
3 more affected than B-cell-dependent functions (U.S. EPA, 2006, [088089](#)). Generally, there is an  
4 early immunosuppressive effect that subsides with continued O<sub>3</sub> exposure, resulting in either a return  
5 to normal responses or an enhancement of immune responses. However, this is not always the case  
6 as Aranyi (1983, [040512](#)) showed decreased T-cell mitogen reactions in mice after chronic (90-day)  
7 exposure to 0.1 ppm O<sub>3</sub>. Earlier studies report changes in cell populations in lymphatic tissues  
8 (U.S. EPA, 2006, [088089](#)). A more recent study in mice demonstrated that numbers of certain T cell  
9 subsets in the spleen were reduced after exposure to 0.6 ppm O<sub>3</sub> (10h/day x 15d) (Feng et al., 2006,  
10 [596381](#)).

11 O<sub>3</sub> has also been found to alter responses to antigenic stimulation. For example, antibody  
12 responses to a T-cell-dependent antigen were suppressed after a 56-day exposure of mice to 0.8 ppm  
13 O<sub>3</sub>, and a 14-day exposure to 0.5 ppm O<sub>3</sub> decreased the antiviral antibody response following  
14 influenza virus infection (Jakab and Hmieleski, 1988, [041806](#)); the latter impairment may pave the  
15 way for lowered resistance to reinfection. The immune response is highly influenced by the temporal  
16 relationship between O<sub>3</sub> exposure and antigenic stimulation. When O<sub>3</sub> exposure preceded *Listeria*  
17 infection, there were no effects on delayed-type hypersensitivity or splenic lymphoproliferative  
18 responses; however, when O<sub>3</sub> exposure occurred during or after *Listeria* infection was initiated, these  
19 immune responses were suppressed (van Loveren et al., 1988, [041847](#)). In another study, a reduction  
20 in mitogen activated T-cell proliferation was observed after exposure to 0.6 ppm for 15 d, and could  
21 be ameliorated by antioxidant supplementation. Antigen-specific proliferation decreased by 60%,  
22 indicating attenuation of the acquired immunity needed for subsequent memory responses (Feng et  
23 al., 2006, [596381](#)). Generally, continuous exposure to O<sub>3</sub> impairs immune responses for the first  
24 several days of exposure, followed by an adaptation to O<sub>3</sub> that allows a return of normal immune  
25 responses. Most species show little effect of O<sub>3</sub> exposures prior to immunization, but show a  
26 suppression of responses to antigen in O<sub>3</sub> exposures post-immunization. In a recent study, exposure  
27 of mice to 0.6 ppm O<sub>3</sub> skewed the ex-vivo cytokine responses elicited by non-specific stimulation  
28 toward inflammation, decreasing IL-2 and increasing IFN- $\gamma$  (Feng et al., 2006, [596381](#)).

### ***Models of Microbial Infection***

#### *Bacterial infection*

29 A relatively large body of evidence shows that O<sub>3</sub> increases susceptibility to bacterial  
30 infections. Known contributing factors are impaired mucociliary streaming, altered  
31 chemotaxis/motility, defective phagocytosis of bacteria, decreased production of lysosomal enzymes  
32 or superoxide radicals by alveolar macrophages, and decreased IFN- $\gamma$  levels. In animal models of

1 bacterial infection, exposure to 0.08 ppm O<sub>3</sub> increases mortality, regardless of whether O<sub>3</sub> exposure  
2 precedes or follows infection. Exercise and co-pollutants can enhance ozone's effects in infectivity  
3 models. Recent studies in mice continue to demonstrate increased susceptibility to experimental  
4 infectious pneumonia with exposure to O<sub>3</sub>, albeit at high levels (2 ppm) (Mikero et al., 2008,  
5 [597493](#); Mikerov et al., 2008, [201537](#)).

#### *Viral infection*

7 Only a few studies, described in previous AQCDs, have examined the effects of O<sub>3</sub> exposure  
8 on the outcome of viral respiratory infection. Some studies show increased mortality, while others  
9 show diminished severity and increased survival time. In vitro cell culture studies of human  
10 bronchial epithelial cells indicate O<sub>3</sub>-induced exacerbation of human rhinovirus infection  
11 (Spannhake et al., 2002, [030637](#)). New studies on the interactions of O<sub>3</sub> and viral infections have not  
12 been published. Natural killer (NK) cells, which destroy virally infected cells and tumors in the lung,  
13 appear to be inhibited by higher doses of O<sub>3</sub> and either unaffected or stimulated at lower doses.  
14 Several studies show decreases in NK cell activity following acute exposures ranging from 0.8 to  
15 1 ppm (Burlison et al., 1989, [042214](#); Gilmour and Jakab, 1991, [042391](#); Van Loveren et al., 1990,  
16 [042264](#)). However, Van Loveren et al. (1990, [042264](#)) showed that a 1-week exposure to 0.2 or  
17 0.4 ppm O<sub>3</sub> increased NK cell activity, and an urban pattern of exposure (base of 0.06 ppm with  
18 peaks of 0.25 ppm) had no effect on NK cell activity after 1, 3, 13, 52, or 78 weeks of exposure  
19 (Selgrade et al., 1990, [042363](#)). A more recent study demonstrated a 35% reduction in NK cell  
20 activity after exposure of mice to 0.6 ppm O<sub>3</sub> (10h/day x 15d) (Feng et al., 2006, [596381](#)). The  
21 defective IL-2 production demonstrated in this study may impair NK cell activation. Alternatively,  
22 NK cell surface charge may be altered by ROS, decreasing their adherence to target cells (Nakamura  
23 and Matsunaga, 1998, [625133](#)).

### 6.2.6. Allergic and Asthma-Related Responses

24 Effects resulting from combined exposures to O<sub>3</sub> and allergens have been studied in a variety  
25 of animal species, generally as models of experimental asthma. Pulmonary function and airways  
26 hyperresponsiveness in animal models of asthma are discussed in Sections 6.2.1.7 and 6.2.2.2.  
27 Previous evidence indicates that O<sub>3</sub> exposure skews immune responses toward an allergic phenotype.  
28 For example, Gershwin et al. (1981, [039729](#)) reported that O<sub>3</sub> (0.8 and 0.5 ppm for 4 days) exposure  
29 caused a 34-fold increase in the number of IgE (allergic antibody)-containing cells in the lungs of  
30 mice. In general, the number of IgE-containing cells correlated positively with levels of anaphylactic  
31 sensitivity. In humans, allergic rhinoconjunctivitis symptoms are associated with increases in  
32 ambient O<sub>3</sub> concentrations (Riediker et al., 2001, [051776](#)). Five weeks of continuous exposure to  
33 0.4 ppm O<sub>3</sub> (but not 0.1 or 0.2 ppm O<sub>3</sub>) augmented sneezing and nasal secretions in a guinea pig  
34 model of nasal allergy. Nasal eosinophils and allergic antibody levels in serum were also elevated by  
35 exposure to concentrations as low as 0.2 ppm (Iijima and Kobayashi, 2004, [596389](#)). Short-term  
36 exposure (2 days) to 1 ppm O<sub>3</sub> exacerbated allergic rhinitis and lower airway allergic inflammation

1 in Brown Norway rats, a rat strain that is comparatively less sensitive to O<sub>3</sub> than other rats or humans  
2 (Wagner et al., 2007, [596420](#); Wagner et al., 2009, [201574](#)). OVA-sensitized rats were intranasally  
3 challenged with OVA on days 1 and 2, and exposed to 0 or 1 ppm O<sub>3</sub> (8 h/day) on days 4 and 5.  
4 Analysis at day 6 indicated that O<sub>3</sub> exposure enhanced intraepithelial mucosubstances in the nose  
5 and airways, induced cys-LTs, MCP-1, and IL-6 production in BALF, and upregulated expression of  
6 the proallergic cytokines IL-5 and IL-13. These changes were not evident in non-allergic controls.  
7 All of these responses were blunted by gamma-tocopherol (γT; vitamin E) therapy. γT neutralizes  
8 oxidized lipid radicals, and protects lipids and proteins from nitrosative damage from NO-derived  
9 metabolites. Farraj et al. (2010, [380846](#)) exposed allergen-sensitized adult male BALB/c mice to  
10 0.5 ppm O<sub>3</sub> for 5 hours once per week for 4 weeks. Ozone exposure and O<sub>3</sub>/DEP (2.0 mg/m<sup>3</sup>) co-  
11 exposure of OVA-sensitized mice elicited significantly greater serum IgE levels than in DEP-  
12 exposed OVA-sensitized mice (98% and 89% increases, respectively). Ozone slightly enhanced  
13 levels of BAL IL-5, but despite increases in IgE, caused a significant decrease in BAL IL-4 levels.  
14 IL-10, IL-13, and IFN-γ levels were unaffected. In addition to ozone's pro-allergic effects, it could  
15 also make airborne allergens more allergenic. When combined with NO<sub>2</sub>, O<sub>3</sub> has been shown to  
16 enhance nitration of common protein allergens, which may increase their allergenicity (Franze et al.,  
17 2005, [066088](#)).

## 6.2.7. Hospital Admissions, Emergency Department Visits, and Physicians Visits

### 6.2.7.1. Summary of Findings from 2006 Ozone AQCD

18 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) evaluated numerous respiratory ED visits and  
19 hospital admissions studies, which consisted primarily of time-series studies conducted in the U.S.,  
20 Canada, Europe, South America, Australia and Asia. Upon collectively evaluating the scientific  
21 evidence, the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) concluded that “the overall evidence  
22 supports a causal relationship between acute ambient O<sub>3</sub> exposures and increased respiratory  
23 morbidity resulting in increased ED visits and [hospital admissions] during the warm season”  
24 (U.S. EPA, 2006, [088089](#)). This conclusion is “strongly supported by the human clinical, animal  
25 toxicologic[al], and epidemiologic evidence for [O<sub>3</sub>-induced] lung function decrements, increased  
26 respiratory symptoms, airway inflammation, and airway hyperreactivity” (U.S. EPA, 2006, [088089](#)).

27 Since the completion of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), relatively fewer  
28 studies conducted in the U.S., Canada, and Europe have examined the association between short-  
29 term exposure to ambient O<sub>3</sub> and respiratory hospital admissions and ED visits, but a growing  
30 number of studies have been conducted in Asia. This section focuses primarily on multicity studies  
31 because they examine the effect of O<sub>3</sub> on respiratory-related hospital admissions and ED visits over a  
32 large geographic area using a consistent statistical methodology. Single-city studies that encompass a  
33 large number of hospital admissions or ED visits, or included a long study-duration were also

1 evaluated because these studies have more power to detect whether an association exists between  
2 short-term exposure to O<sub>3</sub> and respiratory hospital admissions and ED visits compared to smaller  
3 single-city studies. Additional single-city studies were also evaluated within this section, if they were  
4 conducted in locations not represented by the larger single-city and multicity studies, or examined  
5 population-specific characteristics not included in the larger studies that may modify the association  
6 between short-term exposure to O<sub>3</sub> and respiratory-related hospital admissions or ED visits. The  
7 remaining single-city studies identified were not evaluated in this section due to factors such as  
8 inadequate study design or insufficient sample size.

9         It should be mentioned that when examining the association between short-term O<sub>3</sub> exposure  
10 and respiratory health effects that require medical attention, it is important to distinguish between  
11 hospital admissions and ED visits. This is because it is likely that a small percentage of respiratory  
12 ED visits will be admitted to the hospital; therefore, respiratory ED visits may represent potentially  
13 less serious, but more common outcomes. As a result, in the following sections respiratory hospital  
14 admission and ED visit studies are evaluated individually. Additionally, within each section, results  
15 are presented as either a collection of respiratory diagnoses or as individual diseases (e.g., asthma,  
16 COPD, pneumonia and other respiratory infections) in order to evaluate the potential effect of short-  
17 term O<sub>3</sub> exposure on each respiratory-related outcome. Table 6-19 presents the studies discussed  
18 within this section along with the air quality characteristics of the city, or across all cities, included in  
19 each study.

**Table 6-19. Mean and upper percentile concentrations of respiratory-related hospital admission and emergency department visit studies evaluated**

Study	Location	Type of Visit (ICD9/10)	Metric	Mean Concentration (ppb) <sup>a</sup>	Range of Concentrations (ppb) <sup>a</sup>
Katsouyanni et al. (2009, <a href="#">199899</a> ) <sup>b,c</sup>	90 U.S. cities (NMMAPS) <sup>d</sup> 32 European cities (APHEA) <sup>d</sup> 12 Canadian cities	Hospital Admissions: NMMAPS: All respiratory (460-519) APHEA: All respiratory (460-519) 12 Canadian cities: All respiratory (460-519) <sup>e</sup>	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: 8.9-12.4
Cakmak et al. (2006, <a href="#">093272</a> )	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, <a href="#">087395</a> ) <sup>c</sup>	4 Italian cities <sup>f</sup>	Hospital Admissions: All respiratory (460-519)	8-h max	Warm season <sup>g</sup> : 5.7-60.0	95th: 86.1-90.0 <sup>n</sup> Max: 107.5-115.1
Dales et al. (2006, <a href="#">090744</a> )	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. (2008, <a href="#">195856</a> )	11 New York regions	Hospital Admissions: Respiratory diseases (466, 490-493, 496)	8-h max <sup>i</sup>	44.1	75th: 54.0 Max: 217.0
Wong et al. (2009, <a href="#">196722</a> ) <sup>c</sup>	Hong Kong	Hospital Admissions: All respiratory (460-519) COPD (490-496) Acute respiratory diseases (460-466, 480-487)	8-h max <sup>i</sup>	18.8	75th: 25.9 Max: 100.3
Medina-Ramon et al. (2006, <a href="#">087721</a> ) <sup>j</sup>	36 U.S. cities	Hospital Admissions: COPD (490-496, excluding 493) Pneumonia (480-487)	8-h max	Warm season <sup>g</sup> : 45.8 Cool season: 27.6	NR
Yang et al. (2005, <a href="#">090184</a> ) <sup>k</sup>	Vancouver, Canada	Hospital Admissions: COPD (490-492, 494, 496)	24-h avg	All year: 14.1 Winter: 13.2 Spring: 19.4 Summer: 13.8 Fall: 10.0	Max: 38.6
Zanobetti and Schwartz (2006, <a href="#">090195</a> )	Boston, MA	Hospital Admissions: Pneumonia (480-487)	24-h avg	22.4 <sup>b</sup>	75th: 31.0 95th: 47.6
Silverman and Ito (2010, <a href="#">386252</a> )	New York, NY	Hospital Admissions: Asthma (493)	8-h max	Warm <sup>l</sup> : 41.0 <sup>b</sup>	75th: 53 90th: 68
Stieb et al. (2009, <a href="#">195858</a> )	7 Canadian cities	Emergency Department 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, <a href="#">090316</a> ) <sup>m</sup>	Atlanta, GA	Emergency Department 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	53.0	75th: 67.0 90th: 82.1 Max: 147.5
Darrow et al. (2011, <a href="#">202800</a> )	Atlanta, GA	Emergency Department Visits: All respiratory (460-466, 477, 480-486, 491, 492, 493, 496, 786.09)	8-h max 1-h max 24-h avg Commute Day-time Night-time	8-h max: 53 1-h max: 62 24-h avg: 30 Commute: 35 <sup>n</sup> Day-time: 45 <sup>n</sup> Night-time: 14 <sup>n</sup>	8-h max: 75th: 67 24-h avg: 148 1-h Commute: 75th: 45 Max: 106 76 Max: 180 Day-time: 75th: 58 Max: 123 Night-time: 75th: 22 Max: 64
Ito et al. (2007, <a href="#">156594</a> )	New York, NY	Emergency Department Visits: Asthma (493)	8-h max	All year: 30.4 Warm months <sup>o</sup> : 42.7 Cold months: 18.0	All year: 95th: 68.0 Warm months: 95th: 77.0 Cold months: 95th: 33.0
Strickland et al. (2010, <a href="#">624878</a> )	Atlanta, GA	Emergency Department Visits: Asthma (493) Wheeze (786.07, 786.09)	8-h max	All year: 45.4 <sup>p</sup> Warm <sup>l</sup> : 55.2 <sup>p</sup> Cold <sup>q</sup> : 34.5 <sup>p</sup>	NR
Arbex et al. (2009, <a href="#">184334</a> )	Sao Paulo, Brazil	Emergency Department Visits: COPD (J40-44)	1-h max	48.8	75th: 61.0 Max: 143.8

Study	Location	Type of Visit (ICD9/10)	Metric	Mean Concentration (ppb) <sup>a</sup>	Range of Concentrations (ppb) <sup>a</sup>
<a href="#">Orazzo et al. (2009, 202801)<sup>c</sup></a>	6 Italian cities	Emergency Department Visits: Wheezing	8-h max <sup>r</sup>	Summer <sup>s</sup> : 21.1-44.3 Winter: 11.5-27.9	NR
<a href="#">Burra et al. (2009, 195868)</a>	Toronto, Canada	Physician Visits: Asthma (493)	1-h max	33.3	95th: 66 Max: 121
<a href="#">Villeneuve et al. (2006, 091179)</a>	Toronto, Canada	Physician Visits: Allergic rhinitis (177)	8-h max	30.0	Max: 98.7
<a href="#">Sinclair et al. (2010, 386271)<sup>s</sup></a>	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

<sup>a</sup>Some studies did not present an overall value for the mean, middle and/or upper percentiles of the O<sub>3</sub> 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.

<sup>b</sup>Study only presented median concentrations.

<sup>c</sup>Study presented concentrations as µg/m<sup>3</sup>. Concentration was converted to ppb using the conversion factor of 0.51 assuming standard temperature (25°C) and pressure (1 atm).

<sup>d</sup>A 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.

<sup>e</sup>Hospital 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.

<sup>f</sup>Only 4 of the 8 cities included in the study collected O<sub>3</sub> data.

<sup>g</sup>Warm season defined as May-September.

<sup>h</sup>95th percentile only presented for 3 of the 5 cities with O<sub>3</sub> data.

<sup>i</sup>O<sub>3</sub> measured from 10:00 a.m. to 6:00 p.m.

<sup>j</sup>Only 35 of the 36 cities included in the analysis had O<sub>3</sub> data.

<sup>k</sup>Study defined seasons as Winter (January-March), Spring (April-June); Summer (July-September), and Fall (October-December).

<sup>l</sup>Study only examined warm months (April-August).

<sup>m</sup>Study only examined warm months (April-October).

<sup>n</sup>Commute (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.).

<sup>o</sup>Warm/Summer months defined as April-September.

<sup>p</sup>Means represent population-weighted O<sub>3</sub> concentrations.

<sup>q</sup>Warm months defined as May-October and Cold months defined as November-April.

<sup>r</sup>O<sub>3</sub> measured from 8:00 a.m. to 4:00 p.m.

<sup>s</sup>This 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 O<sub>3</sub>, and daily respiratory-related  
2 hospital admissions has primarily been examined using all respiratory-related hospital admissions  
3 within the range of ICD-9 codes 460-519. Newly identified studies attempt to further examine the  
4 effect of O<sub>3</sub> exposure on respiratory-related hospital admissions through a multicity design that  
5 examines O<sub>3</sub> effects across countries using a standardized methodology; multicity studies that  
6 examine effects within one country; and multi- and single-city studies that attempt to examine  
7 potential modifiers of the O<sub>3</sub>-respiratory-related hospital admission relationship.

8 The Air Pollution and Health: A European and North American Approach (APHENA) study  
9 combined data from existing multicity study databases from Canada, Europe (APHEA2)  
10 (Katsouyanni et al., 2001, [019008](#)), and the U.S. (NMMAPS) (Samet et al., 2000, [010269](#)) in order  
11 to “develop more reliable estimates of the potential acute effects of air pollution on human health  
12 [and] provide a common basis for [the] comparison of risks across geographic areas” (Katsouyanni

1 et al., 2009, [199899](#)). In an attempt to address both of these issues, the investigators conducted  
2 extensive sensitivity analyses to evaluate the robustness of the results to different model  
3 specifications (e.g., penalized splines [PS] versus natural splines [NS]) and the extent of smoothing  
4 to control for seasonal and temporal trends. The trend analyses consisted of subjecting the models to  
5 varying extent of smoothing selected either a priori (e.g., 3 df/year, 8 df/year, and 12 df/year) or by  
6 using the absolute sum of the residuals of the partial autocorrelation function (PACF). However, the  
7 investigators did not identify the model they deemed to be the most appropriate for comparing the  
8 results across study locations. As a result, when discussing the results across the three study locations  
9 below, the 8 df/year results are presented for both the PS and NS models because: (1) 8 df/year is  
10 most consistent with the extent of temporal adjustment used in previous and recent large multicity  
11 studies in the U.S. (e.g., NMMAPS); (2) the risk estimates for 8 df/year and 12 df/year are  
12 comparable for all three locations; (3) the models that used the PACF method did not report the  
13 actual degrees of freedom chosen; and (4) the 3 df/year and the PACF method resulted in negative O<sub>3</sub>  
14 risk estimates, which is inconsistent with the results obtained using more aggressive seasonal  
15 adjustments. Additionally, when comparing results across studies in figures, only the results from  
16 one of the spline models (e.g., NS) is presented because it has been previously demonstrated that  
17 alternative spline models result in relatively similar effect estimates (Health Effects Institute, 2003,  
18 [042829](#)). However, it should be noted that the underlying data and model specifications could result  
19 in varying degrees of bias and precision in effect estimates with different spline models (Ostro et al.,  
20 2006, [087991](#)).

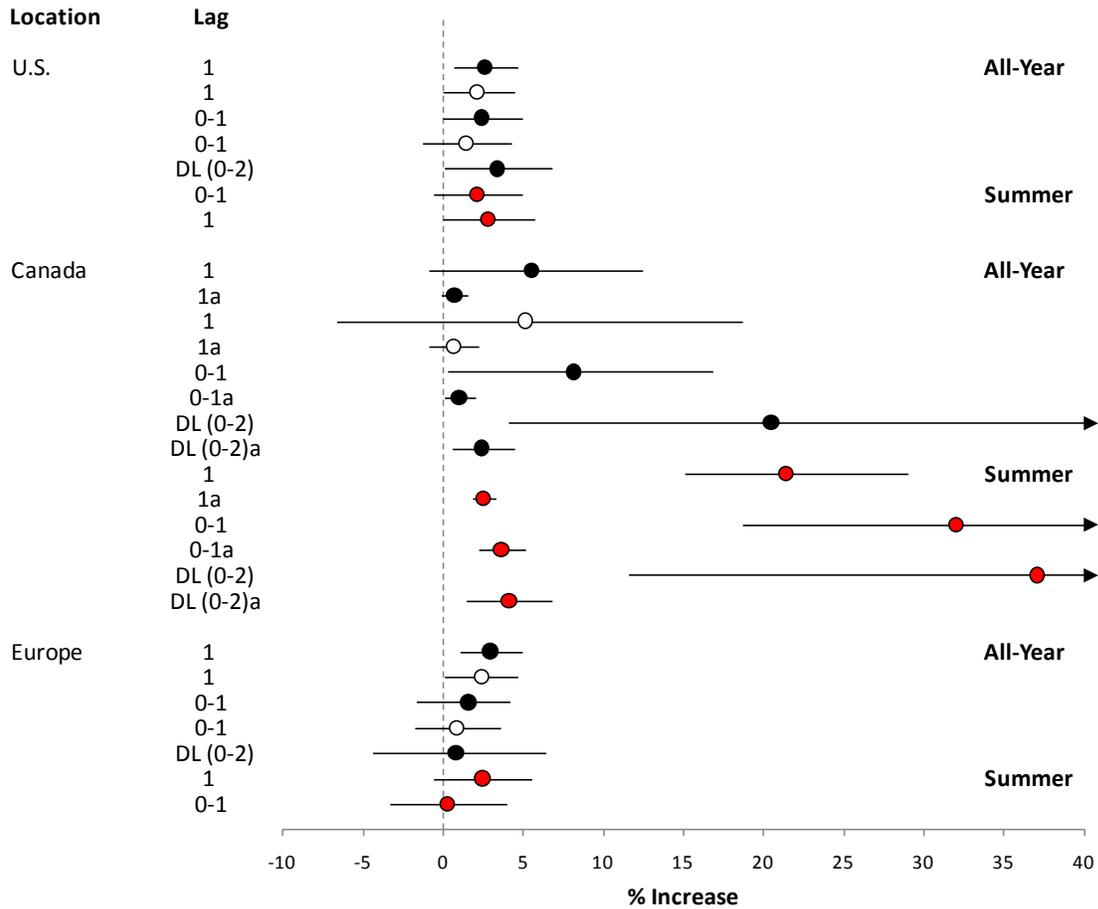
21 Katsouyanni et al. (2009, [199899](#)) examined respiratory hospital admissions (ICD-9: 460-519)  
22 for people aged 65 years and older using 1-h max O<sub>3</sub> data. The extent of hospital admission and O<sub>3</sub>  
23 data varied across the 3 datasets: Canadian dataset included 12 cities with data for 3 years  
24 (1993-1996) per city; European dataset included 8 cities with each city having data for between 2  
25 and 8 years from 1988-1997; and U.S. dataset included 14 cities with each city having data for  
26 between 4 and 10 years from 1985-1994 and 7 cities having only summer O<sub>3</sub> data. The investigators  
27 used a three-stage hierarchical model to account for within-city, within region, and between region  
28 variability. Results were presented individually for each region (Figure 6-15; Table 6-20). Ozone and  
29 PM<sub>10</sub> concentrations were weakly correlated in all locations in the summer ( $r=0.27-0.40$ ), but not in  
30 the winter. In the Canadian cities, using all-year data, a 40-ppb increase in 1-h max O<sub>3</sub>  
31 concentrations at lag 0-1 was associated with an increase in respiratory hospital admissions of 8.9%  
32 (95% CI: 0.79, 16.8%) in a PS model and 8.1% (95% CI: 0.24, 16.8%) in a NS model. The results  
33 were somewhat sensitive to the lag day selected, reduced when using a single-day lag (e.g., lag 1)  
34 (PS: 6.0%; NS: 5.5%) and increased when using a distributed lag model (PS: 18.6%; NS: 20.4%).  
35 When adjusting for PM<sub>10</sub>, the magnitude of the effect estimate was slightly larger in the NS model  
36 (5.1% [95% CI: -6.6, 18.6%]) compared to the PS model (3.1% [95% CI: -8.3, 15.9%]); however,  
37 the co-pollutant analysis was only conducted using a 1-day lag. The large confidence intervals for  
38 both models could be attributed to the reduction in days included in the co-pollutant analyses as a  
39 result of the every-6th-day PM sampling schedule. When restricting the analysis to the summer

1 months, stronger associations were observed between O<sub>3</sub> and respiratory hospital admissions across  
2 the lags examined, ranging from ~22 to 37% (the study does not specify whether these effect  
3 estimates are from a NS or PS model). Because O<sub>3</sub> concentrations across the cities included in the  
4 Canadian dataset (Katsouyanni et al. (2009, [199899](#)) are low (median concentrations ranging from  
5 6.7-8.3 ppb [Table 6-19]), the standardized increment of 40 ppb for a 1-h max increase in O<sub>3</sub>  
6 concentrations does not accurately reflect the observed risk of O<sub>3</sub>-related respiratory hospital  
7 admissions. Although this increment accurately characterizes the distribution of 1-h max O<sub>3</sub>  
8 concentrations across the U.S. and European datasets, it misrepresents the observed O<sub>3</sub>  
9 concentrations in the Canadian dataset. As a result in summary figures, for comparability, effect  
10 estimates from the Canadian dataset are presented for both a 5.1-ppb increase in 1-h max O<sub>3</sub>  
11 concentrations (i.e., an approximate interquartile range [IQR] increase in O<sub>3</sub> concentrations across  
12 the Canadian cities) as well as the standardized increment used throughout the ISA.

13 In Europe, weaker but positive associations were also observed in year round analyses; 2.9%  
14 (95% CI: 0.63, 5.0%) in the PS model and 1.6% (95% CI: -1.7, 4.2%) in the NS model at lag 0-1 for  
15 a 40-ppb increase in 1-h max O<sub>3</sub> concentrations. Additionally, at lag 1, associations between O<sub>3</sub> and  
16 respiratory hospital admissions were also reduced, but in contrast to the lag 0-1 analysis, greater  
17 effects were observed in the NS model (2.9% [95% CI: 1.0, 4.9%]) compared to the PS model (1.5%  
18 [95% CI: -2.2, 5.4]). Unlike the Canadian analysis, a distributed lag model provided limited evidence  
19 of an association between O<sub>3</sub> and respiratory hospital admissions. To compare with the Canadian  
20 results, when adjusting for PM<sub>10</sub> at lag 1, effect estimates were increased in the PS model (2.5%  
21 [95% CI: 0.39-4.8%]) and remained robust in the NS model (2.4% [95% CI: 0.08, 4.6%]). However,  
22 the European analysis also examined the effect of adjusting for PM<sub>10</sub> at lag 0-1 and found results  
23 were attenuated in both models (PS: 0.8% [95% CI: -2.3, 4.0%]; NS: 0.8% [95% CI: -1.8, 3.6%]).  
24 Unlike the Canadian and U.S. datasets, the European dataset consisted of daily PM data. The  
25 investigators did not observe stronger associations in the summer-only analyses for the European  
26 cities at lag 0-1 (PS: 0.4% [95% CI: -3.2, 4.0%]; NS: 0.2% [95% CI: -3.3, 3.9%]), but did observe  
27 some evidence for larger effects during the summer, an ~2.5% increase, at lag 1 in both models (the  
28 study does not present the extent of temporal smoothing used for these models).

29 For the U.S. in year round analyses, the investigators reported a 1.4% (95% CI: -0.9, 3.9%)  
30 increase in the PS model and 2.4% (95% CI: 0.0, 4.9%) increase in the NS model in respiratory  
31 hospital admissions at lag 0-1 for a 40-ppb increase in 1-h max O<sub>3</sub> concentrations with similar results  
32 for both models at lag 1. The distributed lag model provided results similar to those observed in the  
33 European dataset with the PS model (1.1% [95% CI: -3.0, 5.3%]), but larger effects in the NS model  
34 (3.3% [95% CI: 0.02, 6.8%]), which is consistent with the Canadian results. When adjusting for  
35 PM<sub>10</sub> using the U.S. data (i.e., every-6th-day PM data), results were attenuated at lag 0-1 (PS: 0.6%  
36 [95% CI: -2.0, 3.3%]; NS: 1.4% [95% CI: -1.3, 4.2%]) which is consistent with the results presented  
37 for the European dataset. However, at lag 1, U.S. risk estimates remained robust to the inclusion of  
38 PM<sub>10</sub> in co-pollutant models as was observed in the Canadian and European datasets. Compared to  
39 the all-year analyses, the investigators did not observe stronger associations in the summer-only

1 analysis at either lag 0-1 (~2.2%) or lag 1 (~2.8%) in both the PS and NS models (the study does not  
 2 present the extent of temporal smoothing used for these models).



**Figure 6-15. Percent increase in respiratory hospital admissions from natural spline models for a 40-ppb increase in 1-h max ozone concentrations for each location of the APHENA study. □**

**Black circles = all-year results; open circles = all-year results in co-pollutant model with PM<sub>10</sub>; 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 ozone concentrations.**

**Table 6-20. Corresponding effect estimates for Figure 6-15**

Location	Season	Lag <sup>a</sup>	Co-pollutant	% Increase (95% CI) <sup>b</sup>	
U.S.	All-year	1		2.62 (0.63, 4.64)	
		1	PM <sub>10</sub>	2.14 (-0.08, 4.40)	
		0-1		2.38 (0.00, 4.89)	
		0-1	PM <sub>10</sub>	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 <sub>10</sub>	5.13 (-6.62, 18.6)	
		1a	PM <sub>10</sub>	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)	
	0-1a		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 <sub>10</sub>	2.38 (0.08, 4.64)	
		0-1		1.58 (-1.71, 4.15)	
		0-1	PM <sub>10</sub>	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)	

<sup>a</sup>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 O<sub>3</sub> concentrations.

<sup>b</sup>Unless noted, risk estimates standardized to 40 ppb for a 1-h max increase in O<sub>3</sub> concentrations.

1           Several additional multicity studies examined respiratory disease hospital admissions in  
2 Canada and Europe. Cakmak et al. (2006, [093272](#)) evaluated the association between ambient O<sub>3</sub>  
3 concentrations and respiratory hospital admissions for all ages in 10 Canadian cities from April 1993  
4 to March 2000. The primary objective of this study was to examine the potential modification of the  
5 effect of ambient air pollution on daily respiratory hospital admissions (defined as acute bronchitis  
6 and bronchiolitis [ICD-9: 466], pneumonia [480-486], bronchitis [490, 491], emphysema [492],  
7 asthma [493], bronchiectasis [494], and COPD [496]) by education and income using a time-series  
8 analysis conducted at the city-level. The authors calculated a pooled estimate across cities for each  
9 pollutant using a random effects model by first selecting the lag day with the strongest association  
10 from the city-specific models. For O<sub>3</sub>, the mean lag day across cities that provided the strongest  
11 association and for which the pooled effect estimate was calculated was 1.2 days. In this study,  
12 all-year O<sub>3</sub> concentrations were used in the analysis, and additional seasonal analyses were not

1 conducted. Cakmak et al. (2006, [093272](#)) reported a 4.4% increase (95% CI: 2.2, 6.5%) in  
2 respiratory hospital admissions for a 20 ppb increase in 24 h average O<sub>3</sub> concentrations. The  
3 investigators only examined the potential effect of confounding by other pollutants through the use  
4 of a multi-pollutant model, which is difficult to interpret. Cakmak et al. (2006, [093272](#)) also  
5 conducted an extensive analysis of potential modifiers, specifically gender, educational attainment,  
6 and family income, on the association between air pollution and respiratory hospital admissions.  
7 When stratifying by gender, the increase in respiratory hospital admissions due to short-term O<sub>3</sub>  
8 exposure were similar in males (5.2% [95% CI: 3.0, 7.3%]) and females (4.2% [95% CI: 1.8, 6.6%]).  
9 In addition, the examination of effect modification by income found no consistent trend across the  
10 quartiles of family income. However, there was evidence that individuals with an education level  
11 less than the 9th grade were disproportionately affected by O<sub>3</sub> exposure (4.6% [95% CI: 1.8, 7.5%])  
12 compared to individuals that completed grades 9-13 (1.7% [95% CI: -1.9, 5.3%]), some university or  
13 trade school (1.4% [95% CI: -2.0, 5.1%]), or have a university diploma (0.66% [95% CI: -3.3,  
14 4.7%]). The association between O<sub>3</sub> and individuals with an education level less than the 9th grade  
15 was the strongest association across all of the pollutants examined.

16 A multicity study conducted in Europe by Biggeri et al. (2005, [087395](#)) examined the  
17 association between short-term O<sub>3</sub> exposure and respiratory hospital admissions (ICD-9: 460-519)  
18 for all ages in four Italian cities from 1990 to 1999. In this study, O<sub>3</sub> was only measured during the  
19 warm season (May-September). The authors examined associations between daily respiratory  
20 hospital admissions and short-term O<sub>3</sub> exposure at the city-level using a time-series analysis. Pooled  
21 estimates were calculated by combining city-specific estimates using fixed and random effects  
22 models. The investigators found no evidence of an association between O<sub>3</sub> exposure and respiratory  
23 hospital admissions in the warm season in both the random (0.1% [95% CI: -5.2, 5.7%]; distributed  
24 lag 0-3) and fixed effects (0.1% [95% CI: -5.2, 5.7%]; distributed lag 0-3) models for a 30-ppb  
25 increase in 8-h max O<sub>3</sub> concentrations.

26 In another multicity study conducted in Canada, Dales et al. (2006, [090744](#)) examined the  
27 association between all-year ambient O<sub>3</sub> concentrations and neonatal (ages 0-27 days) respiratory  
28 hospital admissions (defined as respiratory asphyxia [ICD-9: 799], respiratory failure [769],  
29 unspecified birth asphyxia [768.9], other respiratory problems after birth [770.8], and pneumonia  
30 [486]) in 11 Canadian cities from 1986 to 2000. The investigators used a statistical analysis approach  
31 similar to Cakmak et al. (2006, [093272](#)) (i.e., time-series analysis to examine city-specific  
32 associations, and then a random effects model to pool estimates across cities). The authors reported  
33 that for O<sub>3</sub>, the mean lag day across cities that provided the strongest association was 2 days. The  
34 authors reported a 5.4% (95% CI: 2.9, 8.0%) increase in neonatal respiratory hospital admissions for  
35 a 20-ppb increase in 24-h avg O<sub>3</sub> concentrations at lag-2 days. The results from Dales et al. (2006,  
36 [090744](#)) provide support for the associations observed in a smaller scale study that examined O<sub>3</sub>  
37 exposure and pediatric respiratory hospital admissions in New York state (Lin et al., 2008, [195856](#)).  
38 Lin et al. (2008, [195856](#)) observed a positive association between O<sub>3</sub> and pediatric (i.e., <18 years)  
39 respiratory admissions (ICD-9: 466, 490-493, 496) at lag 2 (results not presented quantitatively) in a

1 two-stage Bayesian hierarchical model analysis of 11 geographic regions of New York from 1991 to  
2 2001.

3 Wong et al. (2009, [196722](#)) examined the potential modification of the relationship between  
4 ambient O<sub>3</sub> (along with NO<sub>2</sub>, SO<sub>2</sub>, and PM<sub>10</sub>) and respiratory hospital admissions (ICD-9: 460-519;  
5 ICD-10: J40-J47) by influenza intensity in Hong Kong for the period 1996 – 2002. Influenza  
6 intensity was defined using the proportion of weekly specimens positive for influenza A or B. In  
7 models that examined the baseline effect (i.e., without taking into consideration influenza intensity)  
8 of short-term O<sub>3</sub> exposure, the authors found a 3.6% (95% CI: 1.9, 5.3%) and 3.2% (95% CI: 1.0,  
9 5.4%) increase in respiratory hospital admissions at lag 0-1 for a 30-ppb increase in 8-h max O<sub>3</sub>  
10 concentrations for the all age and 65 age groups, respectively. When examining influenza intensity,  
11 Wong et al. (2009, [196722](#)) reported that the association between short-term exposure to O<sub>3</sub> and  
12 respiratory hospital admissions was stronger with higher levels of influenza intensity: additional  
13 increase in respiratory hospital admissions above baseline of 1.4% (95% CI: 0.24, 2.6%) for all age  
14 groups and 2.4% (95% CI: 0.94, 3.8%) for those 65 and older when influenza activity increased from  
15 0% to 10%. No difference in effects was observed when stratifying by sex.

### **Cause-Specific Respiratory Outcomes**

16 In the 2006 O<sub>3</sub> AQCD a limited number of studies were identified that examined the effect of  
17 short-term O<sub>3</sub> exposure on cause-specific respiratory hospital admissions. The limited evidence  
18 “reported positive O<sub>3</sub> associations with... asthma and COPD, especially... during the summer or  
19 warm season” (U.S. EPA, 2006, [088089](#)). Of the studies evaluated since the completion of the 2006  
20 AQCD, more have focused on identifying whether O<sub>3</sub> exposure is associated with specific  
21 respiratory-related hospital admissions, including COPD, pneumonia, and asthma, but the overall  
22 body of evidence remains small.

### **Chronic Obstructive Pulmonary Disease**

23 Medina-Ramon et al. (2006, [087721](#)) examined the association between short-term exposure  
24 to ambient O<sub>3</sub> and PM<sub>10</sub> concentrations and Medicare hospital admissions among individuals  
25 65 years of age for COPD (ICD-9: 490-496 excluding 493) in 35 cities in the U.S. for the years  
26 1986-1999. The cities included in this analysis were selected because they monitored PM<sub>10</sub> on a  
27 daily basis. In this study, city-specific results were obtained using a monthly time-stratified case-  
28 crossover analysis. A meta-analysis was then conducted using random effects models to combine the  
29 city-specific results. All cities measured O<sub>3</sub> from May through September, while only 16 of the cities  
30 had year-round measurements. The authors reported a 1.6% increase (95% CI: 0.48, 2.9%) in COPD  
31 admissions for lag 0-1 in the warm season for a 30-ppb increase in 8-h max O<sub>3</sub> concentrations. When  
32 examining single-day lags, stronger associations were observed for lag 1 (2.9% [95% CI: 1.8, 4.0%])  
33 compared to lag 0 (-1.5% [95% CI: -2.7, -0.24%]). The authors found no evidence of associations in  
34 the cool season (-1.9% [95% CI: -3.6, -0.06%]; lag 0-1) or year round (0.24% [95% CI: -0.78,  
35 1.2%]; lag 0-1). In a co-pollutant model using warm season data, the association between O<sub>3</sub> and

1 COPD hospital admissions was robust to the inclusion of PM<sub>10</sub> in the model (results not presented  
2 quantitatively). The authors conducted additional analyses to examine potential modification of the  
3 warm season estimates for O<sub>3</sub> and COPD admissions by several city-level characteristics: percentage  
4 living in poverty, emphysema mortality rate (as an indication of smoking), daily summer apparent  
5 temperature, and percentage of households using central air conditioning. Of the city-level  
6 characteristics examined, stronger associations were only reported for cities with a larger variability  
7 in daily apparent summer temperature.

8 In a single-city study conducted in Vancouver from 1994-1998, a location with low ambient  
9 O<sub>3</sub> concentrations (Table 6-19), Yang et al. (2005, [090184](#)) examined the association between O<sub>3</sub> and  
10 COPD (ICD-9: 490-492, 494, 496). Ozone was moderately inversely correlated with CO (r=-0.56),  
11 NO<sub>2</sub> (r=-0.32), and SO<sub>2</sub> (r=-0.34), and weakly inversely correlated with PM<sub>10</sub> (r=-0.09), suggesting  
12 that the observed O<sub>3</sub> effect is likely not only due to a positive correlation with other pollutants. Yang  
13 et al. (2005, [090184](#)) examined 1- to 7-day (e.g., (0-6 days) lagged moving averages and observed an  
14 8.8% (95% CI: -12.5, 32.6%) increase in COPD admissions for lag 0-3 per 20 ppb increase in 24-h  
15 avg O<sub>3</sub> concentrations. In two-pollutant models at lag 0-3, O<sub>3</sub> effect estimates were robust to the  
16 inclusion of NO<sub>2</sub>, SO<sub>2</sub>, and PM<sub>10</sub> in the model, but were increased slightly when adding CO (Figure  
17 6-20; Table 6-22).

### ***Pneumonia***

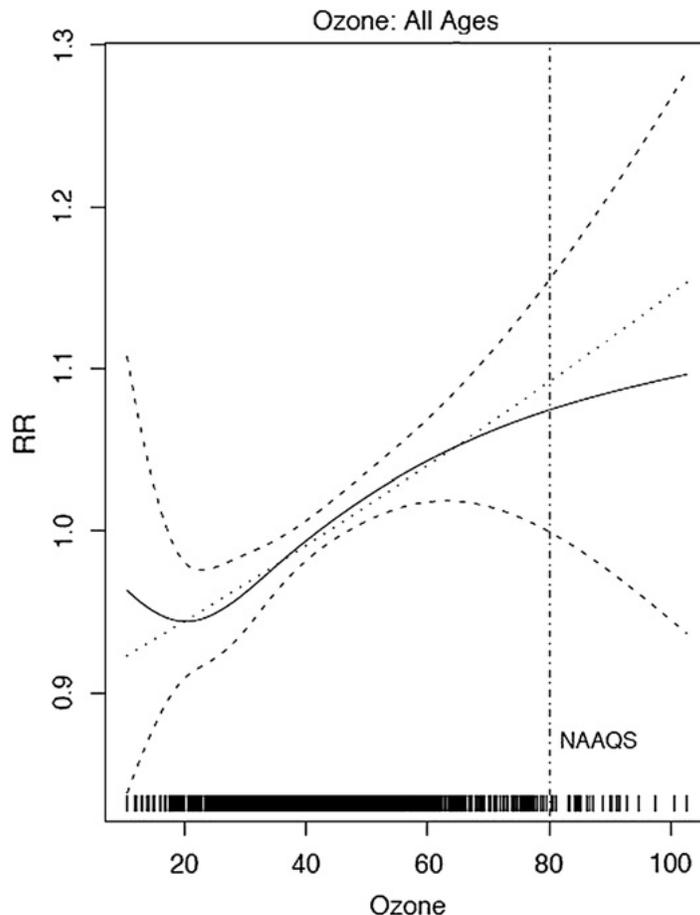
18 In addition to COPD, Medina-Ramon et al. (2006, [087721](#)) examined the association between  
19 short-term exposure to ambient O<sub>3</sub> and PM<sub>10</sub> concentrations and Medicare hospital admissions  
20 among individuals ≥ 65 years of age for pneumonia (ICD-9: 480-487). The authors reported an  
21 increase in pneumonia hospital admissions in the warm season (2.5% [95% CI: 1.6, 3.5%] for a 30-  
22 ppb increase in 8-h max O<sub>3</sub> concentrations; lag 0-1). Similar to the results observed for COPD  
23 hospital admissions, pneumonia hospital admissions associations were stronger at lag 1 (2.6% [95%  
24 CI: 1.8, 3.4%]) compared to lag 0 (0.06% [95% CI: -0.72, 0.78%]), and no evidence of an  
25 association was observed in the cool season or year round. In two-pollutant models, the association  
26 between O<sub>3</sub> exposure and pneumonia hospital admissions was robust to the inclusion of PM<sub>10</sub>  
27 (results not presented quantitatively). The authors also examined potential effect modification of the  
28 warm season estimates for O<sub>3</sub>-related pneumonia hospital admissions, as was done for COPD, by  
29 several city-level characteristics. Stronger associations were reported in cities with a lower  
30 percentage of central air conditioning use. In the cities examined, the percentage of households  
31 having central air conditioning ranged from 6 to 93%. Additionally, the authors found no evidence of  
32 effect modification of the O<sub>3</sub>-pneumonia hospital admission relationship when examining the other  
33 city-level characteristics.

34 Results from a single-city study conducted in Boston did not support the results presented by  
35 Medina-Ramon et al. (2006, [087721](#)). Zanobetti and Schwartz (2006, [090195](#)) examined the  
36 association of O<sub>3</sub> and pneumonia Medicare hospital admissions for the period 1995-1999. Ozone  
37 was weakly positively correlated with PM<sub>2.5</sub> (r=0.20) and weakly inversely correlated with black  
38 carbon, NO<sub>2</sub>, and CO (-0.25, -0.14, and -0.30, respectively). In an all-year analysis, the investigators

1 reported a 3.8% (95% CI: -7.9, -0.1%) decrease in pneumonia admissions for a 20-ppb increase in  
2 24-h average O<sub>3</sub> concentrations at lag 0 and a 6.0% (95% CI: -11.1, -1.4%) decrease for the average  
3 of lags 0 and 1. It should be noted that the mean daily counts of pneumonia admissions was low for  
4 this study, ~14 admissions per day compared to ~271 admissions per day for Medina-Ramon et al.  
5 (2006, [087721](#)), but in additional analyses in Boston positive associations with other pollutants and  
6 pneumonia hospital admissions was observed (Zanobetti and Schwartz, 2006, [090195](#)).

### ***Asthma***

7 There are relatively fewer studies that examined the association between short-term exposure  
8 to O<sub>3</sub> and asthma hospital admissions, presumably due to the limited power given the relative rarity  
9 of asthma hospital admissions compared to ED or physician visits. A study from New York City  
10 examined the association of 8-h max O<sub>3</sub> concentrations with severe acute asthma admissions (i.e.,  
11 those admitted to the Intensive Care Unit [ICU]) during the warm season in the years 1999 through  
12 2006 (Silverman and Ito, 2010, [386252](#)). In this study, O<sub>3</sub> was moderately correlated with PM<sub>10</sub>  
13 (r=0.59). When stratifying by age, the investigators reported positive associations with ICU asthma  
14 admissions for the 6- to 18-year age group (26.8% [95% CI: 1.4, 58.2%] for a 30-ppb increase in  
15 maximum 8-h avg O<sub>3</sub> concentrations at lag 0-1), but little evidence of associations for the other age  
16 groups examined (<6 years, 19-49, 50+, and all ages). However, positive associations were observed  
17 for each age-stratified group and all ages for non-ICU asthma admissions, but again the strongest  
18 association was reported for the 6- to 18-years age group (28.2% [95% CI: 15.3, 41.5%]; lag 0-1). In  
19 two-pollutant models, O<sub>3</sub> effect estimates for both non-ICU and ICU hospital admissions remained  
20 robust to adjustment for PM<sub>2.5</sub>. In an additional analysis, using a smooth function, the authors  
21 examined whether the shape of the C-R curve for O<sub>3</sub> and asthma hospital admissions (i.e., both  
22 general and ICU for all ages) is linear. To account for the potential confounding effects of PM<sub>2.5</sub>,  
23 Silverman and Ito (2010, [386252](#)) also included a smooth function of PM<sub>2.5</sub> lag 0-1. When  
24 comparing the curve to a linear fit line the authors found that the linear fit is a reasonable  
25 approximation of the concentration-response relationship between O<sub>3</sub> and asthma hospital  
26 admissions around and below the level of the current NAAQS (Figure 6-16).



Source: Used with permission from American Academy of Allergy, Asthma & Immunology, Silverman and Ito (2010, [386252](#))

**Figure 6-16. Estimated relative risks (RRs) of ozone-related asthma hospital admissions allowing for possible nonlinear relationships using natural splines. □ The average of 0 day and 1 day lagged ozone was used in a two-pollutant model with PM<sub>2.5</sub> 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.**

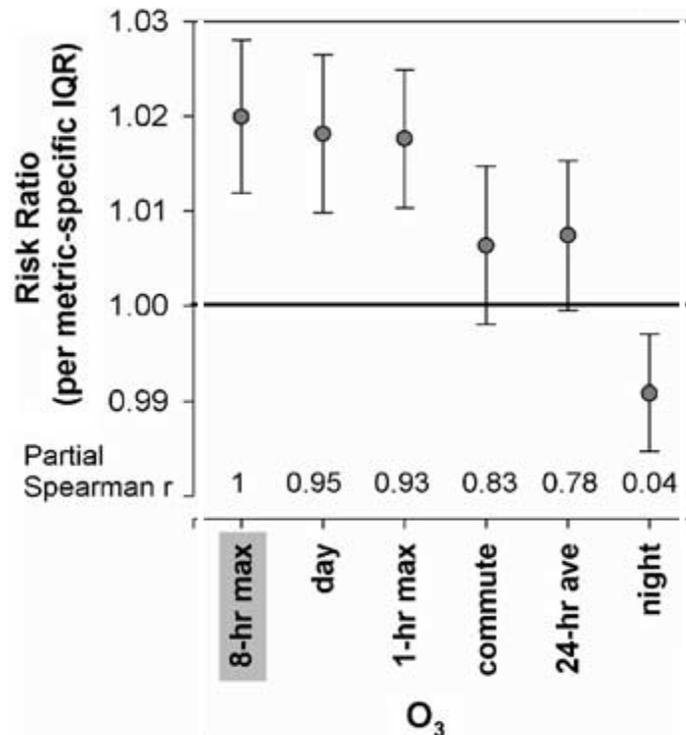
### 6.2.7.3. Emergency Department Visit Studies

1 Overall, relatively fewer studies have examined the association between short-term exposure  
 2 to O<sub>3</sub> and respiratory-related ED visits, compared to hospital admissions. In the 2006 O<sub>3</sub> AQCD  
 3 (U.S. EPA, 2006, [088089](#)), positive, but inconsistent, associations were observed between O<sub>3</sub> and  
 4 respiratory-related ED visits with effects generally occurring during the warm season. Since the  
 5 completion of the previous AQCD, larger studies have been conducted, in terms of sample size,  
 6 study duration, and in some cases multiple cities, to examine the association between O<sub>3</sub> and ED  
 7 visits for all respiratory diseases, COPD, and asthma.

## Respiratory Disease

1 A large single-city study conducted in Atlanta, by Tolbert et al. (2007, [090316](#)), and  
2 subsequently reanalyzed by Darrow et al. (2011, [202800](#)), provides evidence for an association  
3 between short-term exposures to ambient O<sub>3</sub> concentrations and respiratory ED visits. Tolbert et al.  
4 (2007, [090316](#)) examined the association between air pollution, both gaseous pollutants and PM and  
5 its components, and respiratory disease ED visits, defined as: asthma (ICD-9: 493, 786.07, and  
6 786.09), COPD (491, 492, and 496), upper respiratory infection (URI) (460–465, 460.0, and 477),  
7 pneumonia (480-486), and bronchiolitis (466.1, 466.11, and 466.19), in all ages from 1993 to 2004.  
8 The correlations between O<sub>3</sub> and the other pollutants examined ranged from 0.2 for CO and SO<sub>2</sub> to  
9 0.5-0.6 for the PM measures. Using an a priori average of lags 0-2 for each air pollutant examined,  
10 the authors reported a 3.9% (95% CI: 2.7, 5.2%) increase in respiratory ED visits for a 30-ppb  
11 increase in 8-h max O<sub>3</sub> concentrations during the warm season [defined as May-October in other  
12 studies using the same data (Peel et al. (2005, [056305](#)); Strickland et al. (2010, [624878](#)))]. In  
13 co-pollutant models, the O<sub>3</sub> associations with respiratory ED visits remained robust with CO, NO<sub>2</sub>,  
14 and PM<sub>10</sub> (results not presented quantitatively).

15 Darrow et al. (2011, [202800](#)) examined the same data as Tolbert et al. (2007, [090316](#)) to  
16 explore differences in the association between O<sub>3</sub> exposure and respiratory-related ED visits due to  
17 the use of various exposure metrics. The O<sub>3</sub> exposure metrics examined in this study included: 8-h  
18 max, 1-h max, 24-h average, commuting period (7:00 a.m. to 10:00 a.m.; 4:00 p.m. to 7:00 p.m.),  
19 day-time (8:00 a.m. to 7:00 p.m.) and night-time (12:00 a.m. to 6:00 a.m.). To examine the  
20 association between the various O<sub>3</sub> exposure metrics and respiratory ED visits, the authors used a  
21 time-stratified case-crossover approach, selecting control days as those days within the same  
22 calendar month and maximum temperature as the case day. Darrow et al. (2011, [202800](#)) found at  
23 lag 1, the results were somewhat variable across exposure metrics. The strongest associations with  
24 respiratory ED visits were found when using the 8-h max, 1-h max, and day-time exposure metrics  
25 with weaker associations using the 24-h avg and commuting period exposure metrics; a negative  
26 association was observed when using the night-time exposure metric (Figure 6-17).



Source: Used with permission from Nature Publishing Group, Darrow et al. (2011, [202800](#)).

**Figure 6-17. Risk ratio for respiratory ED visits and different ozone exposure metrics in Atlanta from 1993-2004.**

1 Orazzo et al. (2009, [202801](#)) examined respiratory ED visits for ages 0-2 years in 6 Italian  
 2 cities from 1996 to 2000. However, instead of identifying respiratory ED visits using the traditional  
 3 approach of selecting ICD codes as was done by Tolbert et al. (2007, [090316](#)) and Darrow et al.  
 4 (2011, [202800](#)), Orazzo et al. (2009, [202801](#)) used data on wheeze extracted from medical records as  
 5 an indicator of lower respiratory disease. This study examined daily counts of wheeze in relation to  
 6 air pollution using a time-stratified case-crossover approach in which control days were matched on  
 7 day of week in the same month and year as the case day. The authors found no evidence of an  
 8 association between 8-h max O<sub>3</sub> concentrations and respiratory ED visits in children aged 0-2 years  
 9 in models that examined both single-day lags and moving averages of lags from 0-6 days in year-  
 10 round and seasonal analyses (i.e., warm and cool seasons). In all-year analyses, the percent increase  
 11 in total wheeze ranged from -1.4% to -3.3% for a 0-1 to 0-6 day lag, respectively.

### **COPD**

12 Stieb et al. (2009, [195858](#)) also examined the association between short-term O<sub>3</sub> exposure and  
 13 COPD (ICD9: 490-492, 494-496) ED visits in 7 Canadian cities. Across cities, in an all-year  
 14 analysis, O<sub>3</sub> was found to be positively associated with COPD ED visits (4.0% [95% CI: -0.54,  
 15 8.6%] at lag 2 for a 20-ppb increase in 24-h avg O<sub>3</sub> concentrations). In seasonal analyses, larger  
 16 effects were observed between O<sub>3</sub> and COPD ED visits during the warm season (i.e., April-  
 17 September) 6.8% [95% CI: 0.11, 13.9%] (lag day not specified); with no associations observed in the

1 winter season. As stated previously, in analyses of sub-daily time scales, the authors observed no  
2 evidence of consistent associations between any pollutant and respiratory outcome.

3 In a single-city study, Arbex et al. (2009, [184334](#)) examined the association between COPD  
4 and several ambient air pollutants, including O<sub>3</sub>, in Sao Paulo, Brazil for the years 2001-2003 for  
5 individuals over the age of 40. Associations between O<sub>3</sub> exposure and COPD ED visits were  
6 examined in both single-day lag (0-6 days) and polynomial distributed lag models (0-6 days). In  
7 all-year analyses, O<sub>3</sub> was not found to be associated with an increase in COPD ED visits (results not  
8 presented quantitatively). The authors also conducted stratified analyses to examine the potential  
9 modification of the air pollutant-COPD ED visits relationship by age (e.g., 40-64, >64) and sex. In  
10 these analyses O<sub>3</sub> was found to have an increase in COPD ED visits for women, but not for men or  
11 either of the age groups examined.

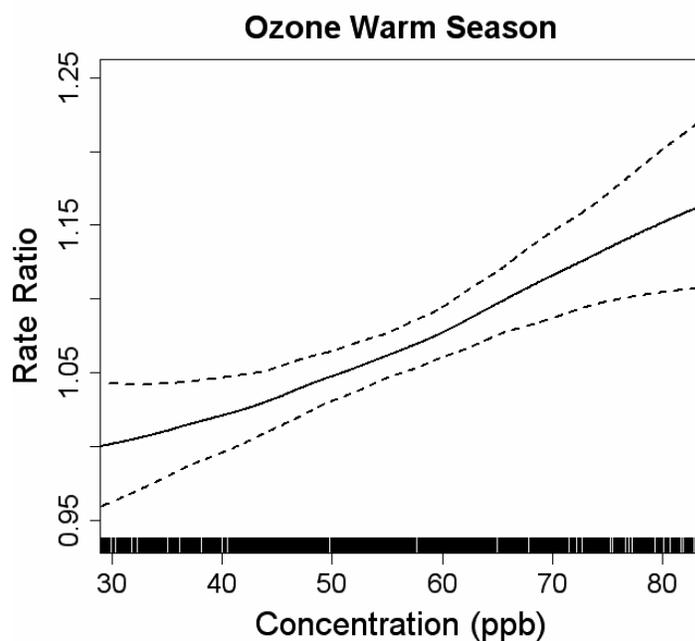
### ***Asthma***

12 In a study of 7 Canadian cities, Stieb et al. (2009, [195858](#)) also examined the association  
13 between exposure to air pollution (i.e., CO, NO<sub>2</sub>, O<sub>3</sub>, SO<sub>2</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and O<sub>3</sub>) and asthma ED  
14 visits. Associations between short-term O<sub>3</sub> exposure and asthma (ICD9: 493) ED visits were  
15 examined at the city-level and then pooled using either fixed or random effects models depending on  
16 whether heterogeneity among effect estimates was found to be statistically significant. Across cities,  
17 in an all-year analysis, the authors found that short-term O<sub>3</sub> exposure was associated with a positive  
18 increase (3.5% [95% CI: 0.33, 6.8%] at lag 2 for a 20-ppb increase in 24-h avg O<sub>3</sub> concentrations) in  
19 asthma ED visits. The authors did not present the results from seasonal analyses for asthma, but do  
20 state that no associations were observed between any pollutant and respiratory ED visits in the  
21 winter season. Stieb et al. (2009, [195858](#)) also examined associations between respiratory ED visits  
22 and sub-daily time scales (i.e., 3-h avg of ED visits versus 3-h avg pollutant concentrations) and  
23 found no evidence of consistent associations between any pollutant and respiratory outcome.

24 Several large single-city studies have also provided evidence of an association between asthma  
25 ED visits and ambient O<sub>3</sub> concentrations. Ito et al. (2007, [156594](#)) examined the association between  
26 short-term exposure to air pollution and asthma ED visits for all ages in New York City from 1999 to  
27 2002. Ito et al. (2007, [156594](#)) used three different weather models with varying extent of smoothing  
28 to account for temporal relationships and multicollinearity among pollutants and meteorological  
29 variables (i.e., temperature and dew point) to examine the effect of model selection on the air  
30 pollutant-asthma ED visit relationship. When examining O<sub>3</sub>, the authors reported a positive  
31 association with asthma ED visits, during the warm season across the models (ranging from 8.6 to  
32 16.9%) and an inverse association in the cool season (ranging from -23.4 to -25.1%), at lag 0-1 for a  
33 30-ppb increase in 8-h max O<sub>3</sub> concentrations. Using a simplified version of the weather model used  
34 in NMMAPS analyses (i.e., terms for same-day temperature and 1-3 day average temperature), Ito et  
35 al. (2007, [156594](#)) found that O<sub>3</sub> effects were not substantially changed in co-pollutant models with  
36 PM<sub>2.5</sub>, NO<sub>2</sub>, SO<sub>2</sub>, and CO during the warm season (Figure 6-20; Table 6-22).

37 Strickland et al. (2010, [624878](#)) examined the association between O<sub>3</sub> exposure and pediatric  
38 asthma ED visits (ages 5-17 years; ICD-9 codes 493.0; 786.09 before October 1, 1998 or 786.07

1 after October 1, 1998) in Atlanta between 1993 and 2004 using the same air quality data as Darrow  
 2 et al. (2011, [202800](#)) and Tolbert et al. (2007, [090316](#)). In this study, the authors developed a  
 3 statistical model using hospital-specific time-series data that is essentially equivalent to a time-  
 4 stratified case-crossover analysis (i.e., using interaction terms between year, month, and day-of-week  
 5 to mimic the approach of selecting referent days within the same month and year as the case day).  
 6 The authors observed a 6.4% (95% CI: 3.2, 9.6%) increase in ED visits for a 30-ppb increase in 8-h  
 7 max O<sub>3</sub> concentrations at lag 0-2 in an all-year analysis. In seasonal analyses, stronger associations  
 8 were observed during the warm season (i.e., May-October) (8.4% [95% CI: 4.4, 12.7%]; lag 0-2)  
 9 than the cold season (4.5% [95% CI: -0.82, 10.0%]; lag 0-2). In co-pollutant analyses O<sub>3</sub> effect  
 10 estimates were not substantially changed when controlling for other pollutants (CO, NO<sub>2</sub>, PM<sub>2.5</sub>  
 11 elemental carbon, PM<sub>2.5</sub> sulfate) (results not presented quantitatively). The authors also examined the  
 12 C-R relationship between O<sub>3</sub> exposure and pediatric asthma ED visits and found that both quintile  
 13 and loess dose-response analyses (Figure 6-18) suggest that there are elevated associations with O<sub>3</sub>  
 14 at relatively low concentrations, between 30 and 40 ppb, with stronger evidence at concentrations of  
 15 40 ppb and above. These dose-response analyses do not provide evidence of a threshold level.



Source: Used with permission from American Thoracic Society, Strickland et al. (2010, [624878](#))

**Figure 6-18. Loess dose-response estimates and twice-standard error estimates from generalized additive models for associations between 3-day avg ozone concentrations and ED visits for pediatric asthma. 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 dose-response estimates at the distribution tails.**

#### 6.2.7.4. Outpatient and Physician Visit Studies

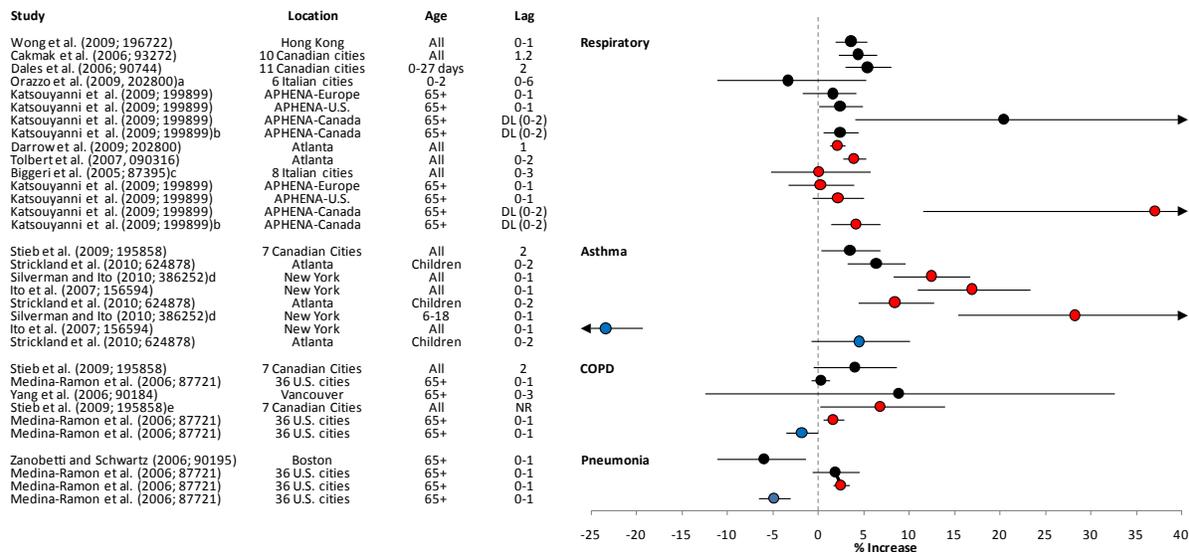
1 Several studies have examined the association between ambient O<sub>3</sub> concentrations and  
2 physician or outpatient (non-hospital, non-ED) visits for acute conditions in various geographic  
3 locations. Burra et al. (2009, [195868](#)) examined asthma physician visits among patients aged 1-17  
4 and 18-64 years in Toronto, Canada from 1992 to 2001. The authors found little or no evidence of an  
5 association between asthma physician visits and O<sub>3</sub>; however, seasonal analyses were not conducted.  
6 It should be noted that in this study, most of the relative risks for O<sub>3</sub> were less than one and  
7 statistically significant, perhaps indicating an inverse correlation with another pollutant or an artifact  
8 of the strong seasonality of asthma visits. Villeneuve et al. (2006, [091179](#)) also focused on physician  
9 visits to examine the effect of short-term O<sub>3</sub> exposure on allergic rhinitis among individuals aged 65  
10 or older in Toronto from 1995 to 2000. The authors did not observe any evidence of an association  
11 between allergic rhinitis physician visits and ambient O<sub>3</sub> concentrations in single-day lag models in  
12 an all-year analysis (results not presented quantitatively).

13 In a study conducted in Atlanta, Sinclair et al. (2010, [386271](#)) examined the association of  
14 acute asthma and respiratory infection (e.g., upper respiratory infections and lower respiratory  
15 infections) outpatient visits from a managed care organization with ambient O<sub>3</sub> concentrations as  
16 well as multiple PM size fractions and species from August 1998 through December 2002. The  
17 authors separated the analysis into two time periods (the first 25 months of the study period and the  
18 second 28 months of the study period), in order to compare the air pollutant concentrations and  
19 relationships between air pollutants and acute respiratory visits for the 25-month time-period  
20 examined in Sinclair et al. (2004, [088696](#)) to an additional 28-month time-period of available ARIES  
21 data. The authors found little evidence of an association between O<sub>3</sub> and asthma, for both children  
22 and adults, or respiratory infection visits in all-year analyses and seasonal analyses. For example, a  
23 slightly elevated relative risk (RR) for childhood asthma was observed during the 25-month period  
24 in the cold season (RR: 1.12 [95% CI: 0.86, 1.41]; lag 0-2 for a 30-ppb increase in 8-h max O<sub>3</sub>), but  
25 not in the warm season (RR: 0.97 [95% CI: 0.86, 1.10]; lag 0-2). During the 28-month period at lag  
26 0-2, a slightly larger positive effect was observed during the warm season (RR: 1.06 [95% CI: 0.97,  
27 1.17]), compared to the cold season (RR: 1.03 [95% CI: 0.87, 1.21]). Overall, these results contradict  
28 those from Strickland et al. (2010, [624878](#)) discussed above. Although the mean number of asthma  
29 visits and O<sub>3</sub> concentrations in Sinclair et al. (2010, [386271](#)) and Strickland et al. (2010, [624878](#)) are  
30 similar the difference in results between the two studies could be attributed to the severity of O<sub>3</sub>-  
31 induced asthma exacerbations (i.e., more severe symptoms requiring a visit to a hospital) and  
32 behavior, such as delaying a visit to the doctor for less severe symptoms.

#### 6.2.7.5. Summary

33 The results of the recent studies evaluated largely support the conclusion of the 2006 O<sub>3</sub>  
34 AQCD. While fewer studies were published overall since the previous review, several multicity  
35 studies (e.g., (Cakmak et al., 2006, [093272](#); Dales et al., 2006, [090744](#)) and a multi-continent study

1 (Katsouyanni et al., 2009, [199899](#)) provide supporting evidence for an association between short-  
 2 term O<sub>3</sub> exposure and an increase in respiratory-related hospital admissions and ED visits.  
 3 Collectively, in the studies evaluated, both single-city and multicity, there is continued evidence for  
 4 increases in both hospital admissions and ED visits when examining all respiratory outcomes  
 5 combined. Additionally, new studies support an association between short-term O<sub>3</sub> exposure and  
 6 asthma (e.g., (Stieb et al., 2009, [195858](#); Strickland et al., 2010, [624878](#)) and COPD (e.g., (Medina-  
 7 Ramon et al., 2006, [087721](#); Stieb et al., 2009, [195858](#)) hospital admissions and ED visits, with more  
 8 limited evidence for pneumonia (e.g., (Medina-Ramon et al., 2006, [087721](#); Zanobetti and Schwartz,  
 9 2006, [090195](#)). In seasonal analyses, stronger associations were observed in the warm season or  
 10 summer months compared to the cold season, particularly for asthma (e.g., (Ito et al., 2007, [156594](#);  
 11 Strickland et al., 2010, [624878](#)) and COPD (e.g., (Medina-Ramon et al., 2006, [087721](#)) (Figure 6-19;  
 12 Table 6-21), which is consistent with the conclusions of the 2006 O<sub>3</sub> AQCD. There is also continued  
 13 evidence that children are particularly susceptible to O<sub>3</sub>-induced respiratory effects (Dales et al.,  
 14 2006, [090744](#); Silverman and Ito, 2010, [386252](#); Strickland et al., 2010, [624878](#)). Studies that  
 15 focused on respiratory-related outpatient or physician visits found no evidence of an association with  
 16 short-term O<sub>3</sub> exposure, but this could be attributed to the severity of O<sub>3</sub>-induced respiratory effects  
 17 requiring more immediate treatment or behavioral factors that result in delayed visits to a physician.



<sup>a</sup> Wheeze used as indicator of lower respiratory disease.  
<sup>b</sup> APHENA-Canada results standardized to approximate IQR of 5.1 ppb for 1 h max O<sub>3</sub> concentrations.  
<sup>c</sup> Study included 8 cities; but of those 8, only 4 had O<sub>3</sub> data.  
<sup>d</sup> non-ICU effect estimates.  
<sup>e</sup> The study did not specify the lag day of the summer season estimate.

**Figure 6-19. Percent increase in respiratory-related hospital admission and ED visits in studies that presented all-year and seasonal analyses. 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 ozone concentrations. Black=All-year analysis; Red=Summer only analysis; Blue=Winter only analysis.**

**Table 6-21. Corresponding Effect Estimates for Figure 6-19**

Study	ED Visit or Hospital Admission	Location	Age	Lag	Avg Time	% Increase (95% CI)
<b>Respiratory</b>						
All-year						
Wong et al. (2009, <a href="#">196722</a> )	Hospital Admission	Hong Kong	All	0-1	8-h max	3.58 (1.90, 5.29)
Cakmak et al. (2006, <a href="#">093272</a> )	Hospital Admission	10 Canadian cities	All	1.2	24-h avg	4.38 (2.19, 6.46)
Dales et al. (2006, <a href="#">090744</a> )	Hospital Admission	11 Canadian cities	0-27 days	2	24-h avg	5.41 (2.88, 7.96)
Orazzo et al. (2011, <a href="#">202800</a> ) <sup>a</sup>	ED Visit	6 Italian cities	0-2	0-6	8-h max	-3.34 (-11.2, 5.28)
Katsouyanni et al. (2009, <a href="#">199899</a> )	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) <sup>o</sup>	1-h max	2.4 (0.51, 4.40)
Warm						
Darrow et al. (2011, <a href="#">202800</a> )	ED Visit	Atlanta	All	1	8-h max	2.08 (1.25, 2.91)
Tolbert et al. (2007, <a href="#">090316</a> )	ED Visit	Atlanta	All	0-2	8-h max	3.90 (2.70, 5.20)
Biggeri et al. (2005, <a href="#">087395</a> ) <sup>c</sup>	Hospital Admission	8 Italian cities	All	0-3	8-h max	0.06 (-5.24, 5.66)
Katsouyanni et al. (2009, <a href="#">199899</a> )	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) <sup>o</sup>	1-h max	4.1 (1.40, 6.80)
<b>Asthma</b>						
All-year						
Stieb et al. (2009, <a href="#">195858</a> )	ED Visit	7 Canadian cities	All	2	24-h avg	3.48 (0.33, 6.76)
Strickland et al. (2010, <a href="#">624878</a> )	ED Visit	Atlanta	Children	0-2	8-h max	6.38 (3.19, 9.57)
Warm						
Silverman and Ito (2010, <a href="#">386252</a> ) <sup>d</sup>	Hospital Admission	New York	All	0-1	8-h max	12.5 (8.27, 16.7)
Ito et al. (2007, <a href="#">156594</a> )	ED Visit	New York	All	0-1	8-h max	16.9 (10.9, 23.4)
Strickland et al. (2010, <a href="#">624878</a> )	ED Visit	Atlanta	Children	0-2	8-h max	8.43 (4.42, 12.7)
Silverman and Ito (2010, <a href="#">386252</a> ) <sup>d</sup>	Hospital Admission	New York	6-18	0-1	8-h max	28.2 (15.3, 41.5)
Cold						
Ito et al. (2007, <a href="#">156594</a> )	ED Visit	New York	All	0-1	8-h max	-23.4 (-27.3, -19.3)
Strickland et al. (2010, <a href="#">624878</a> )	ED Visit	Atlanta	Children	0-2	8-h max	4.52 (-0.82, 10.1)
<b>COPD</b>						
All-year						
Stieb et al. (2009, <a href="#">195858</a> )	ED Visit	7 Canadian cities	All	2	24-h avg	4.03 (-0.54, 8.62)
Medina-Ramon et al. (2006, <a href="#">087721</a> )	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	0.24 (-0.78, 1.21)
Yang et al. (2005, <a href="#">090184</a> )	Hospital Admission	Vancouver	65+	0-3	24-h avg	8.80 (-12.5, 32.6)
Warm						
Stieb et al. (2009, <a href="#">195858</a> ) <sup>e</sup>	ED Visit	7 Canadian cities	All	NR	24-h avg	6.76 (0.11, 13.9)
Medina-Ramon et al. (2006, <a href="#">087721</a> )	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	1.63 (0.48, 2.85)
Cold						
Medina-Ramon et al. (2006, <a href="#">087721</a> )	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	-1.85 (-3.60, -0.06)
<b>Pneumonia</b>						
All-year						
Zanobetti and Schwartz (2006, <a href="#">090195</a> )	Hospital Admission	Boston	65+	0-1	24-h avg	-5.96 (-11.1, -1.36)
Medina-Ramon et al. (2006, <a href="#">087721</a> )	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	1.81 (-0.72, 4.52)

Warm						
Medina-Ramon et al. (2006, <a href="#">087721</a> )	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	2.49 (1.57, 3.47)
Cold						
Medina-Ramon et al. (2006, <a href="#">087721</a> )	Hospital Admission	36 U.S. cities	65+	0-1	8-h max	-4.88 (-6.59, -3.14)

<sup>a</sup>Wheeze used as indicator of lower respiratory disease.

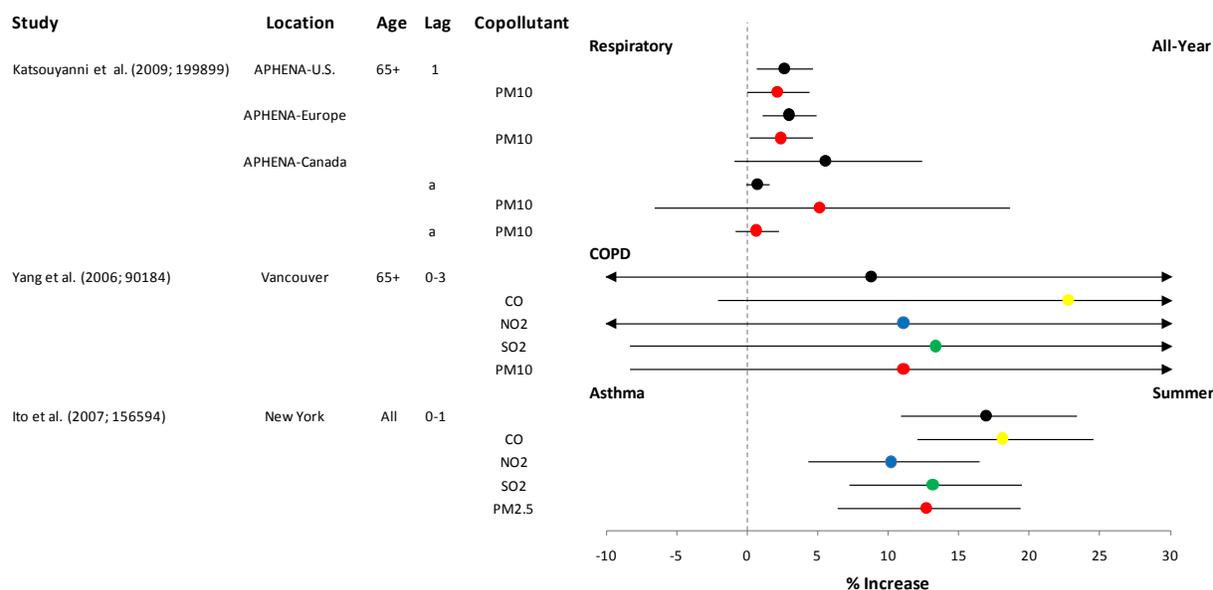
<sup>b</sup>APHENA-Canada results standardized to approximate IQR of 5.1 ppb for 1-h max O<sub>3</sub> concentrations.

<sup>c</sup>Study included 8 cities, but of those 8 only 4 had O<sub>3</sub> data.

<sup>d</sup>Non-ICU effect estimates.

<sup>e</sup>The study did not specify the lag day of the summer season estimate.

1 Although limited in number, the studies that examined the potential confounding effects of  
 2 co-pollutants found that O<sub>3</sub> effect estimates remained relatively robust upon the inclusion of PM and  
 3 gaseous pollutants in two-pollutant models (Medina-Ramon et al., 2006, [087721](#); Strickland et al.,  
 4 2010, [624878](#); Tolbert et al., 2007, [090316](#)) (Figure 6-20; Table 6-22).



**Figure 6-20. Percent increase in respiratory-related hospital admissions and ED visits for studies that presented single and co-pollutant model results. 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 ozone concentrations. An "a" represent risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in ozone concentrations. Black = results from single-pollutant models; Red = results from co-pollutant models with PM<sub>10</sub> or PM<sub>2.5</sub>; Yellow = results from co-pollutant models with CO; Blue = results from co-pollutant models with NO<sub>2</sub>; Green = results from co-pollutant models with SO<sub>2</sub>.**

**Table 6-22. Corresponding effect estimates for Figure 6-20**

Study <sup>a</sup>	Location	Age	Lag	Co-Pollutant	% Increase (95% CI)
All-year Respiratory					
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-U.S.	65+	1		2.62 (0.63, 4.64)
				PM <sub>10</sub>	2.14 (-0.08, 4.40)
	APHENA-Europe				2.94 (1.02, 4.89)
				PM <sub>10</sub>	2.38 (0.08, 4.64)
	APHENA-Canada				5.54 (-0.94, 12.4)
				PM <sub>10</sub>	0.69 (-0.12, 1.50) <sup>b</sup>
			PM <sub>10</sub>	5.13 (-6.62, 18.6)	
			PM <sub>10</sub>	0.64 (-0.87, 2.20) <sup>b</sup>	
COPD					
Yang et al. (2005, <a href="#">090184</a> )	Vancouver	65+	0-3		8.80 (-12.5, 32.6)
				CO	22.8 (-2.14, 50.7)
				NO <sub>2</sub>	11.1 (-10.4, 37.6)
				SO <sub>2</sub>	13.4 (-8.40, 40.2)
				PM <sub>10</sub>	11.1 (-8.40, 37.6)
Summer Asthma					
Ito et al. (2007, <a href="#">156594</a> )	New York	All	0-1		16.9 (10.9, 23.4)
				CO	18.1 (12.1, 24.5)
				NO <sub>2</sub>	10.2 (4.29, 16.4)
				SO <sub>2</sub>	13.1 (7.16, 19.5)
				PM <sub>2.5</sub>	12.7 (6.37, 19.3)

<sup>a</sup>Averaging times: Katsouyanni et al. (2009, [199899](#)) = 1-h max; Yang et al. (2005, [090184](#)) = 24-h avg; and Ito et al. (2007, [156594](#)) = 8-h max.

<sup>b</sup>Risk estimates standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O<sub>3</sub> concentrations.

1            Additionally, a preliminary examination of the C-R relationship found no evidence of a  
2 threshold between short-term O<sub>3</sub> exposure and pediatric asthma ED visits (Silverman and Ito, 2010,  
3 [386252](#); Strickland et al., 2010, [624878](#)). Overall, the new body of evidence supports an association  
4 between short-term O<sub>3</sub> exposure and respiratory-related hospital admissions and ED visits, with  
5 additional evidence for stronger associations during the warm season for specific respiratory  
6 outcomes such as asthma and COPD.

### 6.2.8. Respiratory Mortality

7            The 2006 O<sub>3</sub> AQCD found inconsistent evidence for an association between short-term O<sub>3</sub>  
8 exposure and respiratory mortality (U.S. EPA, 2006, [088089](#)). Although some studies reported a  
9 strong positive association between O<sub>3</sub> exposure and respiratory mortality, additional studies  
10 reported a small association or no association. Recent multicity studies found consistent positive  
11 associations between short-term O<sub>3</sub> exposure and respiratory mortality, specifically during the  
12 summer months.

13            The APHENA study, described earlier in Section 6.2.7.2, (Katsouyanni et al., 2009, [199899](#))  
14 found consistent positive associations for respiratory mortality in all-year analyses with stronger  
15 associations in analyses restricted to the summer season. Additional multicity studies from the U.S.

1 (Zanobetti and Schwartz, 2008, [101596](#)), Europe (Samoli et al., 2009, [195855](#)), and Italy (Stafoggia  
2 et al., 2010, [625034](#)) that conducted summer season analyses provide additional support for an  
3 association between short-term O<sub>3</sub> exposure and respiratory mortality.

4 Of the studies evaluated, only the APHENA study (Katsouyanni et al., 2009, [199899](#)) and the  
5 Italian multicity study (Stafoggia et al., 2010, [625034](#)) conducted an analysis of the potential for  
6 co-pollutant confounding of the O<sub>3</sub>-respiratory mortality relationship. In the APHENA study, in the  
7 European dataset, when focusing on the natural spline model with 8 df/year (as discussed in Section  
8 6.2.7.2) and lag 1 results (as discussed in Section 6.6.2.1), respiratory mortality risk estimates were  
9 robust to the inclusion of PM<sub>10</sub> in co-pollutant models in all-year analyses with O<sub>3</sub> respiratory  
10 mortality risk estimates increasing in the Canadian and U.S. datasets. In summer season analyses,  
11 respiratory O<sub>3</sub> mortality risk estimates were robust in the U.S. dataset and attenuated in the European  
12 dataset. Similarly, in the Italian multicity study (Stafoggia et al., 2010, [625034](#)), which was limited  
13 to the summer season, respiratory mortality risk estimates were attenuated in co-pollutant models  
14 with PM<sub>10</sub>. Based on the APHENA and Italian multicity results, O<sub>3</sub> respiratory mortality risk  
15 estimates appear to be moderately to substantially sensitive (e.g., increased or attenuated) to  
16 inclusion of PM<sub>10</sub>. However, in the APHENA study, the mostly every-6th-day sampling schedule for  
17 PM<sub>10</sub> in the Canadian and U.S. datasets greatly reduced their sample size and limits the interpretation  
18 of these results.

## 6.2.9. Summary and Causal Determination

19 The 2006 O<sub>3</sub> AQCD concluded that there was clear, consistent evidence of a causal  
20 relationship between short-term O<sub>3</sub> exposure and respiratory health effects (U.S. EPA, 2006,  
21 [088089](#)). This causal association was substantiated by the coherence of effects observed across  
22 controlled human exposure, epidemiologic, and toxicological studies indicating associations of  
23 short-term O<sub>3</sub> exposures with a range of respiratory health endpoints from respiratory tract  
24 inflammation to respiratory hospital admissions and ED visits. Across disciplines, acute O<sub>3</sub>  
25 exposures induced or were associated with statistically significant declines in lung function. An  
26 equally strong body of evidence from controlled human exposure and toxicological studies  
27 demonstrated O<sub>3</sub>-induced inflammatory responses, increased epithelial permeability, and airway  
28 hyperresponsiveness (both specific and nonspecific). Toxicological studies provided additional  
29 evidence for O<sub>3</sub>-induced impairment of host defenses. Coherent with inflammation and airway  
30 hyperresponsiveness, epidemiologic studies consistently demonstrated positive associations of  
31 increases in ambient O<sub>3</sub> concentrations with increases in respiratory symptoms and asthma  
32 medication use in asthmatic children and with respiratory-related hospital admissions and asthma-  
33 related ED visits. Although O<sub>3</sub> was consistently associated with nonaccidental and cardiopulmonary  
34 mortality, the contribution of respiratory causes to these findings was uncertain.

35 Building on the strong body of evidence presented in the 2006 AQCD, recent studies continue  
36 to support associations between short-term O<sub>3</sub> exposure and respiratory effects. In young healthy  
37 adults exposed to O<sub>3</sub> for 6.6 h, studies demonstrate mean FEV<sub>1</sub> decrements of about 3% at 60 ppb

1 (Adams, 2006, [087681](#); Brown et al., 2008, [195140](#)); 5% at 70 ppb (Schelegle et al., 2009, [618629](#));  
2 and 6-8% at 80 ppb (Adams, 2003, [042245](#); Adams, 2006, [087681](#); Horstman et al., 1990, [042187](#);  
3 McDonnell et al., 1991, [042384](#)). These studies also show considerable intersubject variability in  
4 responsiveness to O<sub>3</sub>, with the percentage of subjects with >10% decrement in FEV<sub>1</sub> increasing with  
5 increasing concentration of O<sub>3</sub> exposure. The proportion (uncorrected for FA responses) of  
6 individuals with >10% FEV<sub>1</sub> decrements ranges from 3 to 20% at an average O<sub>3</sub> exposure level of  
7 60 ppb (Adams, 1998; (Adams, 2006, [087681](#); Schelegle et al., 2009, [618629](#)) and from 17 to 29% at  
8 80 ppb (Adams, 2006, [087681](#); McDonnell, 1996, [082679](#)).

9 The collective body of epidemiologic evidence supports demonstrates associations between  
10 ambient O<sub>3</sub> and decrements in lung function, although recent studies contributed more mixed  
11 evidence. A notable difference among newer studies is the limited investigation of populations  
12 engaged in outdoor recreation, exercise, or work, which contributed to the strength of evidence in  
13 previous AQCDs (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)). Some recent evidence  
14 suggests that public attention to daily AQI may be reducing exposures of some groups. Recent  
15 epidemiologic studies contributed insight into susceptibility factors for O<sub>3</sub>-associated respiratory  
16 morbidity. Among subjects with atopy (Khatri et al., 2009, [594282](#)), asthmatics with concurrent  
17 respiratory infection (Lewis et al., 2005, [081079](#)), elderly with AHR or obesity (Alexeeff et al.,  
18 2007, [195862](#)), or groups with diminished antioxidant enzyme activity (Alexeeff et al., 2008,  
19 [195864](#)), lung function responses to ambient O<sub>3</sub> exposures generally were exacerbated. The  
20 susceptibility of these populations is supported by extensive laboratory evidence (human and animal)  
21 for O<sub>3</sub>-induced exacerbation of allergic inflammation, increased susceptibility to bacterial and viral  
22 infections, exacerbation of O<sub>3</sub>-induced AHR by obesity, and modulation of O<sub>3</sub> effects by the  
23 oxidative stress/antioxidant balance. In recent controlled human exposure studies, lung function  
24 responses to O<sub>3</sub> are enhanced in subjects with higher BMI (Bennett et al., 2007, [418827](#); McDonnell  
25 et al., 2010, [383972](#)).

26 As with lung function, recent controlled human exposure studies demonstrate increases in  
27 respiratory symptoms in healthy, young adults following 5.6- to 6.6-h exposures to O<sub>3</sub> at levels  
28 <80 ppb (Adams, 2006, [087681](#); Schelegle et al., 2009, [618629](#)). The collective body of  
29 epidemiologic studies strongly demonstrates positive associations of ambient O<sub>3</sub> exposure with  
30 respiratory symptoms and asthma medication use among asthmatic subjects, especially in  
31 populations with additional susceptibility factors such as asthmatics with atopy (Escamilla-Nuñez et  
32 al., 2008, [594284](#); Feo Brito et al., 2007, [093259](#); Khatri et al., 2009, [594282](#)), asthmatics with  
33 diminished antioxidant enzyme activity (Romieu et al., 2006, [090969](#)), or infants with asthmatic  
34 mothers (Triche et al., 2006, [093274](#)).

35 Recent studies in animals and in vitro models also continue to demonstrate O<sub>3</sub>-induced lung  
36 injury and inflammatory responses. Building on the extensive experimental evidence, new  
37 epidemiologic evidence emerged for ambient O<sub>3</sub>-associated increases in mediators of inflammation  
38 measured in upper and lower airway samples, including eNO (Barraza-Villarreal et al., 2008,  
39 [156254](#); Khatri et al., 2009, [594282](#)), cytokines such as IL-6 or IL-8 (Barraza-Villarreal et al., 2008,

1 [156254](#); Sienna-Monge et al., 2004, [196422](#)), and inflammatory cells such as eosinophils (Khatri et  
2 al., 2009, [594282](#)). Epidemiologic studies also report associations of increases in ambient O<sub>3</sub> with  
3 decreased levels of glutathione (Sienna-Monge et al., 2004, [196422](#)) and increased levels of  
4 malondialdehyde in airways (Romieu et al., 2008, [179908](#)). At the time of the 2006 O<sub>3</sub> AQCD,  
5 controlled human studies of dietary antioxidant supplementation had shown some protective effects  
6 of alpha-tocopherol and ascorbate on lung function from O<sub>3</sub> exposure, but not on the intensity of  
7 subjective symptoms and inflammatory response. More recent evidence indicates that diminished  
8 activity of oxidant metabolizing enzymes (e.g., GSTM1, GSTP1) or intake of antioxidant vitamins  
9 influences inflammatory responses to O<sub>3</sub> exposure (Romieu et al., 2009, [548788](#); Sienna-Monge et  
10 al., 2004, [196422](#)). Across all three disciplines, evidence suggests a role antioxidant defenses in  
11 modulating respiratory responses to O<sub>3</sub>.

12       Recent epidemiologic studies build upon the strong of extant body of evidence of consistently  
13 positive associations between daily changes in O<sub>3</sub> exposure and respiratory-related hospital  
14 admissions and ED visits by demonstrating associations in diverse populations across the U.S.,  
15 Canada, and Europe. In all-year analyses, recent multicity studies and a multicontinent study  
16 (Katsouyanni et al., 2009, [199899](#)) found an approximate 1.6-5.4% increase in all respiratory-related  
17 hospital admissions and ED visits for standardized increases in ambient O<sub>3</sub> concentrations<sup>1</sup>. Positive  
18 associations persisted in analyses restricted to the summer season, but the magnitude varied  
19 depending on the study location (Katsouyanni et al., 2009, [199899](#)). Compared with studies  
20 reviewed in the 2006 O<sub>3</sub> AQCD, more recent studies examine associations between short-term O<sub>3</sub>  
21 exposure and hospital admissions and ED visits for specific respiratory outcomes. Although still  
22 limited in number, both single- and multicity studies found consistent, positive associations of daily  
23 changes in O<sub>3</sub> concentrations with asthma and COPD hospital admissions and ED visits. Evidence  
24 was more limited for pneumonia. Consistent with the conclusions of the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
25 2006, [088089](#)), in studies that conducted seasonal analyses, larger effects were estimated for the  
26 warm season or summer months than for the cold season or for all seasons, particularly for asthma  
27 and COPD. Although the current body of evidence did not include detailed age-stratified results, the  
28 increased risk of asthma hospital admissions (Dales et al., 2006, [090744](#); Silverman and Ito, 2010,  
29 [386252](#); Strickland et al., 2010, [624878](#)) observed for children provided additional support for the  
30 conclusion from the 2006 O<sub>3</sub> AQCD that children are particularly susceptible to O<sub>3</sub>-induced  
31 respiratory effects (U.S. EPA, 2006, [088089](#)). Among studies that evaluated the potential  
32 confounding effects of co-pollutants, O<sub>3</sub> effect estimates for respiratory-related hospital admissions  
33 and ED visits remained relatively robust upon the inclusion of PM and gaseous pollutants in two-  
34 pollutant models (Medina-Ramon et al., 2006, [087721](#); Strickland et al., 2010, [624878](#); Tolbert et al.,  
35 2007, [090316](#)). Although the concentration-response relationship between short-term O<sub>3</sub> exposure  
36 and respiratory-related hospital admissions and ED visits has not been extensively examined,

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<sup>1</sup> Effect estimates were standardized to a 20-ppb increase for 24-h avg O<sub>3</sub>, a 30 ppb increase for 8-h max O<sub>3</sub>, and a 40-ppb increase for 1-h max O<sub>3</sub>.

1 preliminary examinations found no evidence of a threshold between short-term O<sub>3</sub> exposure and  
2 pediatric asthma ED visits (Silverman and Ito, 2010, [386252](#); Strickland et al., 2010, [624878](#)).

3 New evidence extends the potential continuum of well-established O<sub>3</sub>-associated respiratory  
4 effects (e.g., airway inflammation; impaired host defense; lung function decrements; and respiratory  
5 symptoms, ED visits, and hospital admissions) by demonstrating associations between ambient O<sub>3</sub>  
6 exposure and respiratory-related mortality. The multicontinent APHENA study reported primarily  
7 positive associations with respiratory mortality in all-year analyses, with stronger associations  
8 observed in analyses restricted to the summer season. These findings were supported by U.S.  
9 (Zanobetti and Schwartz, 2008, [101596](#)) and European (Samoli et al., 2009, [195855](#)) multicity  
10 studies, in which a majority of respiratory mortality effect estimates ranged from a 2.3 to 6.8%  
11 increase per standardized increase in ambient O<sub>3</sub> concentrations. Although co-pollutant confounding  
12 was not extensively examined, the O<sub>3</sub>-respiratory mortality relationship was moderately to  
13 substantially sensitive (e.g., increased or attenuated) to inclusion of PM<sub>10</sub> in co-pollutant models  
14 (Katsouyanni et al., 2009, [199899](#); Stafoggia et al., 2010, [625034](#)). However, interpretation of these  
15 results requires caution due to the limited PM datasets used in these studies.

16 In summary, new studies evaluated in the current review support or expand upon the strong  
17 body of evidence presented in the 2006 O<sub>3</sub> AQCD that short-term O<sub>3</sub> exposure is causally associated  
18 with respiratory health effects. Recent controlled human exposure studies demonstrate decreases in  
19 FEV<sub>1</sub> in the range of 2.8 to 3.6% with prolonged O<sub>3</sub> exposures (6.6 hours) as low as 60 ppb in  
20 concentration. By demonstrating O<sub>3</sub>-induced airway hyperresponsiveness, activation of neural  
21 reflexes, allergic responses, lung injury, impaired host defense, and airway inflammation,  
22 toxicological studies have characterized O<sub>3</sub> modes of action and provided biological plausibility for  
23 epidemiologic observations of associations of ambient O<sub>3</sub> exposure with decreases in lung function  
24 and increases in respiratory symptoms. The coherence of results across studies for O<sub>3</sub>-associated  
25 changes in lung function, airway inflammation, and respiratory symptoms, in turn, provides the  
26 biological plausibility for epidemiologic findings of consistently positive associations of ambient O<sub>3</sub>  
27 exposure with respiratory hospital admissions and ED visits in diverse populations across the U.S.,  
28 Europe, and Canada. Additionally, a multicontinent study and several multicity studies reported  
29 positive associations between ambient O<sub>3</sub> exposures and respiratory mortality. New epidemiologic  
30 studies provide evidence for associations of ambient O<sub>3</sub> exposure with biological markers of airway  
31 inflammation and oxidative stress and indicated that groups with diminished antioxidant capacity or  
32 comorbidities such as atopy, AHR, or obesity may have increased susceptibility to respiratory  
33 morbidity associated with O<sub>3</sub> exposure. This new information is consistent with previously available  
34 toxicological and clinical evidence as well as current information on modes of action. A common  
35 observation among epidemiologic studies of respiratory morbidity and mortality was stronger  
36 associations in analyses restricted to warm seasons compared to cold seasons. Additionally, although  
37 co-pollutant confounding was evaluated infrequently, O<sub>3</sub> effect estimates generally remained  
38 statistically significant in co-pollutant models with PM<sub>2.5</sub>, PM<sub>10</sub>, or NO<sub>2</sub>. Collectively, the evidence  
39 integrated across controlled human exposure, epidemiologic, and toxicological studies as well as

1 across the spectrum of respiratory health endpoints continues to demonstrate that **there is a causal**  
2 **relationship between short-term O<sub>3</sub> exposure and respiratory health effects.**

## 6.3. Cardiovascular Effects

### 6.3.1. Controlled Human Exposure

3 O<sub>3</sub> reacts rapidly on contact with respiratory system tissue and is not absorbed or transported  
4 to extrapulmonary sites to any significant degree as such. Controlled human exposure studies  
5 discussed in the previous AQCDs (U.S. EPA, 1986, [017607](#); U.S. EPA, 1996, [017831](#)) failed to  
6 demonstrate any consistent extrapulmonary effects. Some controlled human exposure studies have  
7 attempted to identify specific markers of exposure to O<sub>3</sub> in blood. Foster et al. (1996, [079920](#)) found  
8 a reduction in the serum levels of the free radical scavenger  $\alpha$ -tocopherol after O<sub>3</sub> exposure. Liu et al.  
9 (1997, [084627](#); 1999, [012049](#)) used a salicylate metabolite, 2,3, dehydroxybenzoic acid (DHBA), to  
10 indicate increased levels of hydroxyl radical which hydroxylates salicylate to DHBA. Increased  
11 DHBA levels after exposure to 120 and 400 ppb suggest that O<sub>3</sub> increases production of hydroxyl  
12 radical. The levels of DHBA were correlated with changes in spirometry.

13 Gong et al. (1998, [029938](#)) observed a small, statistically significant O<sub>3</sub>-induced increase in  
14 the alveolar-to-arterial PO<sub>2</sub> gradient in both healthy (n = 6) and hypertensive (n = 10) adult males  
15 (aged 41-78 years) exposed for 3 hours with exercise to 300 ppb O<sub>3</sub>. The mechanism for the decrease  
16 in arterial oxygen tension in the Gong et al. (1998, [029938](#)) study could be due to an O<sub>3</sub>-induced  
17 ventilation-perfusion mismatch. Gong et al. (1998, [029938](#)) suggested that by impairing alveolar-  
18 arterial oxygen transfer, the O<sub>3</sub> exposure could potentially lead to adverse cardiac events by  
19 decreasing oxygen supply to the myocardium. The subjects in the Gong et al. (1998, [029938](#)) study  
20 had sufficient functional reserve so as to not experience significant ECG changes or myocardial  
21 ischemia and/or injury. In studies evaluating the exercise performance of healthy adults, no  
22 significant effect of O<sub>3</sub> on arterial O<sub>2</sub> saturation has been observed (Schelegle and Adams, 1986,  
23 [040351](#)).

24 More recently, Fakhri et al. (2009, [191914](#)) evaluated changes in HRV among healthy adult  
25 volunteers (n=50; 27  $\pm$  7 years) during 2-h exposures to PM<sub>2.5</sub> CAPs (127 $\pm$ 62  $\mu$ g/m<sup>3</sup>) and O<sub>3</sub>  
26 (114 $\pm$ 7 ppb), alone and in combination. High frequency HRV was increased following CAPs-only  
27 (p=0.046) and O<sub>3</sub>-only (p=0.051) exposures, but not in combination. Diastolic blood pressure  
28 increased by 2 mmHg following the combined O<sub>3</sub> + CAPs exposure, but was not altered by either O<sub>3</sub>  
29 or CAPs alone. Urch et al. (2005, [081080](#)) also reported a 6 mmHg increase in diastolic blood  
30 pressure following a 2-h resting exposure to O<sub>3</sub> (120 ppb) + PM<sub>2.5</sub> CAPs (150  $\mu$ g/m<sup>3</sup>) in healthy  
31 adults (n=23; 32  $\pm$  107 years), which was statistically different from the 1 mmHg increase seen  
32 following FA exposure.

## 6.3.2. Epidemiology

1 The 2006 O<sub>3</sub> AQCD concluded that the “generally limited body of evidence is highly  
2 suggestive that O<sub>3</sub> directly and/or indirectly contributes to cardiovascular-related morbidity,”  
3 including physiologic effects (e.g., release of platelet activating factor [PAF]), HRV, arrhythmias,  
4 and myocardial infarctions, although the available body of evidence reviewed during the 2006 O<sub>3</sub>  
5 AQCD does not “fully substantiate links between ambient O<sub>3</sub> exposure and adverse cardiovascular  
6 outcomes” (U.S. EPA, 2006, [088089](#)). Since the completion of the 2006 O<sub>3</sub> AQCD an increasing  
7 number of studies have examined the relationship between short-term O<sub>3</sub> exposure and  
8 cardiovascular morbidity and mortality. These new studies, as well as evidence from the previous  
9 AQCDs, are presented within this section.

### 6.3.2.1. Arrhythmia

10 In the 2006 O<sub>3</sub> AQCD, conflicting results were observed when examining the effect of O<sub>3</sub> on  
11 arrhythmias (Dockery et al., 2005, [078995](#); Rich et al., 2005, [079620](#)). A study by Dockery et al.  
12 (2005, [078995](#)) reported no association between O<sub>3</sub> levels and ventricular arrhythmias among  
13 patients with implantable cardioverter defibrillators (ICD) living in Boston, MA, although when O<sub>3</sub>  
14 was categorized into quartiles, there was weak evidence of an association. Rich et al. (2005, [079620](#))  
15 performed a re-analysis of this cohort using a case-crossover design, which did detect a positive  
16 association. Recent studies were conducted in various locations and each used a different cardiac  
17 episode to define an arrhythmic event and a different time period of exposure, which may help  
18 explain observed differences across studies. Ozone levels for each new study are reported in Table 6-  
19 23.

**Table 6-23. Characterization of ozone concentrations (in ppb) from studies of arrhythmias**

Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Sarnat et al. (2006, <a href="#">090489</a> )	Steubenville, Ohio	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
Rich et al. (2006, <a href="#">089814</a> )	St. Louis, Missouri	24 h	21*	75th: 31
Rich et al. (2006, <a href="#">088427</a> )	Boston, Massachusetts	1 h	22.2*	75th: 33 Max: 119.5
		24 h	22.6*	75th: 30.9 Max: 77.5
Anderson et al. (2010, <a href="#">625028</a> )	London, England	8-h max	8.08	75th: 11.5
Metzger et al. (2007, <a href="#">092856</a> )	Atlanta, Georgia	8-h max Summer only	53.9 (23)	Max: 148

\*Median presented (information on mean not given).

20 Multiple studies examined O<sub>3</sub>-related effects on individuals with ICDs. One study of 518 ICD  
21 patients who had at least 1 tachyarrhythmia within a 10-year period (totaling 6287 tachyarrhythmic  
22 event-days; 1993-2002) was conducted in Atlanta, Georgia (Metzger et al., 2007, [092856](#)).

1 Tachyarrhythmic events were defined as any ventricular tachyarrhythmic event, any ventricular  
2 tachyarrhythmic event that resulted in electrical therapy, and any ventricular tachyarrhythmic event  
3 that resulted in defibrillation. In the primary analysis, no evidence of association was observed for a  
4 30-ppb increase in 8-h max O<sub>3</sub> concentrations and tachyarrhythmic events (OR: 1.00 [95% CI: 0.92,  
5 1.08]; lag 0). Season-specific as well as several sensitivity analyses (including the use of an  
6 unconstrained distributed lag model [lags 0-6]) analyses were conducted resulting in similar null  
7 associations. A strength of this study is that it incorporated a much larger sample size over a longer  
8 time period.

9 In a case-crossover analysis, a population of ICD patients in Boston, previously examined in a  
10 similar study (Rich et al., 2005, [079620](#)) was used to assess the association between air pollution and  
11 paroxysmal atrial fibrillation (PAF) episodes (Rich et al., 2006, [088427](#)). In addition to ventricular  
12 arrhythmias, ICD devices may also detect supraventricular arrhythmias, of which atrial fibrillation is  
13 the most common. Although atrial fibrillation is generally not considered lethal, it has been  
14 associated with increased premature mortality as well as hospitalization and stroke. Ninety-one  
15 electrophysiologist-confirmed episodes of PAF were ascertained among 29 patients. An association  
16 (OR: 3.86 [95% CI: 1.44, 10.28] per 40-ppb increase in 1-h max O<sub>3</sub> concentrations) was observed  
17 between increases in O<sub>3</sub> during the concurrent hour and PAF episodes (lag 0). The estimated OR for  
18 the 24-h moving average concentration was elevated (OR: 1.81 [95% CI: 0.86, 3.83] per 20 ppb), but  
19 weaker than the estimate for the shorter exposure window. The association between PAF and O<sub>3</sub> in  
20 the concurrent hour during the cold months was comparable to that during the warm months. In  
21 addition, no evidence of a deviation from linearity between O<sub>3</sub> concentration and the log odds of  
22 PAF was observed. Authors report that the difference between O<sub>3</sub> exposure and observed effect  
23 between this study (PAF and 1 h O<sub>3</sub>) and their previous study (ventricular arrhythmias and 24-h  
24 moving average O<sub>3</sub>) (Rich et al., 2005, [079620](#)) suggest a more rapid response to air pollution for  
25 PAF (Rich et al., 2006, [088427](#)).

26 In an additional study, Rich et al. (2006, [089814](#)) employed a case-crossover design to  
27 examine the association between air pollution and 139 confirmed ventricular arrhythmias among 56  
28 ICD patients in St Louis, Missouri. The authors observed a positive association with O<sub>3</sub> (OR: 1.17  
29 [95% CI: 0.58, 2.38] per 20-ppb increase in 24-h moving avg O<sub>3</sub> concentrations [lags 0-23 hours]).  
30 Although the authors concluded these results were similar to their results from Boston (Rich et al.,  
31 2005, [079620](#)), the pollutants responsible for the increased risk in ventricular arrhythmias are  
32 different (O<sub>3</sub> and PM<sub>2.5</sub> in Boston and sulfur dioxide in St Louis).

33 Anderson et al. (2010, [625028](#)) used a case-crossover framework to assess air pollution and  
34 activation of ICDs among patients from all 9 ICD clinics in the London National Health Service  
35 hospitals. "Activation" was defined as tachycardias for which the defibrillator delivered treatment.  
36 Investigators modeled associations using unconstrained distributed lags from 0 to 5 days. The  
37 sample consisted of 705 patients with 5,462 activation days (O<sub>3</sub> information was for 543 patients and  
38 4,092 activation days). Estimates for O<sub>3</sub> were consistently positive, although weak (OR: 1.09 [95%

1 CI: 0.76, 1.55] per 30 ppb for 0-1 day lag; OR: 1.04 [95% CI: 0.60, 1.81] per 30 ppb for 0-5 day lag)  
2 (Anderson et al., 2010, [625028](#)).

3 In contrast to arrhythmia studies conducted among ICD patients, Sarnat et al. (2006, [090489](#))  
4 recruited non-smoking adults (age range: 54-90 years) to participate in a study of air pollution and  
5 arrhythmias conducted over two 12-week periods during summer and fall of 2000 in a region  
6 characterized by industrial pollution (Steubenville, Ohio). Continuous ECG data acquired on a  
7 weekly basis over a 30-minute sampling period were used to assess ectopy, defined as extra cardiac  
8 depolarizations within the atria (supraventricular ectopy, SVE) or the ventricles (ventricular ectopy,  
9 VE). Increases in the 5-day moving average (days 1-5) of O<sub>3</sub> were associated with an increased odds  
10 of SVE (OR: 2.17 [95% CI: 0.93, 5.07] per 20-ppb increase in 24-h avg O<sub>3</sub> concentrations). A  
11 weaker association was observed for VE (OR: 1.62 [95% CI: 0.54, 4.90] per 20-ppb increase in 24-h  
12 avg O<sub>3</sub> concentrations). The inclusion of SO<sub>4</sub><sup>2-</sup> in the model slightly reduced the effect of 5-day O<sub>3</sub>  
13 on SVE [OR: 1.62 (95% CI: 0.54, 4.90)]. The authors indicate that the strong associations observed  
14 at the 5-day moving averages, as compared to shorter time periods, suggests a relatively long-acting  
15 mechanistic pathways, such as inflammation, may have promoted the ectopic beats in this population  
16 (Sarnat et al., 2006, [090489](#)).

### 6.3.2.2. Heart Rate/Heart Rate Variability

17 In the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), two large population-based studies of air  
18 pollution and HRV were summarized (Liao et al., 2004, [056590](#); Park et al., 2005, [057331](#)). In  
19 addition, the biological mechanisms and potential importance of HRV were discussed. Briefly, the  
20 study of acute adverse effects of air pollution on cardiac autonomic control is based on the  
21 hypothesis that increased air pollution levels may stimulate the autonomic nervous system and lead  
22 to an imbalance of cardiac autonomic control characterized by sympathetic activation unopposed by  
23 parasympathetic control (U.S. EPA, 2006, [088089](#)). Examples of HRV indices include the standard  
24 deviation of normal-to-normal intervals (SDNN), the square root of the mean of the sum of the  
25 squares of differences between adjacent NN intervals (r-MSSD), high-frequency power (HF), low-  
26 frequency power (LF), and the LF/HF ratio. Liao et al. (2004, [056590](#)) examined the association  
27 between air pollution and cardiac autonomic control in the fourth cohort examination (1996-1998) of  
28 the U.S.-based Atherosclerosis Risk in Communities Study. A decrease in log-transformed HF was  
29 associated with an increase in O<sub>3</sub> concentration among white study participants. Park et al. (2005,  
30 [057331](#)) examined the effects of air pollution on indices of HRV in a population-based study among  
31 men from the Normative Aging Study in Boston, Massachusetts. Several associations were observed  
32 with O<sub>3</sub> and HRV outcomes; a reduction in LF was associated with increased O<sub>3</sub> concentration,  
33 which was robust to inclusion of PM<sub>2.5</sub>. The associations with all HRV indices and O<sub>3</sub> were stronger  
34 among those with ischemic heart disease and hypertension. In addition to these population-based  
35 studies included in the 2006 O<sub>3</sub> AQCD was a study by Schwartz et al. (2005, [074317](#)), who  
36 conducted a panel study to assess the relationship between exposure to summertime air pollution and  
37 HRV. A weak association of O<sub>3</sub> during the hour immediately preceding the health measures was

1 observed with r-MSSD among a study population that consisted of mostly older female participants.  
 2 In summary, these studies suggest that short-term exposures to O<sub>3</sub> are predictors of decreased HRV  
 3 and that the relationship may be stronger among certain subgroups. The generally consistent  
 4 (although weak) associations between pollutants and reduced cardiac autonomic control were  
 5 observed at relatively low pollution concentrations typically experienced by the U.S. general  
 6 population on a daily basis (U.S. EPA, 2006, [088089](#)). More recent studies of O<sub>3</sub> and HRV and are  
 7 described below. The O<sub>3</sub> concentrations for these studies are presented in Table 6-24.

**Table 6-24. Characterization of ozone concentrations (in ppb) from studies of heart rate variability**

Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Chuang et al. (2007, <a href="#">091063</a> )	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
Ruidavets et al. (2005, <a href="#">089443</a> )	Toulouse, France	8 h	38.3 (14.8)	75th: 46.9 Max: 80.3
Chan et al. (2005, <a href="#">088988</a> )	Taipei, Taiwan	1 h	21.9 (15.4)	Max: 114.9
Zanobetti et al. (2010, <a href="#">597250</a> )	Boston, Massachusetts	0.5 h	20.7*	75th: 30.33
		2 h	20.5*	75th: 30.08
		3D	21.9*	75th: 28.33
		5D	22.8*	75th: 29.28
Wheeler et al. (2006, <a href="#">088453</a> )	Atlanta, Georgia	4 h	18.5	75th: 22.5
		24 h	29.4	
Baja et al. (2010, <a href="#">626540</a> )	Boston, Massachusetts	0 lag 10-h lag	23 (16) 21 (15)	
Park et al. (2008, <a href="#">093027</a> )	Boston, Massachusetts	24 h	23.4 (13)	
Park et al. (2007, <a href="#">093268</a> )	Boston, Massachusetts	24 h	Range of 17.0-29.1	
Wu et al. (2010, <a href="#">626033</a> )	Taipei, Taiwan	Working period	24.9 (14.0)	Max: 59.2

\*Median presented (information on mean not given).

8 Several follow-up examinations of HRV were conducted among the participants of the  
 9 Normative Aging Study in Boston. A trajectory cluster analysis was used to assess whether pollution  
 10 originating from different locations had varying relationships with HRV (Park et al., 2007, [093268](#)).  
 11 Subjects who were examined on days when air parcels originated in the west had the strongest  
 12 associations with O<sub>3</sub>; however, the O<sub>3</sub> concentration in this cluster was low (24-h avg, 17.0 ppb)  
 13 compared to the other clusters (24-h avg of 21.3-29.1 ppb). LF and SDNN decreased with increases  
 14 in the 4-h moving average of O<sub>3</sub> from the west (LF decreased by 33.4% [95% CI: 0.9, 55.3%] and  
 15 SDNN decreased by 17.1% [95% CI: -0.3, 31.5%] per 17-ppb increase in 4-h avg O<sub>3</sub> concentrations)  
 16 (Park et al., 2007, [093268](#)). The Boston air mass originating in the west traveled over Illinois,  
 17 Indiana, and Ohio; states typically characterized by coal-burning power plants. Due to the low O<sub>3</sub>  
 18 concentrations observed in the west cluster, the authors hypothesize that O<sub>3</sub> on those days could be  
 19 capturing the effects of other, secondary and/or transported pollutants from the coal belt or that the  
 20 relationship between ambient O<sub>3</sub> and personal exposure to O<sub>3</sub> is stronger during that period  
 21 (supported by a comparatively low apparent temperature which could indicate a likelihood to keep  
 22 windows open and reduced air conditioning use) (Park et al., 2007, [093268](#)). An additional follow-up  
 23 evaluation using the Normative Aging Study examined the potential for effect modification by

1 chronic lead exposure on the relationship between air pollution and HRV (Park et al., 2008, [093027](#)).  
2 Authors observed graded reductions in HF and LF of HRV in relation to O<sub>3</sub> (and sulfate) across  
3 increasing quartiles of tibia and patella lead (HF: %change 16.1 [95% CI: -18.9, 66.2] for the first  
4 quartile of tibia Pb and -37.9 [95% CI: -54.6, -14.9] for the fourth quartile of tibia Pb per 16-ppb  
5 increase in 4-h avg O<sub>3</sub> concentrations; LF: %change 4.2 [95% CI: -21.8, 38.8] for the first quartile of  
6 tibia Pb and -38.1 [95% CI: -51.9, -20.4] for the fourth quartile of tibia Pb per 16-ppb increase in 4-h  
7 avg O<sub>3</sub> concentrations). In addition, O<sub>3</sub> associations were similar when education and cumulative  
8 traffic-adjusted bone lead levels were used in analyses. Authors indicate the possibility that O<sub>3</sub>  
9 (which has low indoor concentrations) was acting as a proxy for sulfate (correlation coefficient for  
10 O<sub>3</sub> and sulfate = 0.57). Investigators of a more recent follow-up to the Normative Aging Study  
11 hypothesized that the relationships between short-term air pollution exposures and ventricular  
12 repolarization, as measured by changes in the heart-rate corrected QT interval (QTc), would be  
13 modified by participant characteristics (e.g., obesity, diabetes, smoking history) and genetic  
14 susceptibility to oxidative stress (Baja et al., 2010, [626540](#)). No evidence of an association between  
15 O<sub>3</sub> (using a quadratic constrained distributed lag model and hourly exposure lag models over a 10-h  
16 time window preceding the visit) and QTc was reported (change in mean QTc -0.74 [95% CI: -3.73,  
17 2.25]); therefore, potential effect modification of personal and genetic characteristics with O<sub>3</sub> was  
18 not assessed (Baja et al., 2010, [626540](#)). Collectively, the results from studies that examined the  
19 Normative Aging Study cohort found an association between increases in short-term exposures to O<sub>3</sub>  
20 and decreases in HRV (Park et al., 2005, [057331](#); Park et al., 2007, [093268](#); Park et al., 2008,  
21 [093027](#)) although not consistently in all of the studies (Baja et al., 2010, [626540](#)). Further, observed  
22 relationships appear to be stronger among those with ischemic heart disease, hypertension, and  
23 elevated bone lead levels, as well as when air masses arrive from the west (the coal belt). However,  
24 it is not clear if O<sub>3</sub> is acting as a proxy for other, secondary particle pollutants (such as sulfate) (Park  
25 et al., 2005, [057331](#); 2007, [093268](#); 2008, [093027](#)). In addition, since the Normative Aging Study  
26 participants were older, predominately white men, results may not be generalizable to women,  
27 younger individuals, or those of different racial/ethnic groups (Baja et al., 2010, [626540](#)).

28 A panel study among 18 individuals with COPD and 12 individuals with recent myocardial  
29 infarction (MI) was conducted in Atlanta, Georgia (Wheeler et al., 2006, [088453](#)). HRV was assessed  
30 for each participant on 7 days in fall 1999 and/or spring 2000. The mean 4-h O<sub>3</sub> concentration (time  
31 period immediately preceding the HRV measures) was 18.5 ppb; however, O<sub>3</sub> concentrations  
32 differed substantially within study sites (8.0 – 33.8 ppb). Ozone concentrations were not associated  
33 with HRV (SDNN) among all subjects (percent change of 0.75 [95% CI: -3.6, 5.3] per 9.61-ppb 4-h  
34 O<sub>3</sub> increase) or when stratified by disease type (COPD, recent MI, and baseline FEV<sub>1</sub>) (Wheeler et  
35 al., 2006, [088453](#)).

36 HRV and air pollution was assessed in a panel study among 46 predominately white male  
37 patients (study population: 80.4% male, 93.5% white) aged 43-75 years in Boston, Massachusetts,  
38 with coronary artery disease (Zanobetti et al., 2010, [597250](#)). Up to four home visits were made to  
39 assess HRV over the year following the index event. Pollution lags used in analyses ranged between

1 30 minutes to a few hours and up to 5 days prior to the HRV assessments. Decreases in r-MSSD  
2 were reported for all averaging times of O<sub>3</sub> (percent change of -5.18% [95% CI: -7.89, -2.30] per 20  
3 ppb of 5-day moving average of O<sub>3</sub> concentration), but no evidence of association between O<sub>3</sub> and  
4 HF was observed (quantitative results not provided). In two-pollutant models with O<sub>3</sub> and either  
5 PM<sub>2.5</sub> or BC, the independent effects of O<sub>3</sub> were observed.

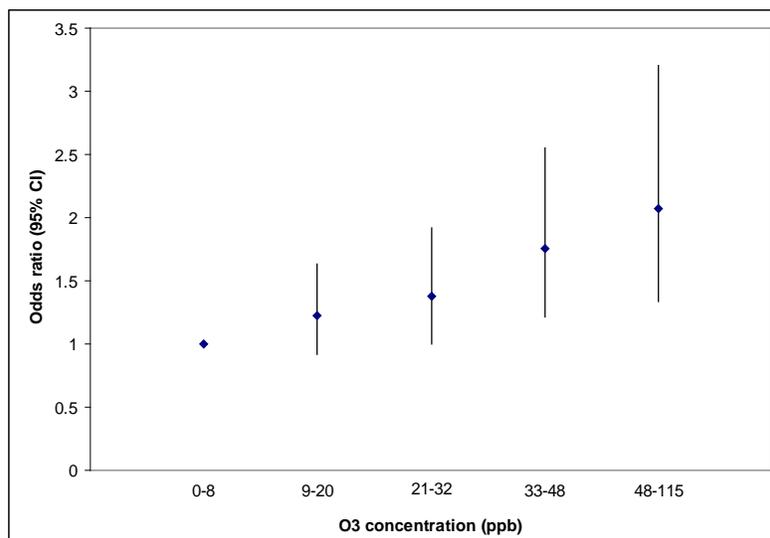
6 A few studies were conducted outside of the U.S. to assess the relationship between air  
7 pollution concentrations and heart rate and HRV (Chan et al., 2005, [088988](#); Chuang et al., 2007,  
8 [098629](#); Ruidavets et al., 2005, [089443](#); Wu et al., 2010, [626033](#)). No associations were reported  
9 between O<sub>3</sub> and HRV among CHD patients and patients with one or more major CHD risk factors  
10 residing in Taipei, Taiwan (Chan et al., 2005, [088988](#)). Another study taking place in Taipei, Taiwan  
11 examined mail carriers and reported O<sub>3</sub> levels measured using personal monitors. No association was  
12 observed between O<sub>3</sub> and the measures of HRV (percent change for SDNN: 0.57 [95% CI: -21.27,  
13 28.46], r-MSSD: -7.10 [95% CI: -24.24, 13.92], HF: -1.92 [95% CI: -23.68, 26.02], LF: -4.82 [95%  
14 CI:  
15 -25.34, 21.35] per 40 ppb O<sub>3</sub>) (Wu et al., 2010, [626033](#)). In addition, no consistent relationships were  
16 identified between O<sub>3</sub> and resting heart rate among middle-aged (35-64 years) participants residing  
17 in Toulouse, France (Ruidavets et al., 2005, [089443](#)). A negative trend was reported for the 3-day  
18 cumulative (lag days 1-3) concentration of O<sub>3</sub> with heart rate (p for trend = 0.02); however, the  
19 individual odds ratios comparing quintiles of exposure showed no association (OR for O<sub>3</sub> of 0.93  
20 [95% CI: 0.86, 1.01] for the highest quintile of resting heart rate compared to the lowest). When  
21 stratified by current smoking status, non-smokers had a decreased trend with increased 3-day  
22 cumulative O<sub>3</sub> concentrations but none of the quintiles for heart rate were statistically significant. A  
23 panel study was conducted in Taiwan to assess the relationship between air pollutants and  
24 inflammation, oxidative stress, blood coagulation, and autonomic dysfunction (Chuang et al., 2007,  
25 [091063](#); Chuang et al., 2007, [098629](#)). Participants were apparently healthy college students (aged  
26 18-25 year) who were living in a university dormitory in metropolitan Taipei. Health endpoints were  
27 measured three times from April to June in 2004 or 2005. Ozone was assessed in statistical models  
28 using the average of the 24, 48, and 72 hours before the hour of each blood sampling. Decreases in  
29 HRV (measured as SDNN, r-MSSD, LF, and HF) were associated with increases in O<sub>3</sub>  
30 concentrations in single-pollutant models (percent change for SDNN: -13.45 [95% CI: -16.26, -  
31 10.60], r-MSSD -13.76 [95% CI: -21.62, -5.44], LF -9.16 [95% CI: -13.29, -4.95], HF -10.76 [95%  
32 CI: -18.88, -2.32] per 20 ppb 3-day avg O<sub>3</sub> concentrations) and remained associated with 3-day O<sub>3</sub>  
33 concentrations in two-pollutant models with sulfate.

### 6.3.2.3. Stroke

34 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) did not identify any studies that examined the  
35 association between short-term O<sub>3</sub> exposure and stroke. However, recent studies have attempted to  
36 examine this relationship. Lisabeth et al. (2008, [155939](#)) used a time-series approach to assess the  
37 relationship between daily counts of ischemic stroke and transient ischemic attack (TIA) with O<sub>3</sub>

1 concentrations in a southeast Texas community among residents 45 years and older (2001-2005;  
2 median age of cases, 72 years). The median O<sub>3</sub> (hourly average per 24-h time-period) concentration  
3 was 25.6 ppb (IQR 18.1-33.8). The associations between same-day (RR: 1.03 [95% CI: 0.96, 1.10]  
4 per 20-ppb increase in 24-h avg O<sub>3</sub> concentrations) and previous-day (RR: 1.05 [95% CI: 0.99, 1.12]  
5 per 20-ppb increase in 24-h avg O<sub>3</sub> concentrations) O<sub>3</sub> concentrations and stroke/TIA risk were  
6 positive. Associations were robust to adjustment for PM<sub>2.5</sub>. The effect of season on the relationship  
7 was not assessed.

8 A case-crossover design was used in a study conducted in Dijon, France between March 1994  
9 and December 2004, among those 40 years of age and older who presented with first-ever stroke  
10 (Henrotin et al., 2007, [093270](#)). The mean O<sub>3</sub> concentration, calculated over 8-h daytime periods,  
11 was 14.95 ppb (IQR: 6-22 ppb). An association between ischemic stroke occurrence and O<sub>3</sub>  
12 concentrations with a 1-day lag was observed (OR: 1.54 [95% CI: 1.14, 2.09] per 30-ppb increase in  
13 8-h max O<sub>3</sub> concentrations). The effect of O<sub>3</sub> persisted in two-pollutant models with PM<sub>10</sub>, SO<sub>2</sub>, NO<sub>2</sub>,  
14 and CO. This association was stronger among men (OR: 2.12 [95% CI: 1.36, 3.30] per 30-ppb  
15 increase in 8 h max O<sub>3</sub> concentrations) than among women (OR: 1.17 [95% CI: 0.77, 1.78] per  
16 30-ppb increase in 8 h max O<sub>3</sub> concentrations). When stroke was examined by subtype among men,  
17 an association was observed for ischemic strokes of large arteries and for transient ischemic attacks  
18 but not for cardioembolic or lacunar ischaemic strokes. The subtype analysis was not performed for  
19 women. Additionally, for men a linear exposure-response was observed when O<sub>3</sub> was assessed based  
20 on quintiles (p for trend = 0.01) (Figure 6-21). A potential limitation of this study is that 67.4% of the  
21 participating men were smokers compared to 9.3% of the women.



Source: Henrotin et al. (2007, [093270](#)).

**Figure 6-21. Odds ratio (95% confidence interval) for stroke by quintiles of ozone.**

### 6.3.2.4. Biomarkers

1 An increasing number of studies have examined the relationship between air pollution and  
 2 biomarkers of inflammation and oxidative stress in an attempt to elucidate the biological  
 3 mechanisms linking air pollution and cardiovascular disease. A wide range of markers assessed as  
 4 well as different types of study designs and locations chosen make comparisons across studies  
 5 difficult. Table 6-25 provides an overview of the O<sub>3</sub> concentrations reported in each of the studies  
 6 evaluated.

**Table 6-25. Characterization of ozone concentrations (in ppb) from studies of biomarkers**

Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Rudez et al. (2009, <a href="#">193783</a> )	Rotterdam, the Netherlands	24 h	22*	75th: 31.5 Max: 90
		24 h	28.4 (12.1)	Max: 49.3
Chuang et al. (2007, <a href="#">091063</a> )	Taipei, Taiwan	48 h	33.3 (8.9)	Max: 47.8
		72 h	33.8 (7.1)	Max: 48.3
		1 h	18.3*	75th: 35.1 Max: 202.3
Baccarelli et al. (2007, <a href="#">091310</a> )	Lombardia, Italy	1 h	18.3*	75th: 35.1 Max: 202.3
Steinvil et al. (2008, <a href="#">188893</a> )	Tel-Aviv, Israel	0.5 h	29.2 (9.7)	75th: 36
Wellenius et al. (2007, <a href="#">092830</a> )	Boston, Massachusetts	1 h/24 h	25.1 (12.9)	
Liao et al. (2005, <a href="#">088677</a> )	3 U.S. counties	8 h	40 (20)	
Goldberg et al. (2008, <a href="#">180380</a> )	Montreal, Quebec	24 h	NS	
Chen et al. (2007, <a href="#">145956</a> )	Los Angeles and San Francisco, California	8 h/2 wk	30.8*	Max: 47.9
		8 h/1 mon	28.3*	Max: 43.1
Thompson et al. (2010, <a href="#">386859</a> )	Toronto, Ontario	1 h/1 yr	21.94 (15.78)	
Chuang et al. (2010, <a href="#">379993</a> )	Taiwan		26.83 (9.7)	Max: 62.1

\*Median presented (information on mean not given).

7 Thompson et al. (2010, [386859](#)) assessed ambient air pollution exposures and measures of  
 8 systemic inflammatory biomarkers, IL-6 and fibrinogen. This retrospective repeated measures  
 9 analysis was conducted among 45 adults (18-40 years of age) in Toronto, Canada between the years  
 10 of 1999 and 2006. Single pollutant models were used to analyze the repeated-measures data using  
 11 moving averages up to 7 days. A positive association was observed between IL-6 and O<sub>3</sub> with the  
 12 strongest effects observed for the 4-day moving average of O<sub>3</sub> (quantitative results not provided). No  
 13 association was seen for shorter averaging times (<1 day). When examined by season using 2-day  
 14 moving averages, the association between O<sub>3</sub> and IL-6 was positive during only the spring and  
 15 summer. No evidence of association was observed for O<sub>3</sub> and fibrinogen.

16 The association between O<sub>3</sub> exposure and markers of lipid peroxidation and antioxidant  
 17 capacity was examined among 120 nonsmoking healthy college students, aged 18-22 years, from the  
 18 University of California, Berkeley (February-June 2002) (Chen et al., 2007, [145956](#)). By design,  
 19 students were chosen that had experienced different geographic concentrations of O<sub>3</sub> over their  
 20 lifetimes and during recent summer vacation in either greater Los Angeles (LA) or the San Francisco  
 21 Bay Area (SF). Long-term (based on lifetime residential history) and shorter-term (based on the  
 22 moving averages of 8-h max concentrations 1-30 days prior to the day of blood collection) O<sub>3</sub>

1 exposures were estimated (lifetime exposure results presented in the chronic exposure section). A  
2 marker of lipid peroxidation, 8-isoprostane (8-iso-PGF), was assessed. This marker is formed  
3 continuously under normal physiological conditions but has been found at elevated concentrations in  
4 response to environmental exposures. A marker of overall antioxidant capacity, ferric reducing  
5 ability of plasma (FRAP), was also measured. Substantial overlap in the more recent O<sub>3</sub> exposure  
6 estimates (8-h moving averages) was observed between the two geographic areas sampled. Levels of  
7 8-iso-PGF were associated with 2-week ( $\beta = 0.035$  [pg/mL]/8-h ppb O<sub>3</sub>,  $p = 0.007$ ) and 1-month ( $\beta =$   
8  $0.031$  [pg/mL]/8-h ppb O<sub>3</sub>,  $p = 0.006$ ) estimated O<sub>3</sub> exposure levels. No evidence of association was  
9 observed between O<sub>3</sub> and FRAP. A chamber study performed among a subset of study participants  
10 supported the primary study results. The concentrations of 8-iso-PGF increased immediately after  
11 the 4-h controlled O<sub>3</sub> exposure ended ( $p = 0.10$ ). However, levels returned to near baseline by  
12 18 hours without further exposure. The authors note that O<sub>3</sub> was highly correlated with PM<sub>10-2.5</sub> and  
13 NO<sub>2</sub> in this study population; however, inclusion of these pollutants in the O<sub>3</sub> models did not  
14 substantially modify the magnitude of the associations with O<sub>3</sub>.

15 A 2-month panel study among 31 congestive heart failure patients (aged 50-85 years) was  
16 conducted to assess the relationship between air pollution and oxygen saturation and pulse rate in  
17 Montreal, Canada from July 2002 to October 2003 (Goldberg et al., 2008, [180380](#)). All participants  
18 had limited physical functioning (New York Heart Association Classification  $\geq$  II) and an ejection  
19 fraction (the fraction of blood pumped out of the heart per beat) less than or equal to 35% (normal is  
20 above 55%). Daily mean O<sub>3</sub> concentrations were calculated based on hourly measures at 10  
21 monitoring stations. There was a negative association between O<sub>3</sub> (lag-0) and oxygen saturation  
22 when adjustment was made for temporal trends (unadjusted mean difference -0.097 [95% CI: -0.178,  
23 -0.015] per 11.85 ppb O<sub>3</sub>). In the models incorporating personal covariates and weather factors, the  
24 association remained suggestive although not statistically significant (adjusted mean difference -  
25 0.074 [95% CI: -0.157, 0.010] per 11.85 ppb O<sub>3</sub>). The associations of O<sub>3</sub> with a lag of 1 day or a  
26 3-day mean were not statistically significant. No evidence of association was observed between O<sub>3</sub>  
27 exposure and pulse rate.

28 A population-based study was conducted to assess the relationship between short-term  
29 exposure to air pollution and markers of blood coagulation/systemic inflammation [fibrinogen, factor  
30 VIII coagulant activity (VIII-C), von Willebrand factor (vWF), white blood cell count (WBC), and  
31 albumin] using the Atherosclerosis Risk in Communities (ARIC) study cohort (Liao et al., 2005,  
32 [088677](#)). Significant curvilinear associations were observed for O<sub>3</sub> (1 day prior to blood draw) and  
33 fibrinogen and vWF (quantitative results not provided for regression models although adjusted  
34 means [SE] of vWF were given as 118% [0.79%] for O<sub>3</sub> concentrations <40 ppb, 117% [0.86%] for  
35 O<sub>3</sub> concentrations 40-70 ppb, and 124% [1.97%] for O<sub>3</sub> concentrations of 70 ppb). The association  
36 between O<sub>3</sub> and fibrinogen was more pronounced among those with a history of cardiovascular  
37 disease (CVD) and was statistically significant among only this subgroup of the population. The  
38 curvilinear relationship between exposure and outcome suggested stronger relationships at higher  
39 concentrations of O<sub>3</sub> which could indicate threshold effects. The authors note that the most

1 pronounced associations occurred when the pollutants were 2-3 standard deviations above the mean.  
2 In addition, the regression coefficients are small, indicating weak associations. The results from this  
3 relatively large-scale cross-sectional study suggest weak associations with O<sub>3</sub> and fibrinogen (among  
4 those with a history of CVD) and vWF.

5 In a repeated-measures study conducted in Boston among 28 patients with congestive heart  
6 failure and impaired systolic function, Wellenius et al. (2007, [092830](#)) found no evidence of an  
7 association between B-type natriuretic peptide (BNP) and short-term O<sub>3</sub> exposures at lags 0-3 days  
8 (quantitative results not provided). BNP was chosen because it is directly associated with cardiac  
9 hemodynamics and symptom severity among those with heart failure and is, therefore, considered a  
10 marker of functional status. However, the authors conclude that the use of BNP may not be useful in  
11 studies of the health effects of ambient air pollutants due to the large amount of within-person  
12 variability in BNP levels observed in this population.

13 International studies were identified that also examined the association between air pollution  
14 and biomarkers of cardiovascular risk (Baccarelli et al., 2007, [091310](#); Chuang et al., 2007, [091063](#);  
15 Rudez et al., 2009, [193783](#); Steinvil et al., 2008, [188893](#)). The relationship between pollutant  
16 concentrations and one-time measures of inflammatory biomarkers was assessed among 3659  
17 apparently healthy individuals in Tel Aviv, Israel (Steinvil et al., 2008, [188893](#)). No evidence of  
18 association was observed between O<sub>3</sub> and high-sensitivity C-reactive protein (hs-CRP) (expected  
19 relative change of -2% [95% CI: -12, 9] and -4% [95% CI: -16, 10] per 15 ppb O<sub>3</sub> averaged over the  
20 last week for men and women, respectively) or WBC (expected absolute change of -25 cells/μL  
21 [95% CI: -178, 191] and 142 cells/μL [95% CI: -79, 363] per 15 ppb O<sub>3</sub> averaged over the last week  
22 for men and women, respectively). In single pollutant models, O<sub>3</sub> was associated with an increase in  
23 fibrinogen at a 4-day lag among men (expected absolute change of 4.2 mg/dL [95% CI: 0.1, 8.3] per  
24 15 ppb O<sub>3</sub>) and a same-day O<sub>3</sub> concentration among women (expected absolute change of 6.5 mg/dL  
25 [95% CI: 1.4, 11.5] per 15 ppb O<sub>3</sub>) but results for other lags (0 through 7 days) were mixed (some  
26 positive, some negative; none statistically significant). The associations for men with 4-day lag and  
27 for women with 0-day lag did not persist in multi-pollutant models and, in fact, several inverse  
28 associations were observed between O<sub>3</sub> and fibrinogen.

29 The effects of air pollution on fasting and postmethionine-load total homocysteine (tHcy)  
30 levels were assessed among 1,213 apparently healthy individuals from Lombardia, Italy from  
31 January 1995 to September 2005 (Baccarelli et al., 2007, [091310](#)). tHcy is an independent risk factor  
32 for vascular disease and measurement of this marker after oral methionine load is used to identify  
33 individuals with mild impairment of homocysteine metabolism. An increase in the 24-h O<sub>3</sub>  
34 concentrations was associated with an increase in fasting tHcy (percent change 6.25 [95% CI: 0.84,  
35 11.91] per 20 ppb O<sub>3</sub>) but no association was observed with postmethionine-load tHcy (percent  
36 change 4.16 [95% CI: -1.76, 10.42] per 20 ppb O<sub>3</sub>). In addition, no evidence of association was  
37 observed between 7-day O<sub>3</sub> concentrations and tHcy (percent change for fasting tHcy 3.36 [95% CI:  
38 -1.30, 8.39] and percent change for postmethionine-load tHcy -0.65 [95% CI: -5.66, 4.71] per 20 ppb

1 O<sub>3</sub>). No evidence of effect modification by smoking was observed. The authors conclude that their  
2 results did not show a consistent pattern of an effect of O<sub>3</sub> on tHcy.

3 A panel study (n=76) of healthy individuals was conducted in Taiwan to assess the relationship  
4 between air pollutants and inflammation, oxidative stress, blood coagulation, and autonomic  
5 dysfunction (Chuang et al., 2007, [091063](#)). Health endpoints were measured three times from April  
6 to June in 2004 or 2005. Ozone effects were assessed in statistical models using the average of the  
7 24 hours (1 day), 48 hours (2 days), and 72 hours (3 days) before the hour of each blood sampling.  
8 Increases in hs-CRP, 8-hydroxy-2'-deoxyguanosine (8-OHdG), fibrinogen, and plasminogen  
9 activator fibrinogen inhibitor-1 (PAI-1) were associated with increases in O<sub>3</sub> concentrations in  
10 single-pollutant models (percent change in hs-CRP: 244.38 [95% CI: 4.54, 585.15] per 20 ppb 3-day  
11 avg O<sub>3</sub>; percent change in 8-OHdG: 2.46 [95% CI: 1.01, 3.92] per 20 ppb 1-day avg O<sub>3</sub>; percent  
12 change in fibrinogen: 11.76 [95% CI: 4.03, 19.71] per 20 ppb 3-day avg O<sub>3</sub>; percent change in PAI-  
13 1: 37.53 [95% CI: 38.91, 84.27] per 20 ppb 3-day avg O<sub>3</sub>). No association was seen between O<sub>3</sub> and  
14 tissue-type plasminogen activator (tPA), a fibrinolytic factor (percent change 16.15 [95% CI: -4.62,  
15 38.34] per 20 ppb 3-day avg O<sub>3</sub>). PAI-1 remained statistically significantly associated with 3-day O<sub>3</sub>  
16 concentrations in two-pollutant models with sulfate.

17 A repeated measures study was conducted in 40 healthy individuals living or working in the  
18 city center of Rotterdam, the Netherlands to assess the relationship between air pollution and  
19 markers of hemostasis and inflammation (platelet aggregation, thrombin generation, fibrinogen, and  
20 CRP) (Rudez et al., 2009, [193783](#)). Each participant provided between 11 and 13 blood samples  
21 throughout a 1-year period (498 samples on 197 days). Examined lags ranged from 6 hours to 3 days  
22 prior to blood sampling. No consistent evidence of association was observed between O<sub>3</sub> and any of  
23 the biomarkers (percent change of max platelet aggregation: -6.87 [95% CI: -21.46, 7.70] per 20 ppb  
24 4-day average O<sub>3</sub>; percent change of endogenous thrombin potential: 0.95 [95% CI: -3.05, 5.23] per  
25 20-ppb 4-day avg O<sub>3</sub>; percent change of fibrinogen: -0.57 [95% CI: -3.05, 2.00] per 20-ppb lag 1-day  
26 O<sub>3</sub>; percent change of CRP: -0.48 [95% CI: -14.05, 13.10] per 20-ppb lag 1-day O<sub>3</sub>). Some  
27 associations with O<sub>3</sub> were in the opposite direction to that hypothesized which may be explained by  
28 the negative correlation between O<sub>3</sub> and the other pollutants (correlation coefficients ranged from -  
29 0.4 to -0.6). The statistically significant inverse effects observed with O<sub>3</sub> in single-pollutant models  
30 were no longer apparent when PM<sub>10</sub> was included in the models (Rudez et al., 2009, [193783](#)).

31 Chuang et al. (2010, [379993](#)) conducted a population-based cross-sectional analysis of data  
32 collected on 7,778 participants during the Taiwanese Survey on Prevalence of Hyperglycemia,  
33 Hyperlipidemia, and Hypertension in 2001. Apolipoprotein B (ApoB), the primary apolipoprotein  
34 among low-density lipoproteins, was associated with 3-day avg O<sub>3</sub> at the p < 0.10 level (change in  
35 ApoB: 0.78 mg/dL [95% CI: -0.06, 1.62] per 12.15 ppb O<sub>3</sub>). The 5-day mean O<sub>3</sub> concentration was  
36 associated with an increase in triglycerides at p < 0.10 (change in triglycerides: 2.15 mg/dL [95% CI:  
37 -0.03, 4.32] per 12.15 ppb O<sub>3</sub>). In addition, the 1-, 3-, and 5-day mean O<sub>3</sub> concentrations were  
38 associated with increased HbA1c levels (a marker used to monitor the degree of control of glucose  
39 metabolism)(p < 0.05; change in HbA1c: 0.06 % [95% CI: 0.02, 0.10], 0.05% [95% CI: 0.02, 0.08],

1 and 0.07% [95% CI: 0.04, 0.10] per 12.15 ppb O<sub>3</sub>, respectively). The 5-day mean O<sub>3</sub> was associated  
 2 with increased fasting glucose levels (p < 0.10) (change in fasting glucose: 0.77 mg/dL [95% CI:  
 3 -0.05, 1.59] per 12.15 ppb O<sub>3</sub>). No association was observed between O<sub>3</sub> concentration and ApoA1  
 4 (change in ApoA1: -0.24 mg/dL [95% CI: -1.04, 0.56], -0.14 [95% CI: -0.94, 0.66], and 0.01 [95%  
 5 CI: -0.69, 0.72] per 12.15 ppb for 1-, 3-, and 5-day averaged O<sub>3</sub>, respectively). Co-pollutant models  
 6 were not assessed.

### 6.3.2.5. Myocardial Infarction (MI)

7 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) reported mixed results on the association  
 8 between short-term O<sub>3</sub> exposure and MI. One study reported a positive association between current  
 9 day O<sub>3</sub> concentration and acute MI, especially among the oldest age group (55- to 64-year olds)  
 10 (Ruidavets et al., 2005, [074091](#)). No association was observed in a case-crossover study of O<sub>3</sub> during  
 11 the hours surrounding the event and MI (Peters et al., 2001, [016546](#)). Since the 2006 O<sub>3</sub> AQCD, no  
 12 new epidemiology studies have examined this association for MI, but one study has been published  
 13 on arterial stiffness. Wu et al. (2010, [626033](#)) examined mail carriers aged 25-46 years and measured  
 14 exposure to O<sub>3</sub> through personal monitors [mean O<sub>3</sub> 24.9 (SD 14.0) ppb]. Ozone exposure was  
 15 positively associated with arterial stiffness (percent change 11.24% [95% CI: 3.67, 19.62] per 40-ppb  
 16 O<sub>3</sub>) and was robust to adjustment for PM.

### 6.3.2.6. Blood Pressure

17 In the 2006 O<sub>3</sub> AQCD, no epidemiologic studies examined O<sub>3</sub>-related effects on blood  
 18 pressure (BP). Recent studies have been conducted to evaluate this relationship and the O<sub>3</sub>  
 19 concentrations for these studies are listed in Table 6-26.

**Table 6-26. Characterization of ozone concentrations (in ppb) from studies of blood pressure**

Reference	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Choi et al. (2007, <a href="#">093196</a> )	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
Delfino et al. (2010, <a href="#">625026</a> )	Los Angeles, California	24 h	27.1 (11.5)	Max: 60.7
Zanobetti et al. (2004, <a href="#">087489</a> )	Boston, Massachusetts	1 h	20	
		5 days	24	
Chuang et al. (2010, <a href="#">379993</a> )	Taiwan		26.83 (9.7)	Max: 62.1

20 Zanobetti et al. (2004, [087489](#)) examined the relationship between air pollutants and BP from  
 21 May 1999 to January 2001 for 631 repeat visits among 62 Boston residents with CVD. In single-  
 22 pollutant models, higher resting diastolic blood pressure (DBP) was associated with the 5-day (0-  
 23 4 days) averages of O<sub>3</sub> (RR: 1.03 [95% CI: 1.00, 1.05] per 20-ppb increase in 24-h O<sub>3</sub>  
 24 concentrations). However, this effect was no longer apparent when PM<sub>2.5</sub> was included in the model  
 25 (data not presented) (Zanobetti et al., 2004, [087489](#)). Delfino et al. (2010, [625026](#)) examined 64

1 subjects 65 years and older with coronary artery disease, no tobacco smoke exposure, and living in  
2 retirement communities in the Los Angeles air basin with hourly (up to 14 h/day) ambulatory BP  
3 monitoring for 5 days during a warm period (July-mid-October) and 5 days during a cool period  
4 (mid-October-February). Investigators assessed lags of 1, 4, and 8 hours, 1 day, and up to 9 days  
5 before each BP measure; no evidence of association was observed for O<sub>3</sub> exposures (change in BP  
6 associated with a 20-ppb change in 24-h O<sub>3</sub> was 0.67 [95% CI: -1.16, 2.51 for systolic BP [SBP] and  
7 -0.25 [95% CI: -1.25, 0.75] for DBP) (Delfino et al., 2010, [625026](#)). Choi et al. (2007, [093196](#))  
8 conducted a cross-sectional study to investigate the relationship between air pollutants and BP  
9 among 10,459 participants of the Inha University Hospital health examination from 2001 to 2003.  
10 These individuals had no medical history of cardiovascular disease or hypertension. Ozone was  
11 associated with an increase in SBP for 1-day lag in the warm season and similar effect estimates  
12 were observed during the cold season but were not statistically significant (quantitative results not  
13 provided). Associations between O<sub>3</sub> and DBP were present in the cold season but not the warm  
14 season (quantitative results not provided). The interaction term between O<sub>3</sub> and season was  
15 statistically significant. Chuang et al. (2010, [379993](#)) conducted a similar type of study among 7,778  
16 participants of the Taiwanese Survey on Prevalence of Hyperglycemia, Hyperlipidemia, and  
17 Hypertension in 2001. Investigators examined 1-, 3-, and 5-day avg O<sub>3</sub> concentrations. An increase  
18 in DBP was associated with the 3-day mean O<sub>3</sub> concentration (change in BP for a 20-ppb increase in  
19 O<sub>3</sub> was 0.61 [95% CI: 0.07, 1.14]) (Chuang et al., 2010, [379993](#)). Associations were not observed for  
20 other days or with DBP.

### **6.3.2.7. Hospital Admissions and Emergency Department Visits**

21 Upon evaluating the collective evidence for O<sub>3</sub>-related cardiovascular HAs and ED visits, the  
22 2006 O<sub>3</sub> AQCD concluded that “a few studies observed positive O<sub>3</sub> associations, largely in the warm  
23 season. Overall, however, the currently available evidence is inconclusive regarding any association  
24 between ambient O<sub>3</sub> exposure on cardiovascular hospitalizations” (U.S. EPA, 2006, [088089](#)). Table  
25 6-27 below provides information on the O<sub>3</sub> concentrations reported in each of the recent HA and ED  
26 visit studies evaluated.

**Table 6-27. Characterization of ozone concentrations (in ppb) from studies of HAs and ED visits**

Study	Location	Averaging Time	Mean Concentration (Standard Deviation)	Upper Range of Concentration
Ballester et al. (2006, <a href="#">088746</a> )	Multicity, Spain	8 h warm season	Ranged from 24.2 to 44.3	
Bell et al. (2008, <a href="#">091268</a> )	Taipei, Taiwan	24 h	21.4	Max: 53.4
Buadong et al. (2009, <a href="#">602060</a> )	Bangkok, Thailand	1 h	14.4 (3.2)	Max: 41.9
Cakmak et al. (2006, <a href="#">099068</a> )	Multicity, Canada	1-h max	17.4	
Chan et al. (2006, <a href="#">090193</a> )	Taipei, Taiwan	1-h max	50.9 (26.4)	Max: 150.3
Halonen et al. (2009, <a href="#">625764</a> )	Helsinki, Finland	8-h max warm season	35.7*	75th: 42.1 Max: 79.6
Hosseinpoor et al. (2005, <a href="#">087413</a> )	Tehran, Iran	8-h max	4.9 (4.8)	75th: 7.2 Max: 99.0
Lanki et al. (2006, <a href="#">089788</a> )	Multicity, Europe	8-h max warm season	Ranged from 31.7 to 57.2*	
Larrieu et al. (2007, <a href="#">093031</a> )	Multicity France	8-h max warm season	Ranged from 34.2 to 53.1	
Lee et al. (2003, <a href="#">095552</a> )	Seoul, Korea	1-h max	36.0 (18.6)	75th: 44.9
Lee et al. (2007, <a href="#">196613</a> )	Kaohsiung, Taiwan	24 h	26.5	75th: 35.5 Max: 83.0
Middleton et al. (2008, <a href="#">156760</a> )	Nicosia, Cyprus	8-h max	Ranged from 28.7 to 54.9	
Peel et al. (2007, <a href="#">090442</a> )	Atlanta, GA	8-h warm season	55.6 (23.8)	
Stieb et al. (2009, <a href="#">195858</a> )	Multicity, Canada	24 h	18.4	
Symons et al. (2006, <a href="#">091258</a> )	Baltimore, MD	8 h warm season	31.0 (20.0)	Max: 120.0
Villeneuve et al. (2006, <a href="#">090191</a> )	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
Von Klot et al. (2005, <a href="#">088070</a> )	Multicity, Europe	8-h max warm season	Ranged from 16.4 to 28.0	
Wellenius et al. (2005, <a href="#">087483</a> )	Allegheny County, PA	24 h	24.3 (12.2)	75th: 32.0
Yang (2008, <a href="#">157160</a> )	Taipei, Taiwan	24 h	21.0	75th: 26.3 Max: 62.8
Zanobetti and Schwartz (2006, <a href="#">090195</a> )	Boston, MA	24 h	22.4*	75th: 31.0

\*Median presented (information on mean not given).

1 Multiple recent studies of O<sub>3</sub> exposure and cardiovascular HAs and ED visits have been  
2 conducted in the U.S. and Canada. Peel et al. (2007, [090442](#)) used a case-crossover framework to  
3 assess the relationship between air pollutants and cardiovascular disease ED visits among those with  
4 and without secondary comorbid conditions (hypertension, diabetes, chronic obstructive pulmonary  
5 disease [COPD], congestive heart failure [CHF], and dysrhythmia). Data on over 4 million ED visits  
6 from 31 hospitals were collected from January 1993 to August 2000. Ozone was monitored from  
7 March to October and 8 h max concentrations were used in case-crossover analyses. This study was  
8 a re-analysis of a time series study conducted to assess the main effects of air pollutants on  
9 cardiovascular ED visits in Atlanta (Metzger et al., 2004, [044222](#); Tolbert et al., 2007, [090316](#)). In  
10 the initial study, no evidence of associations was observed between O<sub>3</sub> and all CVD visits or visits  
11 for CVD subgroups, such as dysrhythmia, CHF, ischemic heart disease (IHD), and peripheral  
12 vascular and cerebrovascular disease. The relative risk for all CVD visits was 1.01 (95% CI: 0.99,  
13 1.02) for a 20-ppb increase in the 3-day moving avg (lags 0-2 days) of 8-h O<sub>3</sub> (Metzger et al., 2004,

1 [044222](#)). Similar to the initial investigation using a time-series analysis, no evidence of association  
2 was observed for the O<sub>3</sub> 3-day moving average and CVD visits among the entire population using  
3 the case-crossover design (Peel et al., 2007, [090442](#)). However, the relationship between O<sub>3</sub> and  
4 peripheral and cerebrovascular disease visits was substantially stronger among patients with  
5 comorbid COPD (OR: 1.19 [95% CI: 1.03-1.36] per 20 ppb, lag 0-2 days) as compared to patients  
6 without COPD (OR: 1.01 [95% CI: 0.97-1.04] per 20 ppb, lag 0-2 days) (comparing O<sub>3</sub> regression  
7 coefficients for visits with and without comorbid COPD:  $p < 0.05$ ). The same research group  
8 expanded upon the number of Atlanta hospitals providing ED visit data (41 hospitals) as well as the  
9 length of the study period (1993-2004) in order to assess multi-pollutant models and updated single-  
10 pollutant models (Tolbert et al., 2007, [090316](#)). The mean concentration for 8-h O<sub>3</sub> was 53.0 ppb.  
11 Similar to the results presented by Metzger et al. (2004, [044222](#)) and Peel et al. (2007, [090442](#))  
12 among the entire study population, no evidence of associations was observed for O<sub>3</sub> and CVD visits  
13 (Tolbert et al., 2007, [090316](#)). Again, models assessing the health effects of O<sub>3</sub> were limited to data  
14 collected from March through October.

15 Cakmak et al. (2006, [093272](#)) investigated the relationship between gaseous air pollutants and  
16 cardiac hospitalizations in 10 large Canadian cities using a time-series approach. A total of 316,234  
17 hospital discharge records for primary diagnosis of congestive heart failure, ischemic heart disease,  
18 or dysrhythmia were obtained from April 1993 through March 2000. Lags 0-5 were examined in  
19 analyses. Correlations between pollutants varied substantially across cities, which could partially  
20 explain discrepancies in effect estimates observed across the cities. In addition, pollutant lags  
21 differed across cities; the average lag for O<sub>3</sub> was 2.9 days. The pooled effect estimate for a 20-ppb  
22 increase in the daily 1-h max O<sub>3</sub> concentration and the percent change in hospitalizations among all  
23 10 cities was 2.3 (95% CI: 0.11, 4.50), and this estimate was not substantially altered in  
24 multi-pollutant analyses. The authors reported no evidence of effect modification by gender,  
25 neighborhood-level education, or neighborhood-level income. Seasonal variation was not assessed. A  
26 similar multicity time-series study was conducted using nearly 400,000 ED visits to 14 hospitals in  
27 seven Canadian cities from 1992 to 2003 (Stieb et al., 2009, [195858](#)). Primary analyses considered  
28 daily O<sub>3</sub> single day lags of 0-2 days; in addition, sub-daily lags of 3-h avg concentrations up to  
29 12 hours before presentation to the ED were considered. Seasonal variation was assessed by  
30 stratifying analyses by warm and cold seasons. No evidence of effect of O<sub>3</sub> on CVD ED visits was  
31 observed. One negative, statistically significant association was reported between a 1-day lag of O<sub>3</sub>  
32 and visits for angina/myocardial infarction. Ozone was negatively correlated with many of the other  
33 pollutants, particularly during the cold season.

34 The effect of air pollution on daily ED visits for ischemic stroke (n=10,881 visits) in  
35 Edmonton, Canada was assessed from April 1992 through March 2002 (Szyzkowicz, 2008,  
36 [192128](#)). A 26.37% (95% CI: 3.16-54.5) increase in stroke ED visits was associated with a 20-ppb  
37 increase in O<sub>3</sub> at lag 1 among men aged 20-64 years in the warm season. No associations among  
38 women or among men age 65 and older reached statistical significance ( $p < 0.1$ ). In addition, no  
39 associations were observed for the cold season or for other lags (lag 0 or lag 2). A similar

1 investigation over the same time period in Edmonton, Canada, assessed the relationship between air  
2 pollutants and ED visits for stroke (ischemic stroke, hemorrhagic stroke, and transient ischemic  
3 attack) among those 65 years of age and older using a case-crossover framework (Villeneuve et al.,  
4 2006, [090191](#)). Lags considered for pollution levels were same day, 1-day lag, and 3-day avg (lag  
5 days 0-2). Two-pollutant models were assessed. In addition, results were stratified by season, gender,  
6 and stroke sub-type. No evidence of association was reported for O<sub>3</sub> and stroke hospitalization  
7 (Villeneuve et al., 2006, [090191](#)).

8 Three additional studies reported no evidence of association between O<sub>3</sub> concentrations and  
9 ED visits, hospitalizations, or symptoms leading to hospitalization (Symons et al., 2006, [091258](#);  
10 Wellenius et al., 2005, [087483](#); Zanobetti and Schwartz, 2006, [090195](#)). Symons et al. (2006,  
11 [091258](#)) used a case-crossover framework to assess the relationship between air pollutants and the  
12 onset of symptoms (dyspnea) severe enough to lead to hospitalization (through the ED) for  
13 congestive heart failure. The study was conducted from April to December of 2002 in Baltimore,  
14 Maryland. Exposures were assigned using 3 index times: 8-h and 24-h periods prior to symptom  
15 onset and date of hospital admission. No evidence of association was reported for O<sub>3</sub> concentrations.  
16 Although seasonal variation was not assessed, the time frame for the study did not involve an entire  
17 year (April to December). Wellenius et al. (2005, [087483](#)) investigated the association between air  
18 pollutants and congestive heart failure hospitalization among Medicare beneficiaries in Pittsburgh,  
19 Pennsylvania from 1987 to 1999 utilizing a case-crossover framework. A total of 55,019 admissions  
20 from the emergency room with a primary discharge diagnosis of CHF were collected. Single- and  
21 two-pollutant models were assessed. In addition, effect modification by age, gender, and presence of  
22 secondary diagnoses was considered, but seasonal variation was not assessed. No evidence of an  
23 association was reported for O<sub>3</sub> and CHF hospitalization (Wellenius et al., 2005, [087483](#)). Finally,  
24 Zanobetti and Schwartz (2006, [090195](#)) assessed the relationship between air pollutants and hospital  
25 admissions through the ED for myocardial infarction and pneumonia among patients aged 65 and  
26 older residing in the greater Boston area (1995-1999) using a case-crossover framework with control  
27 days matched on temperature. Pollution exposures were assigned for the same day and for the mean  
28 of the exposure the day of and the day before the admission. Seasonal variation was assessed. Ozone  
29 was not associated with MI admissions.

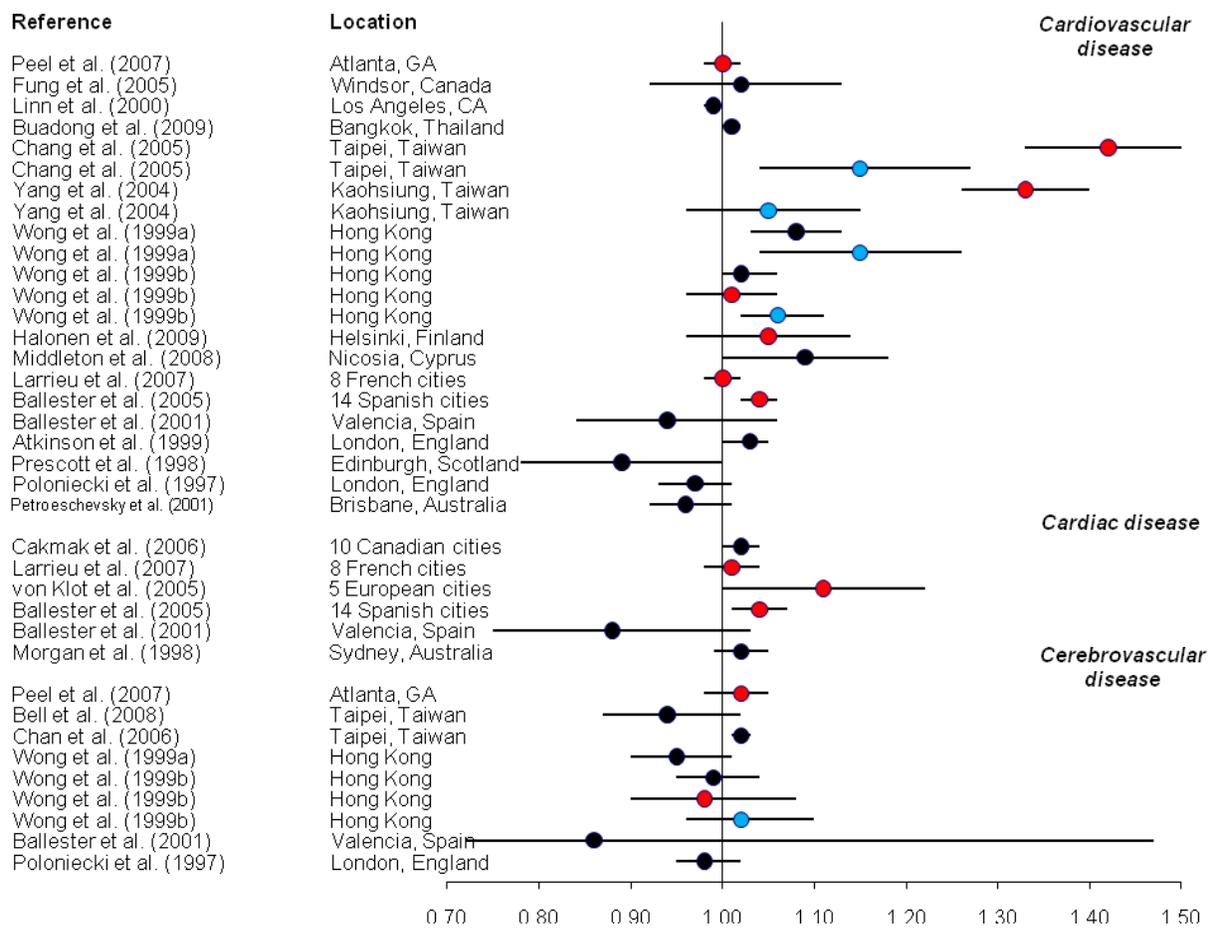
30 Several recent studies have examined the relationship between air pollution and CVD hospital  
31 admissions and/or emergency department visits in Asia. In Taiwan, fairly consistent positive  
32 associations have been reported for O<sub>3</sub> and congestive heart failure hospital admissions (for single-  
33 and multi-pollutant models) in Taipei on warm days (Yang, 2008, [157160](#)) and in Kaohsiung (Lee et  
34 al., 2007, [196613](#)); cerebrovascular disease ED visits (for lag 0 single- and two-pollutant models but  
35 not other lags or 3-pollutant models) in Taipei (Chan et al., 2006, [090193](#)); and arrhythmia ED visits  
36 in Taipei among those without comorbid conditions (Chiu et al., 2009, [190249](#); Lee et al., 2008,  
37 [192076](#)) and in Taipei on warm days among those with and without comorbid conditions (Jansson et  
38 al., 2001, [092076](#); Lee et al., 2008, [192076](#)). However, one study in Taiwan did not shown an  
39 association. Bell et al. (2008, [091268](#)) reported no evidence of an O<sub>3</sub> association with hospital

1 admissions for ischemic heart disease or cerebrovascular disease. Three studies based in Asia but  
2 outside Taiwan were performed. First, a Hong Kong-based investigation (Wong et al., 2009, [196722](#))  
3 reported no consistent evidence of a modifying effect of influenza on the relationship between O<sub>3</sub>  
4 and CVD admissions. Second, among elderly populations in Thailand, O<sub>3</sub> was associated with CVD  
5 visits, but this association was not detected among younger age groups (15-64) (Buadong et al.,  
6 2009, [602060](#)). Third, a study performed in Seoul, Korea reported a positive association between O<sub>3</sub>  
7 levels and HAs for ischemic heart disease; the association was slightly greater among those over  
8 64 years of age (Lee et al., 2003, [095552](#)).

9 Positive effects of O<sub>3</sub> on CVD hospital admissions and/or ED visits have been reported in  
10 other areas of the world as well (Ballester et al., 2006, [088746](#); De Pablo et al., 2006, [196506](#);  
11 Linares and Diaz, 2010, [383413](#); Middleton et al., 2008, [156760](#); Turner et al., 2007, [196637](#);  
12 Von Klot et al., 2005, [088070](#); Yallop et al., 2007, [090702](#)), although not consistently as some studies  
13 reported no association (Barnett et al., 2006, [089770](#); Halonen et al., 2009, [625764](#); Hinwood et al.,  
14 2006, [088976](#); Hosseinpoor et al., 2005, [087413](#); Lanki et al., 2006, [089788](#); Larrieu et al., 2007,  
15 [093031](#); Oudin et al., 2010, [384790](#); Simpson et al., 2005, [087438](#)).

16 Two studies (U.S. and Australia) have examined cardiac arrests where emergency services  
17 attempted treatment/resuscitation. No evidence of an association between O<sub>3</sub> and out-of-hospital  
18 cardiac arrest was observed (Dennekamp et al., 2010, [626767](#); Silverman et al., 2010, [647265](#)).

19 An increasing number of air pollution studies have investigated the relationship between O<sub>3</sub>  
20 concentrations and CVD hospital admissions and/or ED visits. As summarized in the 2006 O<sub>3</sub>  
21 AQCD, some, especially those reporting results stratified by season (or temperature) or comorbid  
22 conditions have reported positive associations. However, even studies performing these stratified  
23 analyses are not consistent and the overall evidence remains inconclusive regarding the effects of O<sub>3</sub>  
24 on CVD HAs and ED visits. These HA and ED visit studies are summarized in Figures 6-22 through  
25 6-26, which are forest plots depicting the associations for studies in which numerical associations  
26 were presented for an overall study population. These figures are followed by Tables 6-28 through  
27 6-32, giving the numerical results displayed in the figures.



Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h avg period, 30 ppb for 8-h avg period, and 40 ppb for 1-h avg period. Ozone concentrations in ppb. Seasons depicted by colors – black: all year; red: warm season. Age groups of study populations were not specified or were adults with the exception of Wellenius et al. (2005, [087483](#)), Fung et al. (2005, [074322](#)), Wong et al. 1999 (1999, [009172](#))b, and Prescott et al. (1998, [084610](#)), which included only individuals aged 65+.

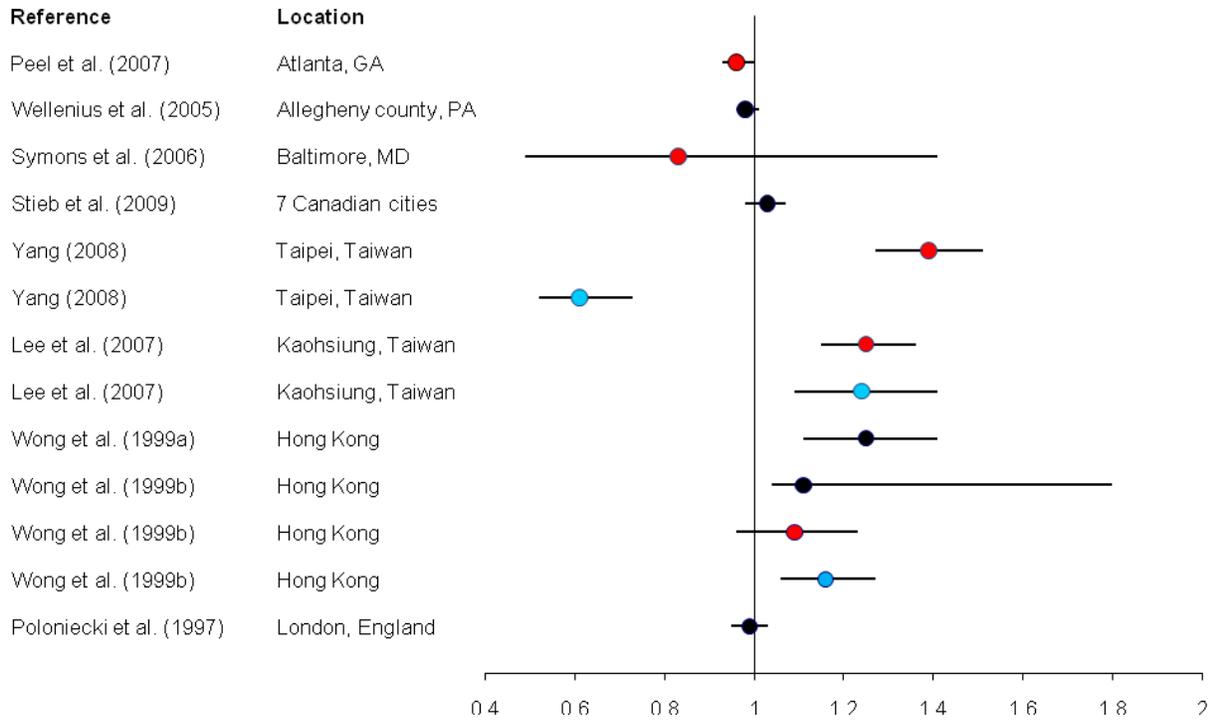
**Figure 6-22. Odds ratio (95% CI) per increment ppb increase in ozone for over all cardiovascular ED visits or HAs.**

**Table 6-28. Odds ratio (95% CI) per increment ppb increase in ozone for overall cardiovascular ED visits or HAs in studies presented in Figure 6-22.**

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Peel et al. (2007, <a href="#">090442</a> )	Atlanta, GA	Cardiovascular disease	8-h warm season	1.00 (0.98, 1.02)
		Cerebrovascular disease	8-h warm season	1.02 (0.98, 1.05)
Fung et al. (2006, <a href="#">099068</a> )	Windsor, Canada	Cardiovascular disease	1-h	1.02 (0.92, 1.13)
Linn et al. (2006, <a href="#">099068</a> )	Los Angeles, California	Cardiovascular disease	24-h	0.99 (0.98, 1.00)
Buadong et al. (2009, <a href="#">602060</a> )	Bangkok, Thailand	Cardiovascular disease	1-h	1.01 (1.00, 1.02)
Chang et al. (2005, <a href="#">080086</a> )	Taipei, Taiwan	Cardiovascular disease	24-h warm season	1.42 (1.33, 1.50)
			24-h cold season	1.15 (1.04, 1.27)
Yang et al. (2005, <a href="#">080086</a> )	Kaohsiung, Taiwan	Cardiovascular disease	24-h warm season	1.33 (1.26, 1.40)
			24-h cold season	1.05 (0.96, 1.15)
Wong et al. (2005, <a href="#">080086</a> )a	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)
			24-h	1.02 (1.03, 1.06)
Wong et al. (1999, <a href="#">011463</a> )b	Hong Kong	Cardiovascular disease	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 cold season	1.02 (0.96, 1.10)
Halonen et al. (2009, <a href="#">625764</a> )	Helsinki, Finland	Cardiovascular disease	8-h max warm season	1.05 (0.96, 1.14)
Middleton et al. (2008, <a href="#">156760</a> )	Nicosia, Cyprus	Cardiovascular disease	8-h max	1.09 (1.00, 1.18)
Larrieu et al. (2007, <a href="#">093031</a> )	Multicity France	Cardiac disease	8-h max warm season	1.01 (0.98, 1.04)
Ballester et al. (2006, <a href="#">088746</a> )	Multicity, Spain	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, <a href="#">088746</a> )	Valencia, Spain	Cardiovascular disease	8-h	0.94 (0.84, 1.06)
		Cerebrovascular disease	8-h	0.86 (0.72, 1.47)
Atkinson et al. (2006, <a href="#">099068</a> )	London, England	Cardiovascular disease	8-h	1.03 (1.00, 1.05)
Prescott et al. (1998, <a href="#">084610</a> )	Edinburgh, Scotland	Cardiovascular disease	24-h	0.89 (0.78, 1.00)
Poloniecki et al. (2006, <a href="#">099068</a> )	London, England	Cardiovascular disease	8-h	0.97 (0.93, 1.01)
		Cerebrovascular disease	8-h	0.98 (0.95, 1.02)
Petroeschvsky et al. (2001, <a href="#">016466</a> )	Brisbane, Australia	Cardiovascular disease	8-h	0.96 (0.92, 1.01)
Cakmak et al. (2006, <a href="#">099068</a> )	Multicity, Canada	Cardiac disease	1-h max	1.02 (1.00, 1.04)
Von Klot et al. (2005, <a href="#">088070</a> )	Multicity, Europe	Cardiac disease	8-h max warm season	1.11 (1.00, 1.22)
Morgan et al. (2008, <a href="#">091268</a> )	Sydney, Australia	Cardiac disease	1-h max	1.02 (0.99, 1.05)
Bell et al. (2008, <a href="#">091268</a> )	Taipei, Taiwan	Cerebrovascular disease	24-h	0.94 (0.87, 1.02)
Chan et al. (2006, <a href="#">090193</a> )	Taipei, Taiwan	Cerebrovascular disease	1-h max	1.02 (1.01, 1.03)

Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Outcomes were all congestive heart failure, with the exception of Symons et al. (2006, [091258](#)), 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, [087483](#)), Fung et al. (2006, [099068](#)), Wong et al. (1999, [011463](#))b, and Prescott et al. (1998, [084610](#)), which included only individuals aged 65+.

Warm season defined as: March–October (Peel et al., 2007, [090442](#)), May–October (Ballester et al., 2005, [600865](#); Wong et al., 1999, [011463](#))b, May–September (Halonen et al., 2009, [625764](#)), April–September (Larrieu et al., 2007, [093031](#); Von Klot et al., 2005, [088070](#)),  $\geq 20^{\circ}\text{C}$  (Chang et al., 2005, [080086](#)) and  $\geq 25^{\circ}\text{C}$  (Yang et al., 2004, [094376](#)). Cold season defined as: November–April (Wong et al., 1999, [011463](#))b,  $<20^{\circ}\text{C}$  (Chang et al., 2005, [080086](#)) and  $<25^{\circ}\text{C}$  (Yang et al., 2004, [094376](#)), December–March (Wong et al., 1999, [009172](#))a



Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. 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, [091258](#)), 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, [087483](#)) and (Wong et al., 1999, [011463](#))b, which included only individuals aged 65+.

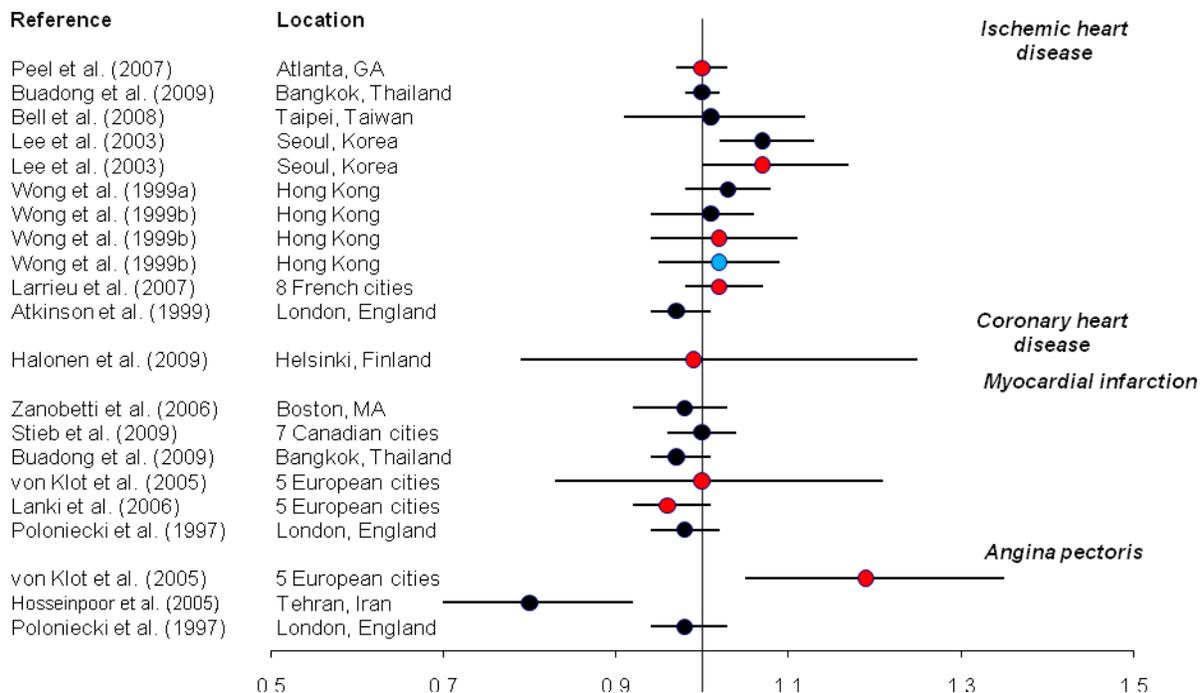
**Figure 6-23. Odds Ratio (95% CI) per increment ppb increase in ozone for congestive heart failure ED visits or HAs.**

**Table 6-29. Odds Ratio (95% CI) per increment ppb increase in ozone for congestive heart failure ED visits or HAs for studies presented in Figure 6-23**

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Peel et al. (2007, <a href="#">090442</a> )	Atlanta, GA	congestive heart failure	8-h warm season	0.96 (0.93, 1.00)
Wellenius et al. (2005, <a href="#">087483</a> )	Allegheny county, PA	congestive heart failure	24-h	0.98 (0.96, 1.01)
Symons et al. (2006, <a href="#">091258</a> )	Baltimore, MD	onset of congestive heart failure symptoms leading to a heart attack	8-h warm season	0.83 (0.49, 1.41)
Stieb et al. (2009, <a href="#">195858</a> )	Multicity, Canada	congestive heart failure	24-h	1.03 (0.98, 1.07)
Yang (2008, <a href="#">157160</a> )	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)
Lee et al. (2007, <a href="#">196613</a> )	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)
Wong et al. (1999, <a href="#">009172</a> )a	Hong Kong	congestive heart failure	24-h	1.25 (1.11, 1.41)
			24-h	1.11 (1.04, 1.80)
Wong et al. (1999, <a href="#">011463</a> )b	Hong Kong	congestive heart failure	24-h warm season	1.09 (0.96, 1.23)
			24-h cold season	1.16 (1.06, 1.27)
Poloniecki et al. (1997, <a href="#">084004</a> )	London, England	congestive heart failure	8-h	0.99 (0.95, 1.03)

Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of Wellenius et al. (2005, [087483](#)) and Wong et al. (1999, [011463](#))b, which included only individuals aged 65.

Warm season defined as: March-October (Peel et al., 2007, [090442](#)), April-November (Symons et al., (2006, [091258](#)), May-October (Wong et al., (1999, [011463](#))b  $\geq 20^{\circ}\text{C}$  (Yang, (2008, [157160](#)), and  $>25^{\circ}\text{C}$  (Lee et al,(2007, [196613](#)). Cold season defined as: November-April (Wong et al., (1999, [011463](#))b,  $<20^{\circ}\text{C}$  (Yang, (2008, [157160](#)), and  $<25^{\circ}\text{C}$  (Lee et al., (2007, [196613](#)).



Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. 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. ((1999, [011463](#))b and Atkinson et al. (2006, [099068](#)), which included only individuals aged 65.

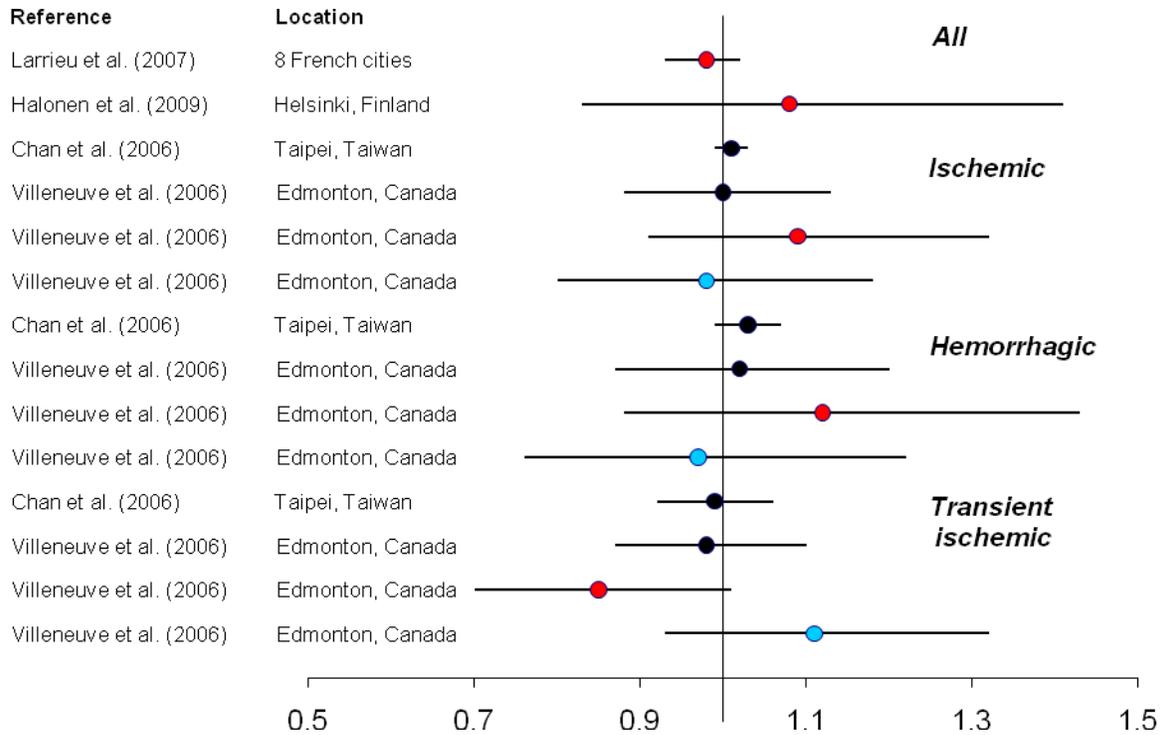
**Figure 6-24. Odds Ratio (95% confidence interval) per increment ppb increase in ozone for myocardial infarction, angina, ischemic heart disease, and coronary heart disease ED visits or HAs.**

**Table 6-30. Odds Ratio (95% CI) per increment ppb increase in ozone for myocardial infarction, angina, ischemic heart disease, and coronary heart disease ED visits or HAs for studies presented in Figure 6-24**

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Peel et al. (2007, <a href="#">090442</a> )	Atlanta, GA	Ischemic heart disease	8-h warm season	1.00 (0.97, 1.03)
Zanobetti and Schwartz (2006, <a href="#">090195</a> )	Boston, MA	Myocardial infarction	24-h	0.98 (0.92, 1.03)
Stieb et al. (2009, <a href="#">195858</a> )	Multicity, Canada	Myocardial infarction	2-h	1.00 (0.96, 1.04)
Bell et al. (2008, <a href="#">091268</a> )	Taipei, Taiwan	Ischemic heart disease	24-h	1.01 (0.91, 1.12)
Lee et al. (2003, <a href="#">095552</a> )	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)
Buadong et al. (2009, <a href="#">602060</a> )	Bangkok, Thailand	Ischemic heart disease	1-h	1.00 (0.98, 1.02)
		Myocardial infarction	1-h	0.97 (0.94, 1.01)
Wong et al. (2008, <a href="#">091268</a> )a	Hong Kong	Ischemic heart disease	24-h	1.03 (0.98, 1.08)
			24-h	1.01 (0.94, 1.06)
Wong et al. (2009, <a href="#">602060</a> )b	Hong Kong	Ischemic heart disease	24-h warm season	1.02 (0.94, 1.11)
			24-h cold season	1.02 (0.95, 1.09)
Hosseinpoor et al. (2005, <a href="#">087413</a> )	Tehran, Iran	Angina	8-h max	0.80 (0.70, 0.92)
Von Klot et al. (2005, <a href="#">088070</a> )	Multicity, Europe	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)
Lanki et al. (2006, <a href="#">089788</a> )	Multicity, Europe	Myocardial infarction	8-h max warm season	0.96 (0.92, 1.01)
Larrieu et al. (2007, <a href="#">093031</a> )	Multicity France	Ischemic heart disease	8-h max warm season	1.02 (0.98, 1.07)
Halonen et al. (2009, <a href="#">625764</a> )	Helsinki, Finland	Coronary heart disease	8-h max warm season	0.99 (0.79, 1.25)
Atkinson et al. (1999, <a href="#">007882</a> )	London, England	Ischemic heart disease	8-h	0.97 (0.94, 1.01)
Poloniecki et al. (1997, <a href="#">084004</a> )	London, England	Myocardial infarction	8-h	0.98 (0.94, 1.02)
		Angina	8-h	0.98 (0.94, 1.03)

Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of Wong et al. ((1999, [011463](#))b and Atkinson et al. (2006, [099068](#)), which included only individuals aged 65.

Warm season defined as: March-October (Peel et al., (2007, [090442](#)), June-August (Lee et al., (2003, [095552](#)), May-September (Halonen et al., (2009, [625764](#)), May-October (Wong et al., (2009, [602060](#))b, and April-September (Lanki et al., (2006, [089788](#)), Larrieu et al., (2007, [093031](#)), von Klot et al., (2005, [088070](#))). Cold season defined as: November-April (Wong et al., (2009, [602060](#))b



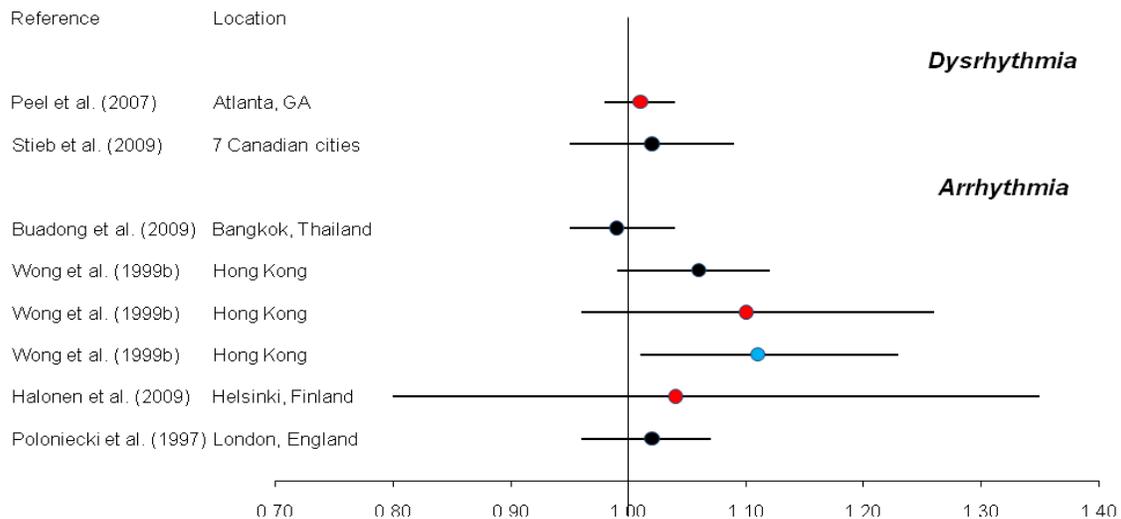
Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Seasons depicted by colors: black: all year; red: warm season; light blue: cold season. Age groups of study populations were not specified or were adults with the exception of Villeneuve et al. (2006, [090191](#)), which included only individuals aged 65+, and Chan et al. (2006, [090193](#)), which included only individuals aged 50+.

**Figure 6-25. Odds Ratio (95% confidence interval) per increment ppb increase in ozone for stroke ED visits or HAs.**

**Table 6-31. Odds Ratio (95% CI) per increment ppb increase in ozone for stroke ED visits or HAs for studies presented in Figure 6-25**

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Villeneuve et al. (2006, <a href="#">090191</a> )	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)
Chan et al. (2006, <a href="#">090193</a> )	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)
Larrieu et al. (2007, <a href="#">093031</a> )	Multicity, France	All/non-specified stroke	8-h max warm season	0.98 (0.93, 1.02)
Halonen et al. (2009, <a href="#">625764</a> )	Helsinki, Finland	All/non-specified stroke	8-h max warm season	1.08 (0.83, 1.41)

Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb.  
 Warm season defined as: May-September (Halonen et al., (2009, [625764](#)), and April-September (Larrieu et al., 2007, [093031](#))(Villeneuve et al., 2006, [090191](#)). Cold season defined as: October-March (Villeneuve et al., 2006, [090191](#)).



Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. 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. (1999, [011463](#))b, which included only individuals aged 65.

**Figure 6-26. Odds Ratio (95% confidence interval) per increment ppb\* increase in ozone for arrhythmia and dysrhythmia ED visits or HAs.**

**Table 6-32. Odds Ratio (95% CI) per increment ppb\* increase in ozone for arrhythmia and dysrhythmia ED visits or HAs for studies presented in Figure 6-26**

Study	Location	Outcome	Averaging Time	Standardized Estimate (95% CI)
Peel et al. (2007, <a href="#">090442</a> )	Atlanta, GA	Dysrhythmia	8-h warm season	1.01 (0.98, 1.04)
Stieb et al. (2009, <a href="#">195858</a> )	Multicity, Canada	Dysrhythmia	24-h	1.02 (0.95, 1.09)
Buadong et al. (2009, <a href="#">602060</a> )	Bangkok, Thailand	Arrhythmia	1-h	0.99 (0.95, 1.04)
			24-h	1.06 (0.99, 1.12)
Wong et al. (2009, <a href="#">602060</a> )b	Hong Kong	Arrhythmia	24-h warm season	1.10 (0.96, 1.26)
			24-h cold season	1.11 (1.01, 1.23)
Halonen et al. (2009, <a href="#">625764</a> )	Helsinki, Finland	Arrhythmia	8-h max warm season	1.04 (0.80, 1.35)
Poloniecki et al. (2009, <a href="#">602060</a> )	London, England	Arrhythmia	8-h	1.02 (0.96, 1.07)

Note: Increase in O<sub>3</sub> standardized to 20 ppb for 24-h averaging period, 30 ppb for 8-h averaging period, and 40 ppb for 1-h averaging period. Ozone concentrations in ppb. Age groups of study populations were not specified or were adults with the exception of (Wong et al., 1999, [011463](#))b, which included only individuals aged 65. Warm season defined as: March-October (Peel et al., 2007, [090442](#)), May-October (Wong et al., 1999, [011463](#))b and May-September (Halonen et al., 2009, [625764](#)). Cold season defined as: November-April (Wong et al., 1999, [011463](#))b.

### 6.3.2.8. Cardiovascular Mortality

1 The 2006 O<sub>3</sub> AQCD provided evidence, primarily from single-city studies, of consistent  
 2 positive associations between short-term O<sub>3</sub> exposure and cardiovascular mortality. Recent multicity  
 3 studies conducted in the U.S., Canada, and Europe further confirm the association between short-  
 4 term O<sub>3</sub> exposure and cardiovascular mortality.

5 As discussed in Section 6.2.7.2, the APHENA study (Katsouyanni et al., 2009, [199899](#)) found  
 6 consistent positive associations for cardiovascular mortality in all-year analyses with associations  
 7 persisting in analyses restricted to the summer season. Additional multicity studies from the U.S.  
 8 (Zanobetti and Schwartz, 2008, [101596](#)), Europe (Samoli et al., 2009, [195855](#)), and Italy (Stafoggia  
 9 et al., 2010, [625034](#)) that conducted summer season analyses provide additional support for an  
 10 association between short-term O<sub>3</sub> exposure and cardiovascular mortality.

11 Of the studies evaluated, only the APHENA study (Katsouyanni et al., 2009, [199899](#)) and the  
 12 Italian multicity study (Stafoggia et al., 2010, [625034](#)) conducted an analysis of the potential for  
 13 co-pollutant confounding of the O<sub>3</sub>-cardiovascular mortality relationship. In the European dataset,  
 14 when focusing on the natural spline model with 8 df/year (Section 6.2.7.2) and lag 1 results in order  
 15 to compare results across study locations (Section 6.6.2.1), cardiovascular mortality risk estimates  
 16 were robust to the inclusion of PM<sub>10</sub> in co-pollutant models in all-year analyses with more variability  
 17 in the Canadian and U.S. datasets (i.e., cardiovascular O<sub>3</sub> mortality risk estimates were reduced or  
 18 increased in co-pollutant models). In summer season analyses, cardiovascular O<sub>3</sub> mortality risk  
 19 estimates were robust in the European dataset and attenuated but remained positive in the U.S.  
 20 dataset. Similarly, in the Italian multicity study (Stafoggia et al., 2010, [625034](#)), which was limited  
 21 to the summer season, cardiovascular mortality risk estimates were robust to the inclusion of PM<sub>10</sub> in  
 22 co-pollutant models. Based on the APHENA and Italian multicity results, O<sub>3</sub> cardiovascular  
 23 mortality risk estimates appear to be robust to inclusion of PM<sub>10</sub> in co-pollutant models. However, in  
 24 the U.S. and Canadian datasets there was evidence that O<sub>3</sub> cardiovascular mortality risk estimates are

1 moderately to substantially sensitive (e.g., increased or attenuated) to PM<sub>10</sub>. The mostly every-6th-  
2 day sampling schedule for PM<sub>10</sub> in the Canadian and U.S. datasets greatly reduced their sample size  
3 and limits the interpretation of these results.

### 6.3.2.9. Summary of Epidemiologic Studies

4 Overall, the available body of evidence examining the relationship between short-term  
5 exposures to O<sub>3</sub> and cardiovascular morbidity is inconsistent. Differences in exposure metrics and  
6 windows of exposure, a wide variety of biomarkers considered, and a lack of consistency among  
7 definitions used for specific cardiovascular disease endpoints (e.g. arrhythmias, HRV) make  
8 comparisons across studies difficult. In addition, several investigators reporting adverse effects of O<sub>3</sub>  
9 discuss the possibility that O<sub>3</sub> may be acting as a proxy for sulfate; differences reported across  
10 multicity studies and across studies conducted in specific cities/regions point to the importance of  
11 considering multi-pollutant relationships that vary across geographic regions. An association  
12 between O<sub>3</sub> and cardiovascular mortality has been observed.

### 6.3.3. Toxicology

#### 6.3.3.1. Summary of Findings from Previous Ozone AQCDs

13 In the previous O<sub>3</sub> AQCDs (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)) experimental  
14 animal studies have reported relatively few cardiovascular system alterations after exposure to O<sub>3</sub>  
15 and other photochemical oxidants. The limited amount of research directed at examining O<sub>3</sub>-induced  
16 cardiovascular effects has primarily found alterations in heart rate (HR) and BP after O<sub>3</sub> exposure. A  
17 group of studies (Arito et al., 1990, [042285](#); Arito et al., 1992, [042759](#); Uchiyama and Yokoyama,  
18 1989, [042051](#); Uchiyama et al., 1986, [040883](#); Yokoyama et al., 1989, [041741](#)) report O<sub>3</sub>  
19 (0.1-1.0 ppm) exposure in rats decreased core temperature (T<sub>CO</sub>), HR, and mean arterial pressure  
20 (MAP). However, these cardiovascular responses to O<sub>3</sub> could be attenuated by increased ambient  
21 temperatures and were the result of the rodent hypothermic response (Watkinson et al., 1993,  
22 [043205](#); Watkinson et al., 2003, [050547](#)). This hypothermic response could be an attempt to  
23 minimize the irritant effects of O<sub>3</sub> inhalation, serving as a physiological and behavioral defense  
24 mechanism (Arito et al., 1997, [082671](#); Iwasaki et al., 1998, [086165](#)). As decreased HR, MAP, and  
25 T<sub>CO</sub> have not been observed in humans except at very high O<sub>3</sub> exposures, caution must be used in  
26 extrapolating the results of these animal studies to humans (Section 6.3.1).

27 Other studies have shown that O<sub>3</sub> can increase BP in multiple animal models. Dogs treated  
28 with 1.0 ppm O<sub>3</sub> daily for 17 months developed excessive systolic pressure and pulmonary arterial  
29 hypertension (Bloch et al., 1971, [015914](#)). Additionally, rats exposed to 0.6 ppm O<sub>3</sub> for 33 days had  
30 increased systolic pressure and HR (Revis et al., 1981, [040017](#)). Increased BP triggers the release of  
31 atrial natriuretic factor (ANF), which has been found in increased levels in the heart, lungs, and  
32 circulation of O<sub>3</sub> exposed (0.5 ppm) rats (Vesely et al., 1994, [076015](#); Vesely et al., 1994, [028877](#);

1 Vesely et al., 1994, [076228](#)). High concentration O<sub>3</sub> exposure has also been found to lead to heart  
2 and lung edema (Friedman et al., 1983, [040547](#)), which could be the result of increased ANF levels.  
3 Thus, O<sub>3</sub> may increase blood pressure and HR, leading to increased ANF and tissue edema.

4 The toxicological studies that have examined the effect of O<sub>3</sub> on the cardiovascular system  
5 clearly demonstrate O<sub>3</sub>-induced responses, but it remains unclear if the mechanism is through a  
6 reflex response or due to O<sub>3</sub> reaction products, which have been sparsely studied. Oxysterols derived  
7 from cholesterol ozonation, such as β-epoxide and 5β,6β-epoxycholesterol (and its metabolite  
8 cholestan-6-oxo-3,5-diol), have been implicated in inflammation associated with cardiovascular  
9 disease (Pulfer and Murphy, 2004, [076673](#); Pulfer et al., 2005, [076663](#)). Two other cholesterol  
10 ozonolysis products, atheronal-A and -B (e.g. cholesterol secoaldehyde), have been found in human  
11 atherosclerotic plaques and shown in vitro to induce foam cell formation and induce cardiomyocyte  
12 apoptosis and necrosis (Sathishkumar et al., 2005, [087958](#); Wentworth et al., 2003, [052486](#));  
13 however, these products have not been found in the lung compartment or systemically after O<sub>3</sub>  
14 exposure. The ability to form these cholesterol ozonation products in the circulation in the absence of  
15 O<sub>3</sub> exposure complicates their implication in O<sub>3</sub> induced cardiovascular disease.

16 Although it has been proposed that O<sub>3</sub> reaction products released after the interaction of O<sub>3</sub>  
17 with RTLTF constituents (See Section 5.1.2 on O<sub>3</sub> interaction with RTLTF) are responsible for systemic  
18 effects, it is not known whether they gain access to the vascular space. Alternatively, extrapulmonary  
19 release of diffusible mediators, such as cytokines or endothelins, may initiate or propagate  
20 inflammatory responses in the vascular or systemic compartments (Cole and Freeman, 2009,  
21 [597507](#)) (Section 5.1.9.1). Ozone reacts within the lung to amplify ROS production, induce  
22 pulmonary inflammation, and activate inflammatory cells, resulting in a cascading proinflammatory  
23 state and extrapulmonary release of diffusible mediators that could lead to cardiovascular injury.

### 6.3.3.2. Recent Ozone-induced Cardiovascular Effects

24 According to recent short-term O<sub>3</sub> exposure animal toxicology studies, O<sub>3</sub> plays a role in  
25 inducing vascular oxidative stress and proinflammatory mediators, altering HR and HRV, and  
26 regulating the pulmonary endothelin system. A number of these effects were variable between strains  
27 examined, suggesting a genetic component to development of O<sub>3</sub> induced cardiovascular effects.  
28 Further, new studies provide evidence that extended O<sub>3</sub> exposure enhances susceptibility to  
29 ischemia-reperfusion (I/R) injury and atherosclerotic lesion development. Still, few studies have  
30 investigated the role of O<sub>3</sub> reaction products in these processes, but more evidence is provided for  
31 elevated inflammatory and reduction-oxidation (redox) cascades known to initiate these  
32 cardiovascular pathologies.

33 A recent study in young mice (C57Bl/6, 6 week old) and rhesus monkeys (*Macaca mulatta*,  
34 180 days old) examined the effects of 1 or 5 days (8 h/day) of O<sub>3</sub> (0.5 ppm) exposure on a number of  
35 cardiovascular endpoints (Chuang et al., 2009, [197202](#)). Mice exposed to O<sub>3</sub> for 5 days had  
36 increased heart rate (HR) as well as mean and diastolic blood pressure. Increased blood pressure  
37 could be explained by the inhibition in endothelial-dependent (acetylcholine) vasorelaxation from

1 decreased bioavailability of aortic nitric oxide ( $\cdot\text{NO}$ ). Ozone caused a decrease in aortic  $\text{NO}_x$  (nitrite  
2 and nitrate levels) and a decrease in total, but not phosphorylated, endothelial nitric oxide synthase  
3 (eNOS). Ozone also increased vascular oxidative stress in the form of increased aortic and lung lipid  
4 peroxidation (F2-isoprostane), increased aortic protein nitration (3-nitrotyrosine), decreased aortic  
5 superoxide dismutase (SOD2) protein and activity, and decreased aortic aconitase activity, indicating  
6 specific inactivation by  $\text{O}_2^-$  and  $\text{ONOO}^-$ . Mitochondrial DNA (mtDNA) damage was also used as a  
7 measure of oxidative and nitrative stress in mice and infant rhesus monkeys exposed to  $\text{O}_3$  (0.5 ppm)  
8 for 5 days (8 h/day). Chuang et al. (2009, [197202](#)) observed that MtDNA damage accumulated in the  
9 lung and aorta of mice after 1 and 5 days of  $\text{O}_3$  exposure and in the proximal and distal aorta of  $\text{O}_3$   
10 treated nonhuman primates. Additionally, ApoE<sup>-/-</sup> mice (6-14 weeks old) exposed to  $\text{O}_3$  (0.5 ppm) for  
11 8 weeks (5 days/week, 8 h/day) had increased aortic atherosclerotic lesion area (Section 7.3.1),  
12 which may be associated with the short-term exposure changes discussed. Overall, this study  
13 suggests that  $\text{O}_3$  initiates an oxidative environment by increasing  $\text{O}_2^-$  production, which leads to  
14 mtDNA damage and  $\cdot\text{NO}$  consumption, known to perturb endothelial function (Chuang et al., 2009,  
15 [197202](#)). Endothelial dysfunction is characteristic of early and advanced atherosclerosis and  
16 coincides with impaired vasodilation and blood pressure regulation.

17 Vascular occlusion resulting from atherosclerosis can block blood flow causing ischemia. The  
18 restoration of blood flow in the vessel or reperfusion can cause injury to the tissue from subsequent  
19 inflammation and oxidative damage. Perepu et al. (2010, [385020](#)) observed that  $\text{O}_3$  exposure  
20 (0.8 ppm for 28 or 56 days) enhanced the sensitivity to myocardial ischemia-reperfusion (I/R) injury  
21 in Sprague-Dawley rats while increasing oxidative stress levels and pro-inflammatory mediators and  
22 decreasing production of anti-inflammatory proteins. Ozone was also found to decrease the left  
23 ventricular developed pressure, rate of change of pressure development, and rate of change of  
24 pressure decay while increasing left ventricular end diastolic pressure in isolated perfused hearts. In  
25 this ex vivo heart model,  $\text{O}_3$  induced oxidative stress by decreasing SOD enzyme activity and  
26 increasing malondialdehyde levels. Ozone also elicited a proinflammatory state which was evident  
27 by an increase in TNF- $\alpha$  and a decrease in the anti-inflammatory cytokine IL-10. Perepu et al. (2010,  
28 [385020](#)) concluded that  $\text{O}_3$  exposure may result in a greater I/R injury.

### **Heart Rate and Heart Rate Variability**

29 Strain differences in HR and HRV have been observed in response to a 2-h  $\text{O}_3$  (0.584 ppm)  
30 pretreatment followed by a 3-h exposure to particulate matter (carbon black (CB),  $536 \mu\text{g}/\text{m}^3$ ) in 18-  
31 to 20-week-old mice (C3H/HeJ [HeJ], C57BL/6J [B6], and C3H/HeOuj [Ouj]) (Hamade and  
32 Tankersley, 2009, [596386](#); Hamade et al., 2008, [156515](#)). These mice were chosen from prior studies  
33 on lung inflammatory and hyperpermeability responses to be susceptible (B6 and Ouj) and resistant  
34 (HeJ) to  $\text{O}_3$ -induced health effects (Kleeberger et al., 2000, [014895](#)). HR decreased during  $\text{O}_3$  pre-  
35 exposure for all strains, but recovered during the CB exposure (Hamade et al., 2008, [156515](#)). This is  
36 contrary to the tachycardia that was reported in 6-week-old B6 mice treated on 1 or 5 days with  $\text{O}_3$ ,  
37 as described above (Chuang et al., 2009, [197202](#)). Percent change in HRV parameters, SDNN

1 (indicating total HRV) and rMSSD (indicating beat-to-beat HRV), were increased in both C3H mice  
2 strains, but not B6 mice, during O<sub>3</sub> pre-exposure and recovered during CB exposure when compared  
3 to the filtered air group. The two C3H strains differ by a mutation in the toll-like receptor 4 (TLR4)  
4 gene, but these effects did not seem to be related to this mutation since similar responses were  
5 observed. Hamade et al. (2008, [156515](#)) speculate that the B6 and C3H strains differ in mechanisms  
6 of HR response after O<sub>3</sub> exposure between withdrawal of sympathetic tone and increase of  
7 parasympathetic tone; however, no direct evidence for this conclusion was reported. The strain  
8 differences observed in HR and HRV suggest that genetic variability affects cardiac responses after  
9 acute air pollutant exposures.

10 Hamade and Tankersley (2009, [596386](#)) continued this investigation of gene-environment  
11 interactions on cardiopulmonary adaptation of O<sub>3</sub> and CB induced changes in HR and HRV using the  
12 prior daily exposure scheme for 3 consecutive days. By comparing day-1 interim values it is possible  
13 to observe that O<sub>3</sub> exposure increased SDNN and rMSSD, but decreased HR in all strains. Measures  
14 of HR and HRV in B6 and HeJ mice recovered to levels consistent with filtered air treated mice by  
15 day 3; however, these responses in OuJ mice remained suppressed. B6 mice had no change in  
16 respiratory rate (RR) after O<sub>3</sub> treatment, whereas HeJ mice on days 1 and 2 had increased RR and  
17 OuJ mice on days 2 and 3 exhibited increased RR. V<sub>T</sub> did not change with treatment among the  
18 strains. Overall, B6 mice were mildly responsive with rapid adaptation, whereas C3 mice were  
19 highly responsive with adaptation only in HeJ mice with regards to changes in cardiac and  
20 respiratory responses. HR and HRV parameters were not equally correlated with V<sub>T</sub> and RR between  
21 the three mice strains, which suggest that strains vary in the integration of the cardiac and respiratory  
22 systems. These complex interactions could help explain variability in interindividual susceptibility to  
23 adverse health effects of air pollution.

24 Hamade et al. (2010, [666324](#)) expanded their investigation to explore the variation of these  
25 strain dependent cardiopulmonary responses with age. As was observed previously, all experimental  
26 mouse strains (B6, HeJ, and OuJ) exhibited decreased HR and increased HRV after O<sub>3</sub> (0.58 ppm,  
27 2 hours) exposure. Younger O<sub>3</sub> exposed mice (5 months) had a significantly lower HR compared to  
28 older exposed mice (12 months), indicating an attenuation of the bradycardic effect of O<sub>3</sub> with age.  
29 Younger mice also had a greater increase in rMSSD in HeJ and OuJ strains and SDNN in HeJ mice.  
30 Conversely, B6 mice had a slightly greater increase in SDNN compared to the aged mice. No change  
31 was observed in the magnitude of the O<sub>3</sub> induced increase of SDNN in OuJ mice or rMSSD in B6  
32 mice. The B6 and HeJ mice genetically vary in respect to the nuclear factor erythroid 2-related factor  
33 2 (Nrf-2). The authors propose that the genetic differences between the mice strains could be altering  
34 the formation of ROS, which tends to increase with age, thus modulating the changes in  
35 cardiopulmonary physiology after O<sub>3</sub> exposure.

36 Strain and age differences in HR and heart function were further investigated in B6 and  
37 129S1/SvImJ (129) mice in response to a sequential O<sub>3</sub> (2 hours, 0.576 ppm) and filtered air or CB  
38 (3 hours, 556 µg/m<sup>3</sup>) exposure (Tankersley et al., 2010, [628062](#)). Young (5 months) 129 mice  
39 showed a decrease in HR after O<sub>3</sub> or O<sub>3</sub> and CB exposure. This bradycardia was not observed in B6

1 or older animals (18 months) in this study, suggesting a possible alteration or adaptation of the  
2 autonomic nervous system activity with age. However, these authors did previously report  
3 bradycardia in similarly aged young B6 mice (Hamade and Tankersley, 2009, [596386](#); Hamade et al.,  
4 2008, [156515](#); Hamade et al., 2010, [666324](#)). Ozone exposure in 129 mice also resulted in an  
5 increase in left ventricular chamber dimensions at end diastole (LVEDD) in young and old mice and  
6 a decrease in left ventricular posterior wall thickness at end systole (PWTES) in older mice. The  
7 increase in LVEDD caused a decrease in fractional shortening, which can be used as a rough  
8 indicator of left ventricular function. Regression analysis revealed a significant interaction between  
9 age and strain on HR and PWTES, which implies that aging affects the HR and function in response  
10 to O<sub>3</sub> differently between mouse strains.

### **Ozone-Induced Effects on Cardiovascular-Related Proteins**

11 Increased BP, changes in HRV, and increased atherosclerosis may be related to increases in the  
12 vasoconstrictor peptide, endothelin-1 (amino acids 1-21, ET-1<sub>[1-21]</sub>). Regulation of the pulmonary  
13 endothelin system can be affected in rats (Fischer 344) by inhalation (4 hours) of PM (0, 5,  
14 50 mg/m<sup>3</sup>, EHC-93) and O<sub>3</sub> (0, 0.4, or 0.8 ppm) (Thomson et al., 2005, [087554](#); Thomson et al.,  
15 2006, [097483](#)). Exposure to either O<sub>3</sub> (0.8 ppm) or PM increased plasma ET-1<sub>[1-21]</sub>, ET-3<sub>[1-21]</sub>, and the  
16 ET-1 precursor peptide, bigET-1. Increases in circulating ET-1<sub>[1-21]</sub> could be a result of a transient  
17 increase in the gene expression of lung preproET-1 and endothelin converting enzyme-1 (ECE-1)  
18 immediately following inhalation of O<sub>3</sub> or PM. These latter gene expression changes (e.g. preproET-  
19 1 and ECE-1) were additive with co-exposure to O<sub>3</sub> and PM. Conversely, preproET-3 decreased  
20 immediately after O<sub>3</sub> exposure, suggesting the increase in ET-3<sub>[1-21]</sub> was not through de novo  
21 production. A recent study also found increased ET-1 gene expression in the aorta of acutely exposed  
22 rats (O<sub>3</sub>, 1.0 ppm, 5 h/day, 2 days) (Kodavanti et al., In Press, [666323](#)). These rats also exhibited an  
23 increase in ET<sub>B</sub>R after O<sub>3</sub> exposure; however, they did not demonstrate increased biomarkers for  
24 vascular inflammation, thrombosis, or oxidation.

25 O<sub>3</sub> can oxidize protein functional groups and disturb the affected protein. For example, the  
26 soluble plasma protein fibrinogen is oxidized by O<sub>3</sub> (0.01-0.03 ppm) in vitro, creating fibrinogen and  
27 fibrin aggregates, characteristically similar to defective fibrinogen (Rosenfeld et al., 2009, [201546](#);  
28 Rozenfeld et al., 2008, [596413](#)). In these studies, oxidized fibrinogen retained the ability to form  
29 fibrin gels that are involved in coagulation, however the aggregation time increased and the gels  
30 were rougher than normal with thicker fibers. Oxidized fibrinogen also developed the ability to self  
31 assemble creating fibrinogen aggregates that may play a role in thrombosis. Since O<sub>3</sub> does not  
32 readily translocate past the ELF and pulmonary epithelium and fibrinogen is primarily a plasma  
33 protein, it is uncertain if O<sub>3</sub> would have the opportunity to react with plasma fibrinogen. However,  
34 fibrinogen can be released from the basolateral face of pulmonary epithelial cells during  
35 inflammation, where the deposition of fibrinogen could lead to lung injury (Lawrence and Simpson-  
36 Haidaris, 2004, [627654](#)).

## Cardiovascular Effects due to Ozone Reaction Products

1 Although recent toxicological studies have demonstrated O<sub>3</sub>-induced effects on the  
2 cardiovascular system, as concluded in previous O<sub>3</sub> AQCDs, it remains unclear if the mechanism is  
3 through a reflex response or the result of effects from O<sub>3</sub> reaction products (U.S. EPA, 1996, [017831](#);  
4 U.S. EPA, 2006, [088089](#)). A new study that examined O<sub>3</sub> reaction byproducts has shown that  
5 cholesterol secoaldehyde (e.g., atheronal A) induces apoptosis in vitro in mouse macrophages (Gao  
6 et al., 2009, [200764](#)) and cardiomyocytes (Sathishkumar et al., 2009, [201549](#)). Additionally,  
7 atheronal-A and -B has been found to induce in vitro macrophage and endothelial cell  
8 proinflammatory events involved in the initiation of atherosclerosis (Takeuchi et al., 2006, [197793](#)).  
9 These O<sub>3</sub> reaction products when complexed with low density lipoprotein upregulate scavenger  
10 receptor class A and induce dose-dependent macrophage chemotaxis. Atheronal-A increases  
11 expression of the adhesion molecule, E-selectin, in endothelial cells, while atheronal-B induces  
12 monocyte differentiation. These events contribute to both monocyte recruitment and foam cell  
13 formation in atherosclerotic vessels. It is unknown whether these O<sub>3</sub> reaction products gain access to  
14 the vascular space from the lungs. Alternative explanations include the extrapulmonary release of  
15 diffusible mediators that may initiate or propagate inflammatory responses in the vascular or  
16 systemic compartments.

### Summary of Toxicological Studies

17 Overall, animal studies suggest that O<sub>3</sub> exposure may disrupt both the ·NO and endothelin  
18 systems, which can result in an increase in HR, HRV, and ANF, as is observed after O<sub>3</sub> exposure.  
19 Studies in rodents also exhibit O<sub>3</sub> induced bradycardia, but it is uncertain if this effect is also  
20 observed in humans. Additionally, O<sub>3</sub> may increase oxidative stress and vascular inflammation  
21 promoting the progression of atherosclerosis and leading to increased susceptibility to I/R injury. As  
22 O<sub>3</sub> reacts quickly with the ELF and does not translocate to the heart and large vessels, studies  
23 suggest that the cardiovascular effects exhibited could be caused by reaction byproducts of O<sub>3</sub>  
24 exposure. However, direct evidence of translocation of O<sub>3</sub> reaction products to the cardiovascular  
25 system has not been demonstrated in vivo. Alternatively, extrapulmonary release of diffusible  
26 mediators, such as cytokines or endothelins, may initiate or propagate inflammatory responses in the  
27 vascular or systemic compartments leading to the reported cardiovascular pathologies.

### 6.3.4. Summary and Causal Determination

28 In past O<sub>3</sub> AQCDs the effects of O<sub>3</sub> to the cardiovascular system did not receive much  
29 attention due to the paucity of information available. However, in recent years, investigation of O<sub>3</sub>-  
30 induced cardiovascular events has advanced. In general, compared with the epidemiologic evidence,  
31 the toxicological evidence is more supportive of an O<sub>3</sub>-induced cardiovascular effects.  
32 Epidemiologic evidence does not consistently demonstrate a positive relationship between short-  
33 term O<sub>3</sub> exposure and cardiovascular-related morbidity. However, most epidemiologic studies have

1 not extensively investigated the cardiovascular effects of O<sub>3</sub> exposure in susceptible populations,  
2 which may further support the toxicological findings. Although the epidemiologic evidence of  
3 cardiovascular morbidity is limited, single-city studies reviewed in the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
4 2006, [088089](#)), recent multicity studies, and the multicontinent APHENA study provide evidence of  
5 consistently positive associations between short-term O<sub>3</sub> exposure and cardiovascular mortality.  
6 However, in contrast with respiratory effects, there is weak coherence between associations for  
7 cardiovascular morbidity and mortality. Further, there is no apparent biological mechanism to  
8 explain the association observed for short-term O<sub>3</sub> exposure with cardiovascular mortality but not  
9 with cardiovascular morbidity.

10 Animal toxicological studies provide evidence for O<sub>3</sub>-induced cardiovascular effects,  
11 specifically enhanced I/R injury, disrupted NO-induced vascular reactivity, decreased cardiac  
12 function, and increased HRV. The observed increase in HRV is supported by a recent controlled  
13 human exposure study that also finds increased high frequency HRV, but not altered blood pressure,  
14 following O<sub>3</sub> exposure. Toxicological studies investigating the role of O<sub>3</sub> in heart rate regulation are  
15 mixed with both bradycardic and tachycardic responses observed. These changes in cardiac function  
16 provide evidence for O<sub>3</sub>-induced alterations in the autonomic nervous system leading to  
17 cardiovascular complications. Epidemiological studies showing positive association between O<sub>3</sub> and  
18 arrhythmias confirm the development of autonomic dysfunction following O<sub>3</sub> exposure. It is still  
19 uncertain how O<sub>3</sub> inhalation may cause systemic toxicity; however the cardiovascular effects of O<sub>3</sub>  
20 found in animals correspond to the development and maintenance of an extrapulmonary oxidative,  
21 proinflammatory environment.

22 In conclusion, animal toxicological studies provide stronger evidence for O<sub>3</sub> exposure leading  
23 to cardiovascular morbidity than do epidemiologic studies, among which there is a lack of coherence  
24 among endpoints. Based on the relatively strong body of toxicological evidence, and the consistent  
25 evidence of an association between O<sub>3</sub> and cardiovascular mortality, but weak coherence and  
26 biological plausibility for O<sub>3</sub>-induced cardiovascular morbidity, the generally limited body of  
27 evidence **is suggestive of a causal relationship between relevant short-term exposures to O<sub>3</sub> and**  
28 **cardiovascular effects.**

## 6.4. Central Nervous System Effects

29 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) included toxicological evidence that acute  
30 exposures to O<sub>3</sub> are associated with alterations in neurotransmitters, motor activity, short and long  
31 term memory, and sleep patterns. Additionally, histological signs of neurodegeneration have been  
32 observed. Research in the area of O<sub>3</sub>-induced neurotoxicity has notably increased over the past few  
33 years, with the majority of the evidence coming from toxicological studies that examined the  
34 association between O<sub>3</sub> exposure and neurobehavioral effects, and more limited evidence from  
35 epidemiologic studies. In an epidemiologic study conducted by Chen and Schwartz (2009, [179945](#)),  
36 data from the NHANES III cohort was utilized to study the relationship between long-term O<sub>3</sub>

1 exposure (mean annual O<sub>3</sub> concentration of 26.5 ppb) and neurobehavioral effects among adults aged  
2 20-59 years. The authors observed an association between annual exposure to O<sub>3</sub> and tests measuring  
3 coding ability and attention/short-term memory. Each 10-ppb increase in annual O<sub>3</sub> levels  
4 corresponded to an aging-related cognitive performance decline of 3.5 years for coding ability and  
5 5.3 years for attention/short-term memory. These associations persisted in both crude and adjusted  
6 models. There was no association between annual O<sub>3</sub> concentrations and reaction time tests. The  
7 authors conclude that overall there is a positive association between O<sub>3</sub> exposure and reduced  
8 performance on neurobehavioral tests. Although Chen and Schwartz (2009, [179945](#)) is a long-term  
9 exposure study, it is included in this section because it is the first epidemiologic study to demonstrate  
10 that exposure to ambient O<sub>3</sub> is associated with decrements in neurocognitive tests related to memory  
11 and attention in humans. This epidemiologic evidence of an adverse effect on the CNS due to  
12 exposure to ambient concentrations of O<sub>3</sub> is coherent with animal studies demonstrating that  
13 exposure to O<sub>3</sub> can produce a variety of CNS effects including behavioral deficits, morphological  
14 changes, and oxidative stress in the brains of rodents. In these rodent studies, interestingly, CNS  
15 effects were reported at O<sub>3</sub> concentrations that were generally lower than those concentrations  
16 commonly observed to produce adverse pulmonary or cardiac effects in rats.

17 A number of new studies demonstrate various perturbations in neurologic function or  
18 histology, including changes consistent with Parkinson's and Alzheimer's disease pathologies.

19 In a subchronic study, rats were exposed to 0.25 ppm O<sub>3</sub> for 4 h/day for 15-90 days (Rivas-  
20 Arancibia et al., 2010, [201544](#)). The exposures caused a complex array of responses, including a  
21 time-dependent increase in lipid peroxidation products and immunohistochemical changes in the  
22 hippocampus, a region of the brain which is important for higher cognitive function including  
23 memory acquisition, that were correlated with decrements in passive avoidance behavioral tests. The  
24 study showed progressive neurodegeneration, and statistically significant decreases in both short and  
25 long-term memory after 15 days of exposure to 0.25 ppm O<sub>3</sub>. Oxidative stress has also been  
26 observed in the striatum and substantia nigra of rats after 15 days of exposure to 0.25 ppm O<sub>3</sub> for  
27 4 h/day (Pereyra-Muñoz et al., 2006, [596408](#)). Perturbed oxidative balance has been observed in  
28 multiple regions of the brains after 15 days of exposure to 0.75 ppm O<sub>3</sub> (Calderon Guzman et al.,  
29 2006, [596371](#)), and these changes were dependent on the nutritional status of the rats (high versus  
30 low protein diet). For example, O<sub>3</sub> produced an increase in glutathione in rats fed the high protein  
31 diet but decreases in glutathione in rats fed low protein chow.

32 Martínez-Canabal et al. (2008, [194376](#)) showed exposure of rats to 0.25 ppm, 4h/day, for 7,  
33 15, or 30 days increased lipoperoxides in the hippocampus. This effect was observed at day 7 and  
34 continued to increase with time, indicating cumulative oxidative damage. The study also observed a  
35 loss of neurons and increased expression of COX-2, which has a role in neurodegenerative disease  
36 and is observed in the tissues of Alzheimer's patients. Consistent with Alzheimer's incidence in the  
37 elderly, O<sub>3</sub>-induced changes in lipid peroxidation and COX-2 positive cells in the hippocampus  
38 could be significantly inhibited by daily treatment with growth hormone (GH). The protective effect  
39 of GH on O<sub>3</sub>-induced oxidative stress was greatest on COX-2 after 15 days of O<sub>3</sub> exposure.

1 Consistent with these findings, lipid peroxidation in the hippocampus of rats was observed to  
2 increase significantly after a 30-day exposure to 0.25 ppm O<sub>3</sub>, but not after a single 4-h exposure to  
3 the same concentration (Mokoena et al., 2010, [677667](#)). However, 4 hours of exposure was sufficient  
4 to cause significant increases in lipid peroxidation when the concentration was increased to 0.7 ppm  
5 O<sub>3</sub>. Acute exposure to 0.7 ppm O<sub>3</sub> and prolonged exposure (30 days) to 0.25 ppm O<sub>3</sub> resulted in  
6 reduced efficacy of an antidepressant (imipramine).

7 A protective effect of estradiol has been observed in ovariectomized female rats exposed to  
8 0.25 ppm O<sub>3</sub> (4 h/day) for 30 or 60 days (Guevara-Guzmán et al., 2009, [596385](#)). In the olfactory  
9 bulb, lipid peroxidation was significantly less in rats exposed to O<sub>3</sub> and treated daily with estradiol.  
10 This protective effect of estradiol was also demonstrated for O<sub>3</sub>-induced decrements in a selective  
11 olfactory recognition memory test and an olfactory-dependent reward test. Similarly, estradiol  
12 protected against O<sub>3</sub>-induced changes in nigral cell morphology and loss of dopamine neurons in rats  
13 exposed to O<sub>3</sub> for 30 days (Angoa-Pérez et al., 2006, [596366](#)). Thus, repeated exposure of rats to O<sub>3</sub>  
14 produces lipid peroxidation at multiple sites in the brain and this oxidative stress is accompanied by  
15 gene expression changes and decrements in behavioral tests. Olfactory changes and loss of  
16 substantia nigra neurons are associated with Parkinson's disease in humans. Inhibition of these  
17 effects with estradiol treatment is consistent with the higher incidence of Parkinson's disease in men  
18 and the amelioration of Parkinsonian symptoms by estrogen therapy.

19 A number of rodent studies have also demonstrated CNS effects after single exposures to O<sub>3</sub>.  
20 Lipid peroxidation, as evidenced by increases in TBARS, occurred in multiple regions of the brain  
21 after a 1- to 9-h exposure to 1 ppm O<sub>3</sub> (Escalante-Membrillo et al., 2005, [596378](#)). Ozone has also  
22 been shown to alter gene expression of endothelin-1 (pituitary) and inducible nitric oxide synthase  
23 (cerebral hemisphere) after a single 4-h exposure to 0.8 ppm O<sub>3</sub>, indicating potential cerebrovascular  
24 effects. This dose-dependent effect was not observed at 0.4 ppm O<sub>3</sub> (Thomson et al., 2007, [196635](#)).  
25 Vascular endothelial growth factor was upregulated in astroglial cells in the central respiratory areas  
26 of the brain of rats exposed to 0.5 ppm O<sub>3</sub> for 3 hours (Araneda et al., 2008, [596367](#)). The  
27 persistence of CNS changes after a single exposure was also examined and the increase in vascular  
28 endothelial growth factor was present after a short (3 hours) recovery period. Evidence for more  
29 persistent oxidative stress-related changes in the CNS have been studied and morphological changes  
30 in the olfactory bulb of rats exposed to 1 ppm O<sub>3</sub> for 4 hours were observed at 2 hours, and 1 and  
31 10 days, but not 15 days, after exposure (Colín-Barenque et al., 2005, [180458](#)). Thus, there is  
32 evidence that O<sub>3</sub>-induced CNS effects are both concentration- and time-dependent.

33 Because O<sub>3</sub> can produce a disruption of the sleep-wake cycle (U.S. EPA, 2006, [088089](#)),  
34 Alfaro-Rodriguez et al. (2005, [596365](#)) examined whether acetylcholine in a region of the brain  
35 involved in sleep regulation was altered by O<sub>3</sub>. After a 24-h exposure to 0.5 ppm O<sub>3</sub>, the  
36 acetylcholine concentration in the medial preoptic area was decreased by 58% and strongly  
37 correlated with a disruption in paradoxical sleep. Such behavioral-biochemical effects of O<sub>3</sub> are  
38 confirmed by a number of studies which have demonstrated morphological and biochemical changes  
39 in rats.

1 Adverse CNS effects have also been demonstrated in newborn and adult rats whose only  
2 exposure to O<sub>3</sub> occurred in utero. Several neurotransmitters were assessed in male offspring of dams  
3 exposed to 1-ppm O<sub>3</sub> during the entire pregnancy (Gonzalez-Pina et al., 2008, [475317](#)). The data  
4 showed that catecholamine neurotransmitters were affected to a greater degree than indole-amine  
5 neurotransmitters in the cerebellum. Adverse CNS changes, including behavioral, cellular, and  
6 biochemical effects, have also been observed after in utero exposure to 0.5 ppm O<sub>3</sub> for 12 h/day from  
7 gestational days 5-20 (Boussouar et al., 2009, [596368](#)). Tyrosine hydroxylase labeling in the nucleus  
8 tractus solitarius was increased after in utero exposure to O<sub>3</sub> whereas Fos protein labeling did not  
9 change. When these offspring were challenged by immobilization stress, neuroplasticity pathways,  
10 which were activated in air-exposed offspring, were inhibited in O<sub>3</sub>-exposed offspring. Although an  
11 O<sub>3</sub> exposure concentration-response was not studied in these two in utero studies, it has been  
12 examined in one study. Santucci et al. (2006, [596414](#)) investigated behavioral effects and gene  
13 expression after in utero exposure of mice to as little as 0.3 ppm O<sub>3</sub>. Increased defensive/submissive  
14 behavior and reduced social investigation were observed in both the 0.3 and 0.6 ppm O<sub>3</sub> groups.  
15 Changes in gene expression of brain-derived neurotrophic factor (BDNF, increased in striatum) and  
16 nerve growth factor (NGF, decreased in hippocampus) accompanied these behavioral changes. Thus,  
17 these three studies demonstrate that CNS effects can occur as a result of in utero exposure to O<sub>3</sub>, and  
18 although the mode of action of these effects is not known, it has been suggested that circulating lipid  
19 peroxidation products may play a role (Boussouar et al., 2009, [596368](#)). Importantly, these adverse  
20 CNS effects occurred in rodent models after in utero only exposure to relevant concentrations of O<sub>3</sub>.

#### 6.4.1. Neuroendocrine Effects

21 According to the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), early studies suggested an  
22 interaction of O<sub>3</sub> with the pituitary-thyroid-adrenal axis, because thyroidectomy, hypophysectomy,  
23 and adrenalectomy protected against the lethal effects of O<sub>3</sub>. Concentrations of 0.7-1.0 ppm O<sub>3</sub> for a  
24 1-day exposure in male rats caused changes in the parathyroid, thymic atrophy, decreased serum  
25 levels of thyroid hormones and protein binding, and increased prolactin. Increased toxicity to O<sub>3</sub> was  
26 reported in hyperthyroid rats and T3 supplementation was shown to increase metabolic rate and  
27 pulmonary injury in the lungs of O<sub>3</sub>-treated animals. The mechanisms by which O<sub>3</sub> affects  
28 neuroendocrine function are not well understood, but previous work suggests that high ambient  
29 levels of O<sub>3</sub> can produce marked neural disturbances in structures involved in the integration of  
30 chemosensory inputs, arousal, and motor control, effects that may be responsible for some of the  
31 behavioral effects seen with O<sub>3</sub> exposure. However, no recent studies have become available to add  
32 to the limited evidence regarding neuroendocrine effects presented in the 2006 O<sub>3</sub> AQCD.

#### 6.4.2. Summary and Causal Determination

33 In rodents, O<sub>3</sub> exposure has been shown to cause physicochemical changes in the brain  
34 indicative of oxidative stress and inflammation. Newer toxicological studies add to earlier evidence

1 that acute exposures to O<sub>3</sub> can produce a range of effects on the central nervous system and behavior.  
2 Previously observed effects, including neurodegeneration, alterations in neurotransmitters, short and  
3 long term memory, and sleep patterns, have been further supported by recent studies. In instances  
4 where pathology and behavior are both examined, animals exhibit decrements in behaviors tied to  
5 the brain regions or chemicals found to be affected or damaged. For example, damage in the  
6 hippocampus, which is important for memory acquisition, was correlated with impaired performance  
7 in tests designed to assess memory. Thus the brain is functionally affected by O<sub>3</sub> exposure. The  
8 single epidemiology study conducted showed that O<sub>3</sub> affects memory in humans as well, albeit on a  
9 long-term exposure basis. Notably, exposure to O<sub>3</sub> levels as low as 0.25 ppm has resulted in  
10 progressive neurodegeneration and deficits in both short and long-term memory in rodents.  
11 Additionally, changes in the CNS, including biochemical, cellular, and behavioral effects, have been  
12 observed in animals whose sole exposure occurred in utero, at levels as a low as 0.3 ppm. Although  
13 evidence from epidemiologic and controlled human exposure studies is lacking, the toxicological  
14 evidence for ozone's impact on the brain and behavior is strong, and at least **is suggestive of a**  
15 **causal relationship between O<sub>3</sub> exposure and adverse CNS effects.**  
16

## 6.5. Effects on Other Organ Systems

### 6.5.1. Effects on the Liver and Xenobiotic Metabolism

17 Early investigations of the effects of O<sub>3</sub> on the liver centered on xenobiotic metabolism, and  
18 the prolongation of sleeping time, which was observed at 0.1 ppm O<sub>3</sub> (Graham et al., 1981, [039415](#)).  
19 In some species, only adults and especially females were affected. In rats, high (1.0-2.0 ppm for  
20 3 hours) acute O<sub>3</sub> exposures caused increased production of NO by hepatocytes and enhanced  
21 protein synthesis (Laskin et al., 1994, [076154](#); Laskin et al., 1996, [015771](#)). The O<sub>3</sub>-associated  
22 effects shown in the liver are thought to be mediated by inflammatory cytokines or other cytotoxic  
23 mediators released by activated macrophages in the lungs (Laskin and Laskin, 2001, [016158](#); Laskin  
24 et al., 1998, [015425](#); Vincent et al., 1996, [080777](#)). Except for the earlier work on xenobiotic  
25 metabolism, the responses occurred only after very high acute O<sub>3</sub> exposures. One study, conducted at  
26 1 ppm O<sub>3</sub> exposure, has been identified (Last et al., 2005, [596400](#)) in which alterations in gene  
27 expression underlying O<sub>3</sub>-induced cachexia and downregulation of xenobiotic metabolism were  
28 examined. A number of the down-regulated genes are known to be interferon (IFN) dependent,  
29 suggesting a role for circulating IFN. A more recent study by Aibo et al. (2010, [378559](#))  
30 demonstrates exacerbation of acetaminophen-induced liver injury in mice after a single 6-h exposure  
31 to 0.25 or 0.5 ppm O<sub>3</sub>. Data indicate that O<sub>3</sub> may worsen drug-induced liver injury by inhibiting  
32 hepatic repair.

33 In summary, mediators generated by O<sub>3</sub> exposure may cause effects on the liver in laboratory  
34 rodents. Ozone exposures as low as 0.1 ppm have been shown to affect drug induced sleeping time,

1 and exposure to 0.25 ppm can exacerbate liver injury induced by a common analgesic. However,  
2 very few studies at relevant concentrations have been conducted, and no data from controlled human  
3 exposure or epidemiologic studies are currently available. Therefore the collective evidence is  
4 **inadequate to determine if a causal relationship exists between short-term O<sub>3</sub> exposure and**  
5 **effects on the liver and metabolism.**

## 6.5.2. Effects on Cutaneous and Ocular Tissues

6 In addition to the lungs, the skin is highly exposed to O<sub>3</sub> and contains O<sub>3</sub> reactive targets  
7 (polyunsaturated fatty acids) that can produce lipid peroxides. The 2006 O<sub>3</sub> AQCD reported that  
8 although there is evidence of oxidative stress at near ambient O<sub>3</sub> concentrations, skin and eyes are  
9 only affected at high concentrations (greater than 1-5 ppm). Ozone exposure (0.8 ppm for 7 days)  
10 induces oxidative stress in the skin of hairless mice, along with proinflammatory cytokines (Valacchi  
11 et al., 2009, [201554](#)). A recent study demonstrated that 0.25 ppm O<sub>3</sub> differentially alters expression  
12 of metalloproteinases in the skin of young and aged mice, indicating age-related susceptibility to  
13 oxidative stress (Fortino et al., 2007, [596382](#)). In young mice, healing of skin wounds is not  
14 significantly affected by O<sub>3</sub> exposure (Lim et al., 2006, [670834](#)). However, exposure to 0.5 ppm O<sub>3</sub>  
15 for 6 h/day significantly delays wound closure in aged mice. As with effects on the liver described  
16 above, the effects of O<sub>3</sub> on the skin and eyes have not been widely studied, and information from  
17 controlled human exposure or epidemiologic studies is not currently available. Therefore the  
18 collective evidence is **inadequate to determine if a causal relationship exists between short-term**  
19 **O<sub>3</sub> exposure and effects on cutaneous and ocular tissues.**

## 6.6. Mortality

### 6.6.1. Summary of Findings from 2006 Ozone AQCD

20 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) reviewed a large number of time-series studies  
21 consisting of single- and multicity studies, and meta-analyses. In the large U.S. multicity studies that  
22 examined all-year data, summary effect estimates corresponding to single-day lags ranged from a  
23 0.5-1% increase in all-cause (nonaccidental) mortality per the standardized unit increase<sup>1</sup> in O<sub>3</sub>. The  
24 association between short-term O<sub>3</sub> exposure and mortality was substantiated by a collection of meta-  
25 analyses and international multicity studies. The studies evaluated found some evidence for  
26 heterogeneity in O<sub>3</sub> mortality risk estimates across cities and studies. Although more limited in  
27 number, studies that conducted seasonal analyses reported larger O<sub>3</sub> mortality risk estimates during  
28 the warm or summer season. Overall, the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) identified  
29 robust associations between various measures of daily ambient O<sub>3</sub> concentrations and all-cause

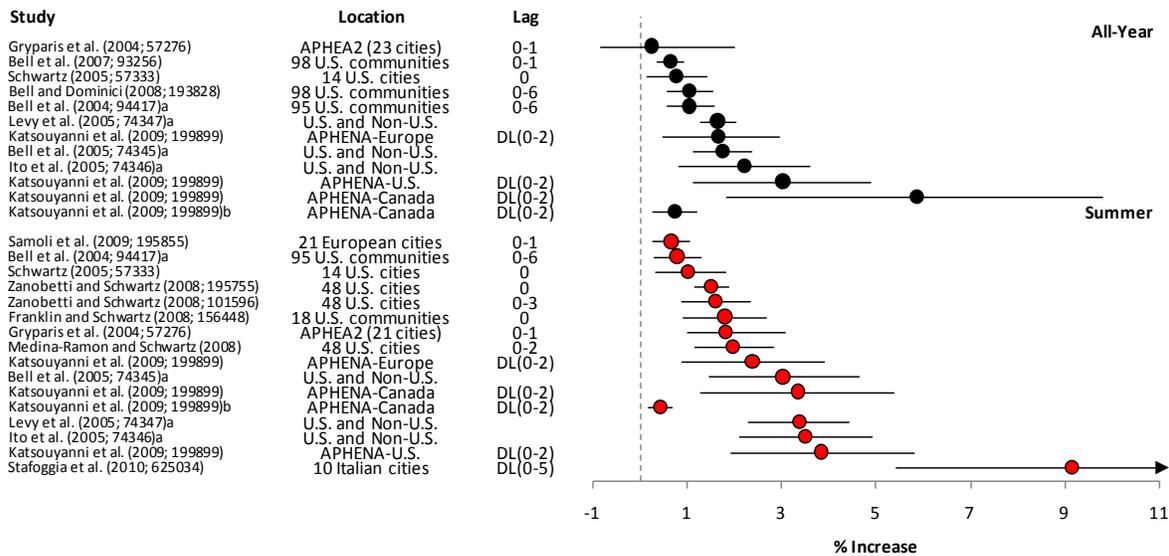
---

<sup>1</sup> In the 2006 O<sub>3</sub> AQCD and throughout this document to compare across studies that used the same exposure metric, effect estimates were standardized to 40 ppb for 1-h maximum, 30 ppb for 8-h maximum, and 20 ppb for 24-h average O<sub>3</sub> concentrations.

1 mortality, with additional evidence for associations with cardiovascular mortality, which could not be  
2 readily explained by confounding due to time, weather, or co-pollutants. However, it was noted that  
3 multiple uncertainties remain regarding the O<sub>3</sub>-mortality relationship including: the extent of residual  
4 confounding by co-pollutants; factors that modify the O<sub>3</sub>-mortality association; the appropriate lag  
5 structure for identifying O<sub>3</sub>-mortality effects (e.g., single-day lags versus distributed lag model); the  
6 shape of the O<sub>3</sub>-mortality C-R function and whether a threshold exists; and the identification of  
7 susceptible populations. Collectively, the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) concluded that  
8 “the overall body of evidence is highly suggestive that O<sub>3</sub> directly or indirectly contributes to non-  
9 accidental and cardiopulmonary-related mortality.”

### 6.6.2. Associations of Mortality and Short-Term Ozone Exposure

10  
11 The recent literature that examined the association between short-term O<sub>3</sub> exposure and  
12 mortality further confirmed the associations reported in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006,  
13 [088089](#)). New multicontinent and multicity studies reported consistent positive associations between  
14 short-term O<sub>3</sub> exposure and all-cause mortality in all-year analyses, with additional evidence for  
15 larger mortality risk estimates during the warm or summer months (Figure 6-27; Table 6-33). These  
16 associations were reported across a range of ambient O<sub>3</sub> concentrations that were in some cases quite  
17 low (Table 6-34).



**Figure 6-27. Summary of mortality risk estimates for short-term ozone exposure and all-cause (nonaccidental) mortality from all-year and summer season analyses.** 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 ozone concentrations. An “a” represent multicity studies and meta-analyses from the 2006 ozone AQCD. Bell et al. (2005, [074345](#)), Ito et al. (2005, [074346](#)), and Levy et al. (2005, [074347](#)) 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 ozone concentrations (see explanation in Section 6.2.7.2).

**Table 6-33. Corresponding effect estimates for Figure 6-27**

Study	Location	Lag	Avg Time	% Increase (95% CI)
<b>All-year</b>				
Gryparis et al. (2004, <a href="#">057276</a> )	APHEA2 (23 cities)	0-1	1-h max	0.24 (-0.86, 1.98)
Bell et al. (2007, <a href="#">093256</a> )	98 U.S. communities	0-1	24-h avg	0.64 (0.34, 0.92)
Schwartz (2005, <a href="#">057333</a> )	14 U.S. cities	0	1-h max	0.76 (0.13, 1.40)
Bell and Dominici (2008, <a href="#">193828</a> )	98 U.S. communities	0-6	24-h avg	1.04 (0.56, 1.55)
Bell et al. (2004, <a href="#">094417</a> )a	95 U.S. communities	0-6	24-h avg	1.04 (0.54, 1.55)
Levy et al. (2005, <a href="#">074347</a> )a	U.S. and Non-U.S.	---	24-h avg	1.64 (1.25, 2.03)
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-Europe	DL(0-2)	1-h max	1.66 (0.47, 2.94)
Bell et al. (2005, <a href="#">074345</a> )a	U.S. and Non-U.S.	---	24-h avg	1.75 (1.10, 2.37)
Ito et al. (2005, <a href="#">074346</a> )a	U.S. and Non-U.S.	---	24-h avg	2.20 (0.80, 3.60)
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-U.S.	DL(0-2)	1-h max	3.02 (1.10, 4.89)
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-Canada	DL(0-2)	1-h max	5.87 (1.82, 9.81)
Katsouyanni et al. (2009, <a href="#">199899</a> )b	APHENA-Canada	DL(0-2)	1-h max	0.73 (0.23, 1.20)
<b>Summer</b>				
Samoli et al. (2009, <a href="#">195855</a> )	21 European cities	0-1	8-h max	0.66 (0.24, 1.05)
Bell et al. (2004, <a href="#">094417</a> )a	95 U.S. communities	0-6	24-h avg	0.78 (0.26, 1.30)
Schwartz (2005, <a href="#">057333</a> )	14 U.S. cities	0	1-h max	1.00 (0.30, 1.80)
Zanobetti and Schwartz (2008, <a href="#">195755</a> )	48 U.S. cities	0	8-h max	1.51 (1.14, 1.87)
Zanobetti and Schwartz (2008, <a href="#">101596</a> )	48 U.S. cities	0-3	8-h max	1.60 (0.84, 2.33)
Franklin and Schwartz (2008, <a href="#">156448</a> )	18 U.S. communities	0	24-h avg	1.79 (0.90, 2.68)
Gryparis et al. (2004, <a href="#">057276</a> )	APHEA2 (21 cities)	0-1	8-h max	1.80 (0.99, 3.06)
Medina-Ramon and Schwartz (2008, <a href="#">193829</a> )	48 U.S. cities	0-2	8-h max	1.96 (1.14, 2.82)
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-Europe	DL(0-2)	1-h max	2.38 (0.87, 3.91)
Bell et al. (2005, <a href="#">074345</a> )a	U.S. and Non-U.S.	---	24-h avg	3.02 (1.45, 4.63)
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-Canada	DL(0-2)	1-h max	3.34 (1.26, 5.38)
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-Canada	DL(0-2)	1-h max	0.42 (0.16, 0.67)
Levy et al. (2005, <a href="#">074347</a> )a	U.S. and Non-U.S.	---	24-h avg	3.38 (2.27, 4.42)
Ito et al. (2005, <a href="#">074346</a> )a	U.S. and Non-U.S.	---	24-h avg	3.50 (2.10, 4.90)
Katsouyanni et al. (2009, <a href="#">199899</a> )	APHENA-U.S.	DL(0-2)	1-h max	3.83 (1.90, 5.79)
Stafoggia et al. (2010, <a href="#">625034</a> )	10 Italian cities	DL(0-5)	8-h max	9.15 (5.41, 13.0)

<sup>a</sup>Multiplicity studies and meta-analyses from the 2006 O<sub>3</sub> AQCD. Bell et al. (2005, [074345](#))a, Ito et al. (2005, [074346](#))a, and Levy et al. (2005, [074347](#))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.

<sup>b</sup>Risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O<sub>3</sub> concentrations (see explanation in Section 6.2.7.2).

**Table 6-34. Range of mean and upper percentile ozone concentrations in previous and recent multicity studies**

Study	Location	Years	Metric	Mean Concentration (ppb) <sup>a</sup>	Middle/Upper Percentile Concentrations (ppb) <sup>a</sup>
Gryparis et al. (2004, <a href="#">057276</a> ) <sup>b</sup>	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 (2005, <a href="#">057333</a> ) <sup>b</sup>	14 U.S. cities	1986-1993	1-h max	35.1-60	25th: 26.5-52 75th: 46.3-69
Bell et al. (2004, <a href="#">094417</a> )	95 U.S. communities (NMMAPS)	1987-2000	24-h avg	26.0	NR
Bell et al. (2007, <a href="#">093256</a> )	98 U.S. communities (NMMAPS)	1987-2000	24-h avg	26.0 d	NR
Bell and Dominici (2008, <a href="#">193828</a> )	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 (Franklin and Schwartz, 2008, <a href="#">156448</a> )	18 U.S. communities	2000-2005 (May-September)	24-h avg	21.4-48.7	NR
Katsouyanni et al. (2009, <a href="#">199899</a> ) <sup>b,e</sup>	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, <a href="#">193829</a> ) <sup>b</sup>	48 U.S. cities	1989-2000 (May-September)	8-h max	16.1-58.8	NR
Samoli et al. (2009, <a href="#">195855</a> ) <sup>b</sup>	21 European cities (APHEA2)	1990-1997 (June-August)	8-h max	20.0-62.8	75th: 27.2-74.8
Stafoggia et al. (2010, <a href="#">625034</a> )	10 Italian cities	2001-2005 (April-September)	8-h max	41.2-58.9	75th: 47.0-71.6
Zanobetti and Schwartz (2008, <a href="#">101596</a> )	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
Zanobetti and Schwartz (2008, <a href="#">195755</a> )	48 U.S. cities <sup>c</sup>	1989-2000 (Winter: December-February) (Spring: March-May) (Summer: June-August) (Autumn: September-November)	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

<sup>a</sup>O<sub>3</sub> concentrations were converted to ppb if the study presented them as µg/m<sup>3</sup> by using the conversion factor of 0.51 assuming standard temperature (25° C) and pressure (1 atm).

<sup>b</sup>Study only reported median O<sub>3</sub> concentrations.

<sup>c</sup>Cities 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.

<sup>d</sup>Bell et al. (2007, [093256](#)) did not report mean O<sub>3</sub> concentrations, however, it used a similar dataset as Bell et al. (2004, [094417](#)) which consisted of 95 U.S. communities for 1987-2000. For comparison purposes the 24-h avg O<sub>3</sub> concentrations for the 95 communities from Bell et al. (2004, [094417](#)) are reported here.

<sup>e</sup>Study did not present air quality data for the summer months.

1 In addition to examining the relationship between short-term O<sub>3</sub> exposure and all-cause  
2 mortality, recent studies attempted to address the uncertainties that remained upon the completion of  
3 the 2006 O<sub>3</sub> AQCD. As a result, given the robust associations between short-term O<sub>3</sub> exposure and  
4 mortality presented across studies in the 2006 O<sub>3</sub> AQCD and supported in the new multicity studies,  
5 the following sections primarily focus on the examination of previously identified uncertainties in  
6 the O<sub>3</sub>-mortality relationship, specifically: confounding, lag structure (e.g., multiday effects and

1 mortality displacement), effect modification (i.e., sources of heterogeneity in risk estimates across  
2 cities); the O<sub>3</sub>-mortality C-R relationship; and O<sub>3</sub> associations with cause-specific mortality.  
3 Focusing specifically on these uncertainties allows for a more detailed characterization of the  
4 relationship between short-term O<sub>3</sub> exposure and mortality.

### 6.6.2.1. Confounding

#### Confounding by PM and PM Constituents

5 An important question in the evaluation of the association between short-term O<sub>3</sub> exposure and  
6 mortality is whether the relationship is confounded by particulate matter, particularly the PM  
7 chemical components that are found in the “summer haze” mixture which also contains O<sub>3</sub>.  
8 However, because of the temporal correlation among these PM components and O<sub>3</sub>, and their  
9 possible interactions, the interpretation of results from multi-pollutant models that attempt to  
10 disentangle the health effects associated with each pollutant is limited.

11 The potential confounding effects of PM<sub>10</sub> and PM<sub>2.5</sub> on the O<sub>3</sub>-mortality relationship were  
12 examined by Bell et al. (2007, [093256](#)) using data on 98 U.S. urban communities for the years  
13 1987-2000 from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). In this  
14 analysis the authors included PM as a covariate in time-series models, and also examined  
15 O<sub>3</sub>-mortality associations on days when O<sub>3</sub> concentrations were below a specified value. This  
16 analysis was limited by the small fraction of days when both PM and O<sub>3</sub> data were available, due to  
17 the every-3rd- or 6th-day sampling schedule for the PM indices, and the limited amount of city-  
18 specific data for PM<sub>2.5</sub> because it was only collected in most cities since 1999. As a result, of the 91  
19 communities with PM<sub>2.5</sub> data, only 9.2% of days in the study period had data for both O<sub>3</sub> and PM<sub>2.5</sub>,  
20 resulting in the use of only 62 communities in the PM<sub>2.5</sub> analysis. An examination of the correlation  
21 between PM and O<sub>3</sub> found that neither PM size fraction was highly correlated with various levels of  
22 daily concentrations of O<sub>3</sub> or PM (e.g., PM<sub>10</sub> and PM<sub>2.5</sub>). These results were also observed when  
23 using 8-h max and 1-h max O<sub>3</sub> exposure metrics. National and community-specific effect estimates  
24 of the association between short-term O<sub>3</sub> exposure and mortality were robust to inclusion of PM<sub>10</sub> or  
25 PM<sub>2.5</sub> in time-series models through the range of O<sub>3</sub> concentrations (i.e., <10 ppb, 10-20, 20-40,  
26 40-60, 60-80, and >80 ppb). For example, the percent increase in nonaccidental deaths per 10 ppb  
27 increase 24-h avg O<sub>3</sub> concentrations at lag 0-1 day were 0.22% (95% CI: -0.22, 0.65) without PM<sub>2.5</sub>  
28 and 0.21% (95% CI: -0.22, 0.64) with PM<sub>2.5</sub> in 62 communities.

29 Although no strong correlations between PM and O<sub>3</sub> were reported by Bell et al. (2007,  
30 [093256](#)) the patterns observed suggest regional differences in their correlation. (Table 6-35). Both  
31 PM<sub>10</sub> and PM<sub>2.5</sub> show positive correlations with O<sub>3</sub> in the Industrial Midwest, Northeast, Urban  
32 Midwest, and Southeast, especially in the summer months, presumably, because of the summer  
33 peaking sulfate. However, the mostly negative or weak correlations between PM and O<sub>3</sub> in the  
34 summer in the Southwest, Northwest, and southern California could be due to winter-peaking nitrate.

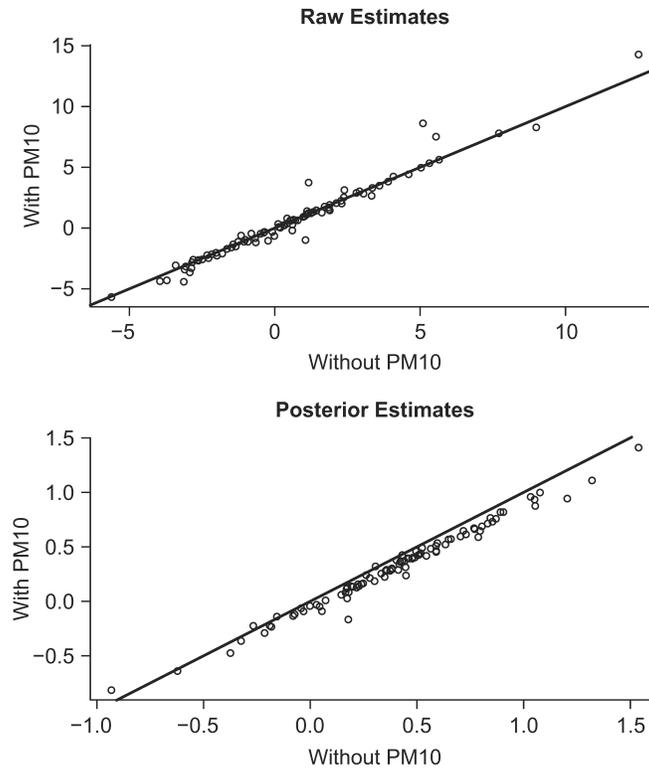
1 Thus, the potential confounding effect of PM on the O<sub>3</sub>-mortality relationship could be influenced by  
 2 the relative contribution of sulfate and nitrate, which varies regionally and seasonally.

**Table 6-35. Correlations between PM and ozone by season and region**

	No. of Communities	Winter	Spring	Summer	Fall	Yearly
PM <sub>10</sub>						
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 <sub>2.5</sub>						
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, [093256](#)).

3 In an attempt to reassess a number of issues associated with the O<sub>3</sub>-mortality relationship,  
 4 including confounding, Smith et al. (2009, [199750](#)) re-analyzed the publicly available NMMAPS  
 5 database for the years 1987-2000. The authors conducted a number of analyses using constrained  
 6 distributed lag models and the average of 0- and 1-day lags. In addition, Smith et al. (2009, [199750](#))  
 7 examined the effect of different averaging times (24-h, 8-h, and 1-h max) on O<sub>3</sub>-mortality regression  
 8 coefficients, and whether PM<sub>10</sub> confounded the O<sub>3</sub>-mortality relationship. The authors reported that,  
 9 in most cases, O<sub>3</sub> mortality risk estimates were reduced by between 22% and 33% in co-pollutant  
 10 models with PM<sub>10</sub>. This is further highlighted in Figure 6-28, which shows scatter plots of  
 11 O<sub>3</sub>-mortality risk estimates with adjustment for PM<sub>10</sub> versus without adjustment for PM<sub>10</sub>. Smith et  
 12 al. (2009, [199750](#)) point out that a larger fraction (89 out of 93) of the posterior estimates lie below  
 13 the diagonal line (i.e., estimates are smaller with PM<sub>10</sub> adjustment) compared to the raw estimates  
 14 (56 out of 93). This observation could be attributed to both sets of posterior estimates being  
 15 calculated by “shrinking towards the mean.” However, the most prominent feature of these plots is  
 16 that the variation of O<sub>3</sub>-mortality risk estimates across cites is much larger than the impact of PM<sub>10</sub>  
 17 adjustment on the O<sub>3</sub>-mortality relationship.

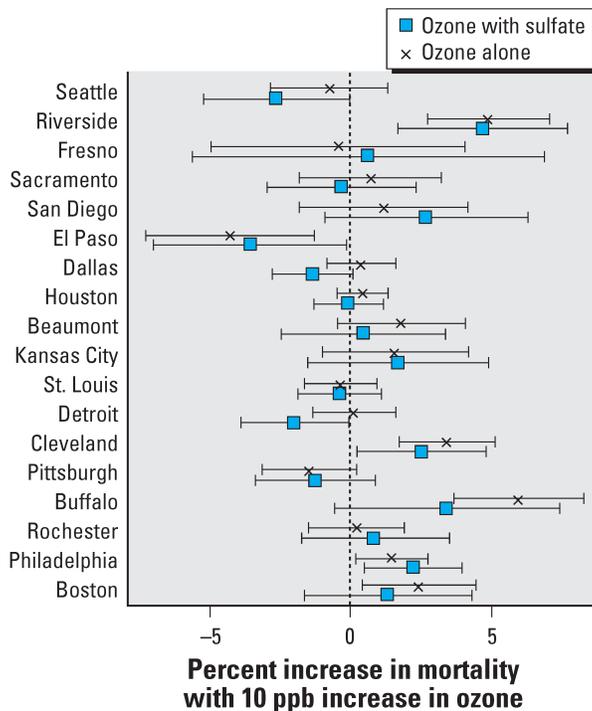


Source: Used with permission from Informa UK Ltd., Smith et al. (2009, [199750](#)).

**Figure 6-28. Scatter plots of ozone mortality risk estimates with versus without adjustment for PM<sub>10</sub> in NMMAPS cities. □The diagonal line indicates 1:1 ratio.**

1 Franklin and Schwartz (2008, [156448](#)) examined the sensitivity of O<sub>3</sub> mortality risk estimates  
 2 to the inclusion of PM<sub>2.5</sub> or PM chemical components associated with secondary aerosols (e.g.,  
 3 sulfate [SO<sub>4</sub><sup>2-</sup>], organic carbon [OC], and nitrate [NO<sub>3</sub><sup>-</sup>]) in co-pollutant models. This analysis  
 4 consisted of between 3 and 6 years of data from May through September 2000-2005 from 18 U.S.  
 5 communities. The association between O<sub>3</sub> and non-accidental mortality was examined in single-  
 6 pollutant models and after adjustment for PM<sub>2.5</sub>, sulfate, organic carbon, or nitrate concentrations.  
 7 The single-city effect estimates were combined into an overall estimate using a random-effects  
 8 model. In the single-pollutant model, the authors found a 0.89% (95% CI: 0.45, 1.33%) increase in  
 9 nonaccidental mortality with a 10-ppb increase in same-day 24-h summertime O<sub>3</sub> concentrations  
 10 across the 18 U.S. communities. Adjustment for PM<sub>2.5</sub> mass, which was available for 84% of the  
 11 days, decreased the O<sub>3</sub>-mortality risk estimate only slightly (from 0.88% to 0.79%), but the inclusion  
 12 of sulfate in the model reduced the risk estimate by 31% (from 0.85% to 0.58%). However, sulfate  
 13 data was only available for 18% of the days. Therefore, a limitation of this study is the limited  
 14 amount of data for PM<sub>2.5</sub> chemical components due to the every-3rd-day or every-6th-day sampling  
 15 schedule. For example, when using a subset of days when organic carbon measurements were  
 16 available (i.e., 17% of the available days), O<sub>3</sub> mortality risk estimates were reduced to 0.51% (95%  
 17 CI: -0.36 to 1.36) in a single-pollutant model.

1 Consistent with the studies previously discussed, the results from Franklin and Schwartz  
 2 (2008, [156448](#)) also demonstrate that the interpretation of the potential confounding effects of  
 3 co-pollutants on O<sub>3</sub> mortality risk estimates is not straightforward. As presented in Figure 6-29, the  
 4 regional and city-to-city variations in O<sub>3</sub> mortality risk estimates appear greater than the impact of  
 5 adjusting for co-pollutants. In addition, in some cases, a negative O<sub>3</sub> mortality risk estimate becomes  
 6 even more negative with the inclusion of sulfate (e.g., Seattle) in a co-pollutant model, or a null O<sub>3</sub>  
 7 mortality risk estimate becomes negative when sulfate is included (e.g., Dallas and Detroit). Thus,  
 8 the reduction in the overall O<sub>3</sub> mortality risk estimate (i.e., across cities) needs to be assessed in the  
 9 context of the heterogeneity in the single-city estimates.



Source: Used with permission of Franklin and Schwartz (2008, [156448](#)).

**Figure 6-29. Community-specific ozone-mortality risk estimates for nonaccidental mortality per 10-ppb increase in same-day 24-h avg summertime ozone concentrations in single-pollutant models and co-pollutant models with sulfate.**

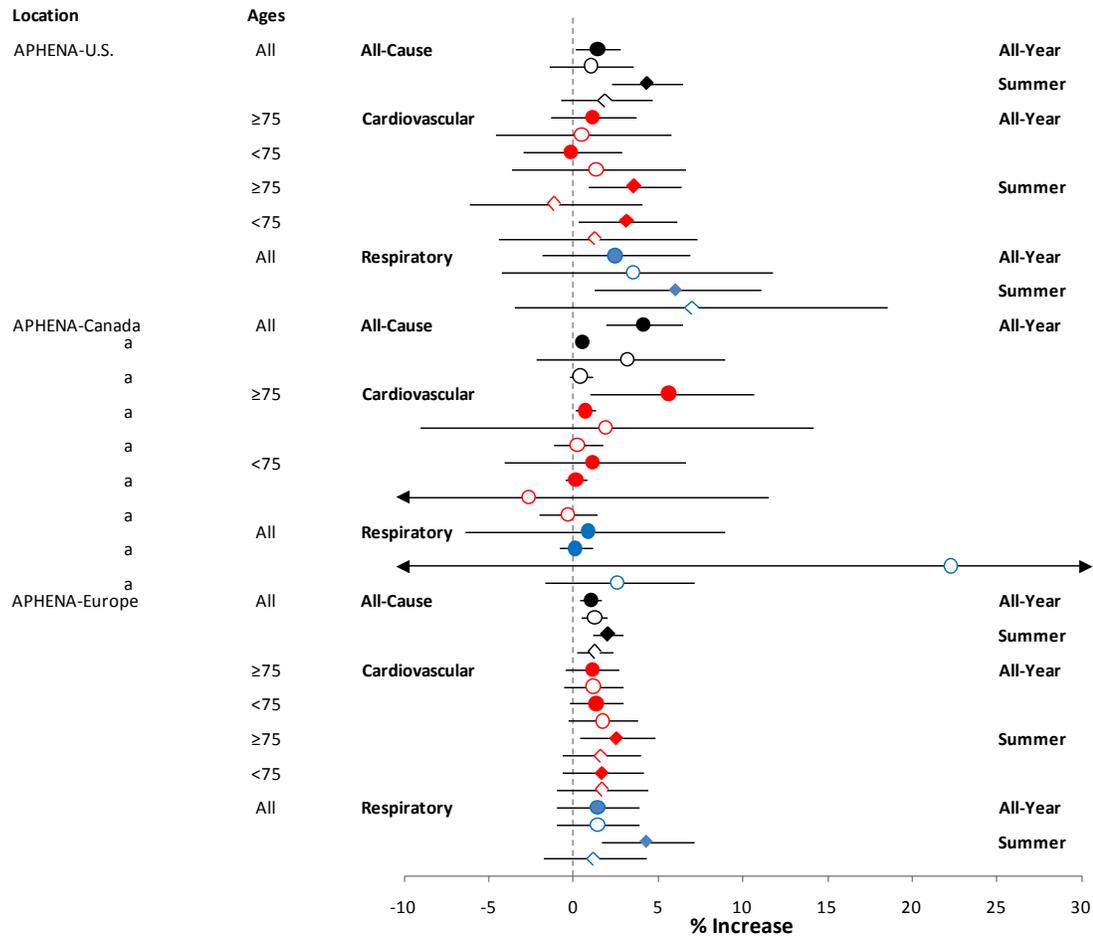
10 In the APHENA study, the investigators from the U.S. (NMMAPS), Canadian, and European  
 11 (APHEA2) multicity studies collaborated and conducted a joint analysis of PM<sub>10</sub> and O<sub>3</sub> using each  
 12 of these datasets (Katsouyanni et al., 2009, [199899](#)). For mortality, each dataset consisted of a  
 13 different number of cities and years of air quality data: U.S. encompassed 90 cities with daily O<sub>3</sub>  
 14 data from 1987-1996 of which 36 cities had summer only O<sub>3</sub> measurements; Europe included 23  
 15 cities with 3-7 years of daily O<sub>3</sub> data during 1990-1997; and Canada consisted of 12 cities with daily

1 O<sub>3</sub> data from 1987 to 1996. As discussed in Section 6.2.7.2, the APHENA study conducted extensive  
2 sensitivity analyses, of which the 8 df/year results for both the penalized spline (PS) and natural  
3 spline (NS) models are presented in the text for comparison purposes, but only the NS results are  
4 presented in figures because alternative spline models have previously been shown to result in  
5 similar effect estimates (Health Effects Institute, 2003, [042829](#)). Additionally, for the Canadian  
6 results, figures contain risk estimates standardized to both a 40-ppb increment for 1-h max O<sub>3</sub>  
7 concentrations, consistent with the rest of the ISA, but also the approximate IQR across the Canadian  
8 cities as discussed previously (Section 6.2.7.2).

9 In the three datasets, the authors found generally positive associations between short-term O<sub>3</sub>  
10 exposure and all-cause, cardiovascular, and respiratory mortality. The estimated excess risks for O<sub>3</sub>  
11 were larger for the Canadian cities than for the U.S. and European cities. When examining the  
12 potential confounding effects of PM<sub>10</sub> on O<sub>3</sub> mortality risk estimates, the sensitivity of the estimates  
13 varied across the data sets and age groups. In the Canadian dataset, adjusting for PM<sub>10</sub> modestly  
14 reduced O<sub>3</sub> risk estimates for all-cause mortality for all ages in the PS (4.5% [95% CI: 2.2, 6.7%])  
15 and NS (4.2% [95% CI: 1.9, 6.5%]) models to 3.8% (95% CI: -1.4, 9.8%) and 3.2% (95% CI: -2.2,  
16 9.0%), respectively, at lag 1 for a 40-ppb increase in 1-h max O<sub>3</sub> concentrations (Figure 6-30; Table  
17 6-36). However, adjusting for PM<sub>10</sub> reduced O<sub>3</sub> mortality risk estimates in the ≥ 75-year age group,  
18 but increased the risk estimates in the <75-year age group. For cardiovascular and respiratory  
19 mortality more variable results were observed with O<sub>3</sub> risk estimates being reduced and increased,  
20 respectively, in co-pollutant models with PM<sub>10</sub> (Figure 6-30; Table 6-36). Unlike the European and  
21 U.S. datasets, the Canadian dataset only conducted co-pollutant analyses at lag 1; as a result, to  
22 provide a comparison across study locations only the lag 1 results are presented for the European and  
23 U.S. datasets in this section.

24 In the European data, O<sub>3</sub> risk estimates were robust when adjusting for PM<sub>10</sub> in the year-round  
25 data for all-cause, cardiovascular and respiratory mortality. When restricting the analysis to the  
26 summer months moderate reductions were observed in O<sub>3</sub> risk estimates for all-cause mortality (e.g.,  
27 lag 1 in a PS (0.29% [95% CI: 0.19, 0.39]) and NS (0.26% [95% CI: 0.14, 0.37]) model was reduced  
28 to 0.19% (95% CI: 0.07, 0.32%) and 0.16% (95% CI: 0.02, 0.29%), respectively) with more  
29 pronounced reductions in respiratory mortality. In the U.S. data, adjusting for PM<sub>10</sub> moderately  
30 reduced O<sub>3</sub> risk estimates for all-cause mortality in a year-round analysis at lag 1 (e.g., both the PS  
31 and NS models were reduced from 0.18% to 0.13%) (Figure 6-30; Table 6-36). Similar to the  
32 European data, when restricting the analysis to the summer months, adjusting for PM<sub>10</sub> moderately  
33 reduced O<sub>3</sub> mortality risk estimates in the U.S. For example, the O<sub>3</sub> risk estimate for all-cause  
34 mortality for all ages at lag 1 day in the PS (3.9% [95% CI: 2.3, 5.5%]) and NS (4.3% [95% CI: 2.2,  
35 6.5%]) models was reduced to 2.1% (95% CI: -0.55, 4.9%) and 1.9% (95% CI: -0.78, 4.6%),  
36 respectively. However, when examining cause-specific mortality risk estimates, consistent with the  
37 results from the Canadian dataset, which employed a similar PM sampling strategy (i.e., every-6th-  
38 day sampling), O<sub>3</sub> risk estimates for cardiovascular and respiratory mortality were more variable;  
39 reduced or increased in all-year and summer analyses. Overall, the estimated O<sub>3</sub> risks appeared to be

- 1 moderately to substantially sensitive to inclusion of PM<sub>10</sub> in co-pollutant models. Despite the
- 2 multicity approach, the mostly every-6th-day sampling schedule for PM<sub>10</sub> in the Canadian and U.S.
- 3 datasets greatly reduced the sample size and limits the interpretation of these results.



**Figure 6-30. Percent increase in all-cause (nonaccidental) and cause-specific mortality from the APHENA study for single- and co-pollutant models. Effect estimates are for a 40-ppb increase in 1-h max ozone 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 co-pollutant models with PM<sub>10</sub>. Black = all-cause mortality; red = cardiovascular mortality; and blue = respiratory mortality. An “a” represents risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in ozone concentrations (see explanation in Section 6.2.7.2).**

**Table 6-36. Corresponding Effect Estimates for Figure 6-30**

Location	Mortality	Ages	Season	Co-pollutant	% Increase (95% CI)	
APHENA-U.S.	All-Cause	All	All-year		1.42 (0.08, 2.78)	
			Summer	PM <sub>10</sub>	1.02 (-1.40, 3.50)	
	Cardiovascular	≥ 75	All-year		4.31 (2.22, 6.45)	
				PM <sub>10</sub>	1.90 (-0.78, 4.64)	
			Summer		1.10 (-1.33, 3.67)	
				PM <sub>10</sub>	0.47 (-4.61, 5.79)	
			All-year	<75		-0.16 (-3.02, 2.86)
				PM <sub>10</sub>	1.34 (-3.63, 6.61)	
	Summer	≥ 75		3.58 (0.87, 6.37)		
		PM <sub>10</sub>	-1.17 (-6.18, 4.07)			
	Respiratory	All	All-year		3.18 (0.31, 6.12)	
				PM <sub>10</sub>	1.26 (-4.46, 7.28)	
Summer				2.46 (-1.87, 6.86)		
			PM <sub>10</sub>	3.50 (-4.23, 11.8)		
All-year			<75		6.04 (1.18, 11.1)	
			PM <sub>10</sub>	7.03 (-3.48, 18.5)		
APHENA-Canada	All-Cause	All	All-year		4.15 (1.90, 6.45)	
			Summer	PM <sub>10</sub>	0.52 (0.24, 0.80)a	
	Cardiovascular	≥ 75	All-year		3.18 (-2.18, 8.96)	
				PM <sub>10</sub>	0.40 (-0.28, 1.10)a	
			Summer		5.62 (0.95, 10.7)	
				PM <sub>10</sub>	0.70 (0.12, 1.30)a	
			All-year	<75		1.90 (-9.03, 14.1)
				PM <sub>10</sub>	0.24 (-1.20, 1.70)a	
	Summer		1.10 (-4.08, 6.61)			
		PM <sub>10</sub>	0.14 (-0.53, 0.82)a			
	Respiratory	All	All-year		-2.64 (-14.7, 11.5)	
				PM <sub>10</sub>	-0.34 (-2.00, 1.40)a	
Summer				0.87 (-6.40, 8.96)		
			PM <sub>10</sub>	0.11 (-0.84, 1.10)a		
All-year			<75		22.3 (-12.6, 71.3)	
			PM <sub>10</sub>	2.60 (-1.70, 7.10)a		
APHENA-Europe	All-Cause	All	All-year		1.02 (0.39, 1.66)	
			Summer	PM <sub>10</sub>	1.26 (0.47, 1.98)	
	Cardiovascular	≥ 75	All-year		2.06 (1.10, 2.94)	
				PM <sub>10</sub>	1.26 (0.16, 2.30)	
			Summer		1.10 (-0.47, 2.70)	
				PM <sub>10</sub>	1.18 (-0.55, 2.94)	
			All-year	<75		1.34 (-0.24, 2.94)
				PM <sub>10</sub>	1.74 (-0.31, 3.75)	
	Summer	≥75		2.54 (0.39, 4.80)		
		PM <sub>10</sub>	1.58 (-0.70, 3.99)			
	Respiratory	All	All-year		1.66 (-0.70, 4.15)	
				PM <sub>10</sub>	1.66 (-1.02, 4.40)	
Summer				1.42 (-1.02, 3.83)		
			PM <sub>10</sub>	1.42 (-1.02, 3.83)		
All-year			<75		4.31 (1.66, 7.11)	
			PM <sub>10</sub>	1.18 (-1.79, 4.31)		

<sup>a</sup>Risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O<sub>3</sub> concentrations (see explanation in Section 6.2.7.2).

1           Stafoggia et al. (2010, [625034](#)) examined the potential confounding effects of PM<sub>10</sub> on the  
2 O<sub>3</sub>-mortality relationship in individuals 35 years of age and older in 10 Italian cities from 2001 to  
3 2005. In a time-stratified case-crossover analysis, using data for the summer months (i.e., April-  
4 September), the authors examined O<sub>3</sub>-mortality associations across each city, and then obtained a  
5 pooled estimate through a random-effects meta-analysis. Stafoggia et al. (2010, [625034](#)) found a  
6 strong association with nonaccidental mortality (9.2% [95% CI: 5.4, 13.0%] for a 30-ppb increase in  
7 8-h max O<sub>3</sub> concentrations) in an unconstrained distributed lag model (lag 0-5) that persisted in  
8 co-pollutant models with PM<sub>10</sub> (9.2% [95% CI: 5.4, 13.7%]). Additionally, when examining cause-  
9 specific mortality, the authors found positive associations between short-term O<sub>3</sub> exposure and  
10 cardiovascular (14.3% [95% CI: 6.7, 22.4%]), cerebrovascular (8.5% [95% CI: 0.1, 16.3%]), and  
11 respiratory (17.6% [95% CI: 1.8, 35.6%]) mortality in single-pollutant models. In co-pollutant  
12 models, O<sub>3</sub>-mortality effect estimates for cardiovascular and cerebrovascular mortality were robust  
13 to the inclusion of PM<sub>10</sub> (9.2% [95% CI: 5.4, 13.7%]) and 7.3% [95% CI: -1.2, 16.3%],  
14 respectively), and attenuated, but remained positive, for respiratory mortality (9.2% [95% CI: -6.9,  
15 28.8%]). Of note, the correlations between O<sub>3</sub> and PM<sub>10</sub> across cities were found to be generally low,  
16 ranging from (-0.03 to 0.49). Unlike the other studies mentioned above that used every-3rd-day  
17 sampling for PM<sub>10</sub>, the authors do not specify the sampling strategy used for PM<sub>10</sub> in this analysis

### **Confounding by Seasonal Trend**

18           The APHENA study (Katsouyanni et al., 2009, [199899](#)), mentioned above, also conducted  
19 extensive sensitivity analyses to identify the appropriate: smoothing method and basis functions to  
20 estimate smooth functions of time in city-specific models; and degrees of freedom to be used in  
21 smooth functions of time, to adjust for seasonal trends. Because O<sub>3</sub> peaks in the summer and  
22 mortality peaks in the winter, not adjusting or not sufficiently adjusting for the seasonal trend would  
23 result in an apparent negative association between the O<sub>3</sub> and mortality time-series. Katsouyanni et  
24 al. (2009, [199899](#)) examined the effect of the extent of smoothing for seasonal trends by using  
25 models with 3 df/year, 8 df/year (the choice for their main model), 12 df/year, and df/year selected  
26 using the sum of absolute values of partial autocorrelation function of the model residuals (PACF)  
27 (i.e., choosing the degrees of freedom that minimizes positive and negative autocorrelations in the  
28 residuals). Table 6-37 presents the results of the degrees of freedom analysis using alternative  
29 methods to calculate a combined estimate: the Berkey et al. (1998, [684190](#)) meta-regression and the  
30 two-level normal independent sampling estimation (TLNISE) hierarchical method. The results show  
31 that the methods used to combine single-city estimates did not influence the overall results, and that  
32 neither 3 df/year nor choosing the df/year by minimizing the sum of absolute values of PACF of  
33 regression residuals was sufficient to adjust for the seasonal negative relationship between O<sub>3</sub> and  
34 mortality. However, it should be noted, the majority of studies in the literature that examined the  
35 mortality effects of short-term O<sub>3</sub> exposure, particularly the multicity studies, used 7 or 8 df/year to  
36 adjust for seasonal trends, and in both methods a positive association was observed between O<sub>3</sub>  
37 exposure and mortality when using 8 df/year to adjust for seasonal trends.

**Table 6-37. Sensitivity of ozone risk estimates per 10 µg/m<sup>3</sup> increase in 24-h avg 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: Used with permission from Health Effects Institute, Katsouyanni et al. (2009, [199899](#)).

### 6.6.2.2. Effect Modification

1           There have been several multicity studies that examined potential effect modifiers, or time-  
 2 invariant factors, that may modify O<sub>3</sub> mortality risk estimates. These effect modifiers can be  
 3 categorized into either individual-level or community-level characteristics, which are traditionally,  
 4 examined in second stage regression models. In addition to potentially modifying the association  
 5 between short-term O<sub>3</sub> exposure and mortality, both individual-level and community-level  
 6 characteristics may also contribute to the apparent geographic pattern of spatial heterogeneity in O<sub>3</sub>  
 7 mortality risk estimates. As a result, the geographic pattern of O<sub>3</sub> mortality risk estimates is also  
 8 evaluated in this section.

#### Individual-Level Characteristics

9           Medina-Ramón and Schwartz (2008, [193829](#)) conducted a case-only study in 48 U.S. cities to  
 10 identify populations particularly susceptible to O<sub>3</sub>-related mortality for the period 1989-2000 (May  
 11 through September of each year [i.e., warm season]). A case-only design predicts the occurrence of  
 12 time-invariant characteristics among cases as a function of the exposure level (Armstrong, 2003,  
 13 [153211](#)). For each potential effect modifier (time-invariant individual-level characteristics), city-  
 14 specific logistic regression models were fitted, and the estimates were pooled across all cities.  
 15 Furthermore, the authors examined potential differences in individual effect modifiers according to  
 16 several city characteristics (e.g., mean O<sub>3</sub> level, mean temperature, households with central air  
 17 conditioning, and population density) in a meta-regression. Across cities the authors found a 1.96%  
 18 (95% CI: 1.14-2.82%) increase in mortality at lag 0-2 for a 30-ppb increase in 8-h max O<sub>3</sub>  
 19 concentrations. Additionally, Medina-Ramón and Schwartz (2008, [193829](#)) examined a number of  
 20 individual-level characteristics (e.g., age, race) and chronic conditions (e.g., secondary causes of  
 21 death) as effect modifiers of the association between short-term O<sub>3</sub> exposure and mortality  
 22 (Table 6-38). The authors found that older adults (i.e., ≥ 65) (1.10% [95% CI: 0.44, 1.77%]), women  
 23 >60 years of age (0.58% [95% CI: 0.18, 0.98%]), black race (0.53% [95% CI: 0.19, 0.87%]), and  
 24 secondary atrial fibrillation (1.66% [95% CI: 0.03, 3.32%]) showed the greatest additional percent

1 change in O<sub>3</sub>-related mortality.<sup>1</sup> In addition, when examining city-level characteristics, the authors  
2 found that older adults, black race, and secondary atrial fibrillation had a larger effect on O<sub>3</sub>  
3 mortality risk estimates in cities with lower O<sub>3</sub> levels. Of note, is a similar case-only study  
4 (Schwartz, 2005, [667864](#)) that examined potential effect modifiers of the association between  
5 temperature and mortality, which would be expected to find results consistent with the Medina-  
6 Ramón and Schwartz (2008, [193829](#)) study due to the high correlation between temperature and O<sub>3</sub>.  
7 However, when stratifying days by temperature Schwartz (2005, [667864](#)) found strong evidence that  
8 diabetes increased the temperature-mortality association on hot days, which was not as evident when  
9 examining the O<sub>3</sub>-mortality association in Medina-Ramón and Schwartz (2008, [193829](#)). This  
10 difference could be due to the study design and populations included in both studies, a multicity  
11 study including all ages (Medina-Ramón and Schwartz, 2008, [193829](#)) compared to a single-city  
12 study of individual $\geq$  65 years of age (Schwartz, 2005, [667864](#)). However, when examining results  
13 stratified by race, nonwhites were found to have higher mortality risks on both hot and cold days,  
14 which provide some support for the additional risk found for black race in Medina-Ramón and  
15 Schwartz (2008, [193829](#)).

16 Individual-level factors that may result in susceptibility to O<sub>3</sub>-related mortality were also  
17 examined by Stafoggia et al. (2010, [625034](#)). As discussed above, using a time-stratified case-  
18 crossover analysis, the authors found an association between short-term O<sub>3</sub> exposure and  
19 nonaccidental mortality in an unconstrained distributed lag model in 10 Italian cities (9.2% [95% CI:  
20 5.4, 13.0%; lag 0-5 for a 30-ppb increase in 8-h max O<sub>3</sub> concentrations). Stafoggia et al. (2010,  
21 [625034](#)) conducted additional analyses to examine whether age, sex, income level, location of death,  
22 and underlying chronic conditions increased the risk of O<sub>3</sub>-related mortality, but data for only nine of  
23 the cities was available for these analyses. Of the individual-level factors examined, the authors  
24 found the strongest evidence for increased risk of O<sub>3</sub>-related mortality in individual $\geq$  85 years of  
25 age (22.4% [95% CI: 15.0, 30.2%]), women (13.7% [95% CI: 8.5, 19.7%]), and out-of-hospital  
26 deaths (13.0% [95% CI: 6.0, 20.4%]). When focusing specifically on out-of hospital deaths and the  
27 subset of individuals with chronic conditions, Stafoggia et al. (2010, [625034](#)) found the strongest  
28 association for individuals with diabetes, which is consistent with the potentially increased  
29 susceptibility of diabetics on hot days observed in Schwartz (2005, [667864](#)).

30 Overall, uncertainties exist in the interpretation of the potential effect modifiers, identified in  
31 Medina-Ramón and Schwartz (2008, [193829](#)) and Stafoggia et al. (2010, [625034](#)), of the O<sub>3</sub>-mortality  
32 relationship due to the expected heterogeneity in O<sub>3</sub> mortality risk estimates across cities as  
33 highlighted in Smith et al. (2009, [199750](#)) (Figure 6-28) and Franklin and Schwartz (2008, [156448](#))  
34 (Figure 6-29). For example, it is difficult to determine the relative importance of a susceptibility  
35 factor that results in an additional percent increase in mortality in a multicity analysis when analyses  
36 of the individual cities within the study did not indicate associations between O<sub>3</sub> and mortality. It

---

<sup>1</sup> These 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 O<sub>3</sub> 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 examined, but instead the difference between effect estimates for persons with versus without the condition.

1 also remains unclear if the individual-level susceptibility factors identified in Medina-Ramón and  
 2 Schwartz (2008, [193829](#)) and Stafoggia et al. (2010, [625034](#)) only modify the O<sub>3</sub>-mortality  
 3 relationship. More than likely, the factors identified span pollutants as is evident by older adults (i.e.,  
 4 ≥ 65) often being identified as an effect modifier of PM mortality risk estimates (U.S. EPA, 2009,  
 5 [179916](#)).

**Table 6-38. Additional percent change in ozone-related mortality for individual-level susceptibility factors**

	Percent <sup>a</sup>	(95% CI)
Socio-demographic characteristics		
Age 65 yr or older	1.10	(0.44 to 1.77)
Women	0.58	(0.18 to 0.98)
Women <60 yr old <sup>b</sup>	-0.09	(-0.76 to 0.58)
Women ≥ 60 yr old <sup>b</sup>	0.60	(0.25 to 0.96)
Black race	0.53	(0.19 to 0.87)
Low education	-0.29	(-0.81 to 0.23)
Chronic conditions (listed as secondary cause)		
Respiratory system diseases		
Asthma	1.35	(-0.31 to 3.03)
COPD	0.01	(-0.49 to 0.52)
Circulatory system diseases		
Atherosclerosis	-0.72	(-1.89 to 0.45)
Atherosclerotic CVD	0.74	(-0.86 to 2.37)
Atherosclerotic heart disease	-0.38	(-1.70 to 0.96)
Congestive heart disease	-0.04	(-0.39 to 0.30)
Atrial fibrillation	1.66	(0.03 to 3.32)
Stroke	0.17	(-0.28 to 0.62)
Other diseases		
Diabetes	0.19	(-0.46 to 0.84)
Inflammatory diseases	0.18	(-1.09 to 1.46)

<sup>a</sup>These 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 O<sub>3</sub> 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.

<sup>b</sup>Compared with males in the same age group.

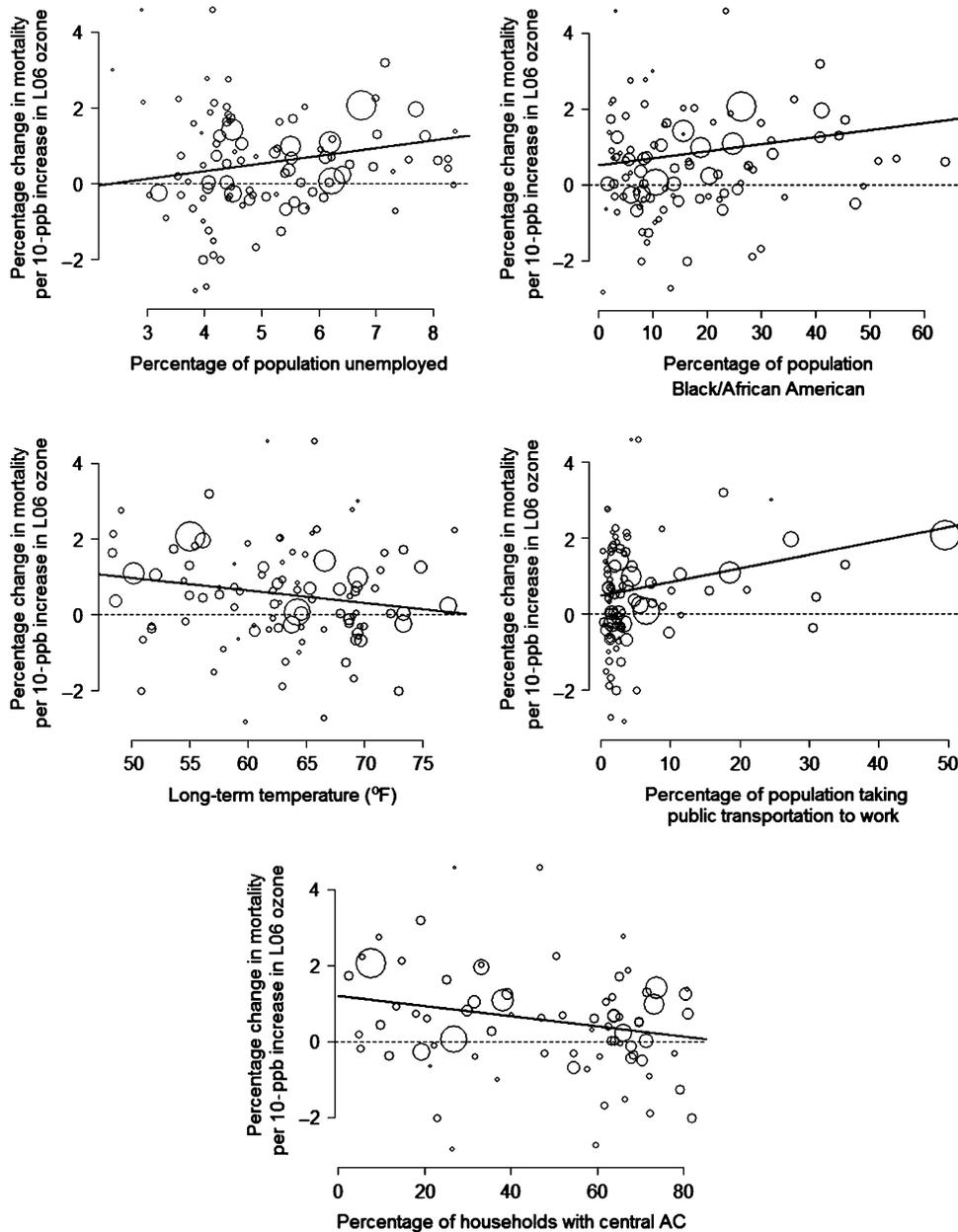
Source: Used with permission from Lippincott Williams & Wilkins, Medina-Ramón and Schwartz (2008, [193829](#)).

## Community-level Characteristics

6 Rather than using individual-level characteristics, several studies examined city-level (i.e.,  
 7 ecological) variables to explain city-to-city variation in estimated O<sub>3</sub> mortality risk estimates. Bell  
 8 and Dominici (2008, [193828](#)) investigated whether community-level characteristics, such as race,  
 9 income, education, urbanization, transportation use, PM and O<sub>3</sub> levels, number of O<sub>3</sub> monitors,  
 10 weather, and air conditioning use could explain the heterogeneity in O<sub>3</sub>-mortality risk estimates  
 11 across cities. The authors analyzed 98 U.S. urban communities from NMMAPS for the period

1 1987-2000. In the all-year regression model that included no community-level variables, a 20-ppb  
2 increase in 24-h avg O<sub>3</sub> concentrations during the previous week was associated with a 1.04% (95%  
3 CI: 0.56, 1.55) increase in mortality. Bell and Dominici (2008, [193828](#)) found that higher  
4 O<sub>3</sub>-mortality effect estimates were associated with higher: percent unemployment, fraction of the  
5 population Black/African-American, percent of the population that take public transportation to  
6 work; and with lower: temperatures and percent of households with central air conditioning  
7 (Figure 6-31). The negative percent change in O<sub>3</sub>-mortality risk estimates reported for city-specific  
8 temperature and prevalence of central air conditioning in this analysis confirm the result from the  
9 meta-analyses reviewed in the 2006 O<sub>3</sub> AQCD.

10 The APHENA project (Katsouyanni et al., 2009, [199899](#)) examined potential effect  
11 modification of O<sub>3</sub> risk estimates in the Canadian, European, and U.S. data sets using a consistent set  
12 of city-specific variables. Table 6-39 presents the results from all age analyses for all-cause mortality  
13 using all-year O<sub>3</sub> data for the average of lag 0-1 day. While there are several significant effect  
14 modifiers in the U.S. data, the results are mostly inconsistent with the results from the Canadian and  
15 European data sets. The positive effect modification by percentage unemployed and the negative  
16 effect modification by mean temperature (i.e., a surrogate for air conditioning rate) are consistent  
17 with the results reported by Bell and Dominici (2008, [193828](#)) discussed above. However, the lack  
18 of consistency across the data sets, even between the Canadian and U.S. data, makes it difficult to  
19 interpret the results. Some of these associations may be due to coincidental correlations with other  
20 unmeasured factors that vary regionally (e.g., mean SO<sub>2</sub> tend to be higher in the eastern U.S.).



Source: Used with permission from Johns Hopkins Bloomberg School of Public Health, Bell and Dominici (2008, [193828](#)).

**Figure 6-31. Ozone mortality risk estimates and community-specific characteristics, U.S., 1987-2000.** 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.

**Table 6-39. Percent change in all-cause mortality, for all ages, associated with a 40-ppb 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 <sub>2</sub> 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 <sub>2</sub>	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 <sub>3</sub> 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 <sub>2</sub> /PM <sub>10</sub>	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 from Health Effects Institute, Katsouyanni et al. (2009, [199899](#)).

## Regional Pattern of Ozone-Mortality Risk Estimates

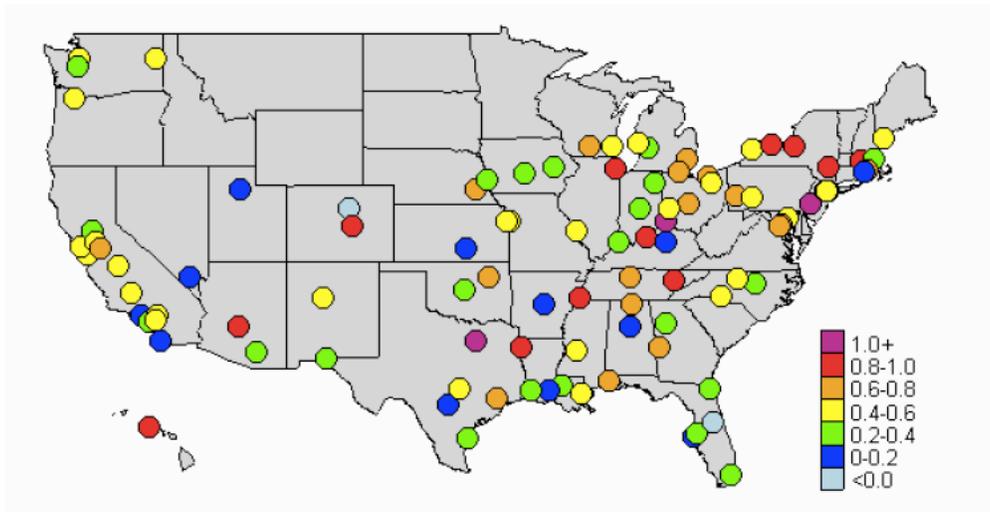
1 In addition to examining whether individual- and community-level factors modify the  
2 O<sub>3</sub>-mortality association, studies also examined whether these associations varied regionally within  
3 the U.S. Bell and Dominici (2008, [193828](#)), in the study discussed above, also noted that  
4 O<sub>3</sub>-mortality risk estimates were higher in the Northeast (1.44% [95% CI: 0.78, 2.10%]) and  
5 Industrial Midwest (0.73% [95% CI: 0.11, 1.35%]), while null associations were observed in the  
6 Southwest and Urban Midwest (Table 6-40). The regional heterogeneity in O<sub>3</sub>-mortality risk  
7 estimates was further reflected by Bell and Dominici (2008, [193828](#)) in a map of community-  
8 specific Bayesian O<sub>3</sub>-mortality risk estimates (Figure 6-32). It is worth noting that in the analysis of  
9 PM<sub>10</sub> using the same data set, Peng et al. (2005, [087463](#)) also found that both the Northeast and  
10 Industrial Midwest showed particularly elevated effects, especially during the summer months. As  
11 mentioned above, although no evidence for confounding of O<sub>3</sub> mortality risk estimates by PM<sub>10</sub> was  
12 observed, Bell et al. (2007, [093256](#)) did find regional differences in the correlation between O<sub>3</sub> and  
13 PM<sub>10</sub>. Thus, the heterogeneity in O<sub>3</sub> mortality risk estimates may need to be examined as a function  
14 of the correlation between PM and O<sub>3</sub>.

1 Smith et al. (2009, [199750](#)), as discussed earlier, also examined the regional difference in O<sub>3</sub>  
2 mortality risk estimates across the same seven regions and similarly found evidence for regional  
3 heterogeneity. In addition, Smith et al. (2009, [199750](#)) constructed spatial maps of the risk estimates  
4 by an extension of a hierarchical model that allows for spatial auto-correlation among the city-  
5 specific random effects. Figure 6-33 presents the spatial map of O<sub>3</sub> mortality coefficients from the  
6 Smith et al. (2009, [199750](#)) analysis that used 8-h max O<sub>3</sub> concentrations during the summer. The  
7 results from the Bell and Dominici (2008, [193828](#)) analysis (Figure 6-32) shows much stronger  
8 apparent heterogeneity in O<sub>3</sub>-mortality risk estimates across cities than the smoothed map from  
9 Smith et al. (2009, [199750](#)) (Figure 6-33), but both maps generally show larger risk estimates in the  
10 eastern region of the U.S.

**Table 6-40. Percentage increase in daily mortality for a 10-ppb increase in 24-h avg ozone concentrations during the previous week by geographic region in the U.S., 1987-2000**

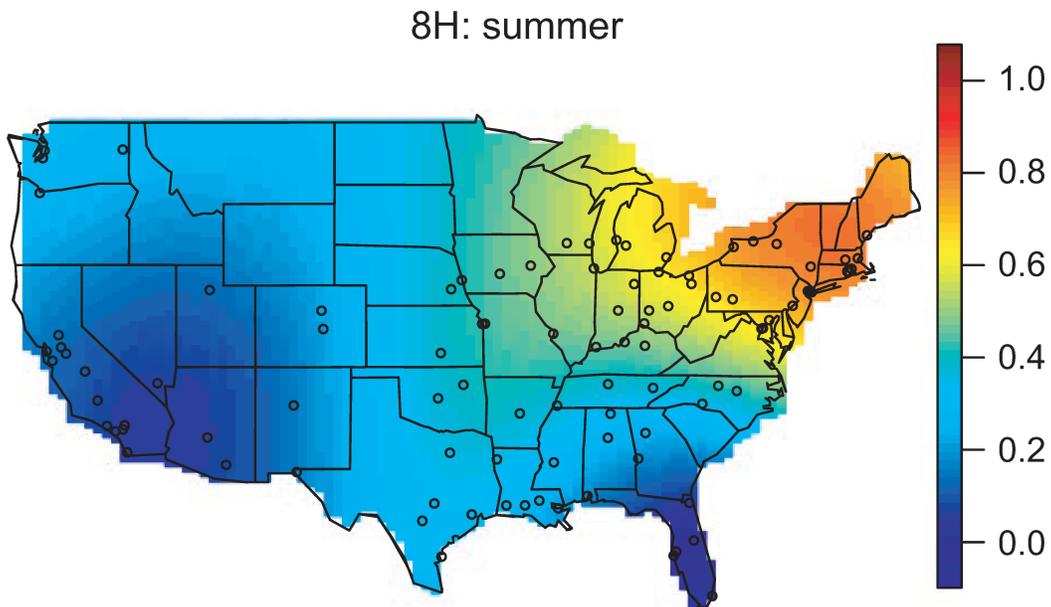
	No. of Communities	Regional Estimate	95% PI*
Regional results			
Industrial Midwest	20	0.73	0.11, 1.35
Northeast	16	1.44	0.78, 2.10
Northwest	12	0.08	-0.92, 1.09
southern California	7	0.21	-0.46, 0.88
Southeast	26	0.38	-0.07, 0.85
Southwest	9	-0.06	-0.92, 0.81
Urban Midwest	7	-0.05	-1.28, 1.19
National results			
All continental communities	97	0.51	0.27, 0.76
All communities	98	0.52	0.28, 0.77

Source: Used with permission from Johns Hopkins Bloomberg School of Public Health, Bell and Dominici (2008, [193828](#)).



Source: Used with permission from Johns Hopkins Bloomberg School of Public Health, Bell and Dominici, online supplement (2008, [193828](#)).

**Figure 6-32. Community-specific Bayesian ozone-mortality risk estimates in 98 U.S. communities.**



Source: Used with permission from Informa UK Ltd., Smith et al. (2009, [199750](#)).

**Figure 6-33. Map of spatially dependent ozone-mortality coefficients for 8-h max ozone concentrations using summer data.**

### 6.6.2.3. Interaction

1 The terms effect modification and interaction are often used interchangeably, but theoretically  
2 they represent different concepts. Although interactions can lead to either antagonistic or synergistic  
3 effects, most studies attempt to identify potential factors that interact synergistically with O<sub>3</sub> to  
4 increase the risk of mortality. Within this section, interactive effects are defined as time-varying  
5 covariates, such as temperature and co-pollutants that are included in 1st stage time-series regression  
6 models. To date, only a few time-series studies have investigated the potential interaction between  
7 O<sub>3</sub> exposure and co-pollutants or weather variables. This can be attributed to the moderate to high  
8 correlation between O<sub>3</sub> and these covariates, which makes such investigations methodologically  
9 challenging.

10 Ren et al. (2008, [093281](#)) examined the possible synergistic effect between O<sub>3</sub> and temperature  
11 on mortality in the 60 largest eastern U.S. communities from the NMMAPS data during the warm  
12 months (i.e., April to October) from 1987-2000. This analysis was restricted to the eastern areas of  
13 the U.S. (i.e., Northeast, Industrial Midwest and Southeast) because a previous study which focused  
14 specifically on the eastern U.S. found that temperature-mortality patterns differ between the  
15 northeast and southeast regions possibly due to climatic differences (Curriero et al., 2002, [055878](#)).  
16 To examine possible geographic differences in the interaction between temperature and O<sub>3</sub>, Ren et al.  
17 (2008, [093281](#)) further divided the NMMAPS regions into the Northeast, which included the  
18 Northeast and Industrial Midwest regions (34 cities), and the Southeast, which included the  
19 Southeast region (26 cities). The potential synergistic effects between O<sub>3</sub> and temperature were  
20 examined using two different models. Model 1 included an interaction term in a Generalized  
21 Additive Model (GAM) for O<sub>3</sub> and maximum temperature (3-day avg values were used for both  
22 terms) to examine the bivariate response surface and the pattern of interaction between the two  
23 variables in each community. Model 2 consisted of a Generalized Linear Model (GLM) that used  
24 interaction terms to stratify by “low,” “moderate,” and “high” temperature days using the first and  
25 third quartiles of temperature as cut-offs to examine the percent increase in mortality in each  
26 community. Furthermore, a two-stage Bayesian hierarchical model was used to estimate the overall  
27 percent increase in all-cause mortality associated with short-term O<sub>3</sub> exposure across temperature  
28 levels and each region using model 2. The same covariates were used in both model 1 and 2. The  
29 bivariate response surfaces from model 1 suggest possible interactive effects between O<sub>3</sub> and  
30 temperature although the interpretation of these results is not straightforward due to the high  
31 correlation between these terms. The apparent interaction between temperature and O<sub>3</sub> as evaluated  
32 in model 2 varied across geographic regions. In the northeast region, a 20-ppb increase in 24-h avg  
33 O<sub>3</sub> concentrations at lag 0-2 was associated with an increase of 4.49% (95% posterior interval [PI]:  
34 2.39, 6.36%), 6.21% (95% PI: 4.47, 7.66%) and 12.8% (95% PI: 9.77, 15.7%) in mortality at low,  
35 moderate and high temperature levels, respectively. The corresponding percent increases in mortality  
36 in the southeast region were 2.27% (95% PI: -2.23, 6.46%) for low temperature, 3.02% (95% PI:  
37 0.44, 5.70%) for moderate temperature, and 2.60% (95% PI: -0.66, 6.01%) for high temperature.

1           When examining the relationship between temperature and O<sub>3</sub>-related mortality, the results  
2 reported by Ren et al. (2008, [093281](#)) (i.e., higher O<sub>3</sub>-mortality risks on days with higher  
3 temperatures) may appear to contradict the results of Bell and Dominici (2008, [193828](#)) described  
4 earlier (i.e., communities with higher temperature have lower O<sub>3</sub>-mortality risk estimates). However,  
5 the observed difference in results can be attributed to the interpretation of effect modification in a  
6 2nd stage regression which uses long-term average temperatures, as was performed by Bell and  
7 Dominici (2008, [193828](#)), compared to a first-stage regression that examines the interaction between  
8 daily temperature and O<sub>3</sub>-related mortality. In this case, the second-stage regression results from Bell  
9 and Dominici (2008, [193828](#)) indicate that a city with lower temperatures, on average, tend to show  
10 a stronger O<sub>3</sub> mortality effect, whereas, in the first-stage regression performed by Ren et al. (2008,  
11 [093281](#)), the days with higher temperature tend to show a larger O<sub>3</sub>-mortality effect. This observed  
12 difference may in part reflect the higher air conditioning use in communities with higher long-term  
13 average temperatures. Therefore, the findings from Ren et al. (2008, [093281](#)) indicating generally  
14 lower O<sub>3</sub> risk estimates in the southeast region where the average temperature is higher than in the  
15 northeast region is consistent with the regional results reported by Bell and Dominici (2008,  
16 [193828](#)). As demonstrated by the results from both Ren et al. (2008, [093281](#)) and Bell and Dominici  
17 (2008, [193828](#)) caution is required when interpreting results from studies that examined interactive  
18 effects using two different approaches because potential effect modification as suggested in a  
19 SECOND stage regression generally does not provide evidence for a short-term interaction  
20 examined in a first-stage regression. Overall, further examination of the potential interactive  
21 (synergistic) effects of O<sub>3</sub> and covariates in time-series regression models is required to more clearly  
22 understand the factors that may influence O<sub>3</sub> mortality risk estimates.

#### 6.6.2.4. Evaluation of the Ozone-Mortality C-R Relationship and Related Issues

23           Evaluation of the O<sub>3</sub>-mortality concentration-response relationship is not straightforward  
24 because the evidence from multicity studies (using log-linear models) suggests that O<sub>3</sub>-mortality  
25 associations are highly heterogeneous across regions. In addition, there are numerous issues that may  
26 influence the shape of the O<sub>3</sub>-mortality concentration-response relationship that warrant examination  
27 including: multi-day effects (distributed lags), potential adaptation, mortality displacement (i.e.,  
28 hastening of death by a short period), and the exposure metric used to compute risks (e.g., 1-h daily  
29 max versus 24-h avg). The following section presents the recent studies identified that conducted an  
30 initial examination of these issues.

##### **Multiday Effects, Mortality Displacement, and Adaptation**

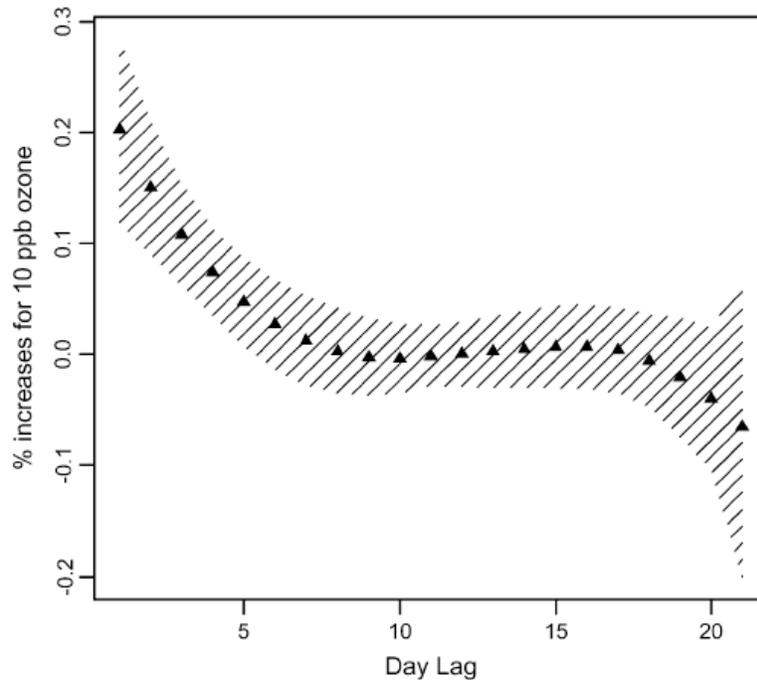
31           The pattern of positive lagged associations followed by negative associations in a distributed  
32 lag model may be considered an indication of “mortality displacement” (i.e., deaths are occurring in  
33 frail individuals and exposure is only moving the day of death to a day slightly earlier). Zanobetti  
34 and Schwartz (2008, [101596](#)) examined this issue in 48 U.S. cities during the warm season (i.e.,  
35 June-August) for the years 1989-2000. In an initial analysis, the authors applied a GLM to examine

1 same-day O<sub>3</sub>-mortality effects, and in the model included an unconstrained distributed lag for  
2 apparent temperature to take into account the effect of temperature today and the previous 7 days. To  
3 examine mortality displacement Zanobetti and Schwartz (2008, [101596](#)) refit models using two  
4 approaches: an unconstrained and a smooth distributed lag each with 21-day lags for O<sub>3</sub>. In this  
5 study, all-cause mortality as well as cause-specific mortality (i.e., cardiovascular, respiratory, and  
6 stroke) were examined for evidence of mortality displacement. The authors found a 0.96% (95% CI:  
7 0.60, 1.30%) increase in all-cause mortality across all 48 cities for a 30-ppb increase in 8-h max O<sub>3</sub>  
8 concentrations at lag 0 whereas the combined estimate of the unconstrained distributed lag model  
9 (lag 0-20) was 1.54% (95% CI: 0.15, 2.91%). Similarly, when examining the cause-specific  
10 mortality results (Table 6-41), larger risk estimates were observed for the distributed lag model  
11 compared to the lag 0 day estimates. However, for stroke a slightly larger effect was observed at lags  
12 4-20 compared to lags 0-3 suggesting a larger window for O<sub>3</sub>-induced stroke mortality. This is  
13 further supported by the sum of lags 0 through 20 days showing the greatest effect. Overall, these  
14 results suggest that estimating the mortality risk using a single day of O<sub>3</sub> exposure may  
15 underestimate the public health impact, but the extent of multi-day effects appear to be limited to a  
16 few days. This is further supported by the shape of the combined smooth distributed lag  
17 (Figure 6-34). It should be noted that the proportion of total variation in the effect estimates due to  
18 the between-cities heterogeneity, as measured by I<sup>2</sup> statistic, was relatively low (4% for the lag 0  
19 estimates and 21% for the distributed lag), but 21 out of the 48 cities exhibited null or negative  
20 estimates. As a result, the estimated shape of the distributed lag cannot be interpreted as a general  
21 form of lag structure of associations applicable to all the cities included in this analysis.

**Table 6-41. 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**

	%	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: Used with permission from American Thoracic Society, Zanobetti and Schwartz (2008, [101596](#)).



Source: Used with permission from American Thoracic Society, Zanobetti and Schwartz (2008, [101596](#)).

**Figure 6-34. Estimated combined smooth distributed lag for 48 U.S. cities during the summer months. The triangles represent the percent increase in all-cause mortality for a 10-ppb increase in 8-h max ozone concentrations at each lag while the shaded areas are the 95% point-wise confidence intervals.**

1 Samoli et al. (2009, [195855](#)) also investigated the temporal pattern of mortality effects in  
 2 response to short-term exposure to O<sub>3</sub> in 21 European cities that were included in the APHEA2  
 3 project. Using a method similar to Zanobetti and Schwartz (2008, [101596](#)), the authors applied  
 4 unconstrained distributed lag models with lags up to 21 days in each city during the summer months  
 5 (i.e., June through August) to examine the effect of O<sub>3</sub> on all-cause, cardiovascular, and respiratory  
 6 mortality. They also applied a generalized additive distributed lag model to obtain smoothed  
 7 distributed lag coefficients. However, unlike Zanobetti and Schwartz (2008, [101596](#)), Samoli et al.  
 8 (2009, [195855](#)) controlled for temperature using a linear term for humidity and an unconstrained  
 9 distributed lag model of temperature at lags 0-3 days. The choice of 0- through 3-day lags of  
 10 temperature was based on a previous European multicity study (Baccini et al., 2008, [633196](#)), which  
 11 suggested that summer temperature effects last only a few days. Upon combining the individual city  
 12 estimates across cities in a second stage regression, Samoli et al. (2009, [195855](#)) found that the  
 13 estimated effects on respiratory mortality were extended for a period of two weeks. However, for all-  
 14 cause and cardiovascular mortality, the 21-day distributed lag models yielded null or (non-  
 15 significant) negative estimates (Table 6-42). Figure 6-35 shows the distributed lag coefficients for  
 16 all-cause mortality, which exhibit a declining trend and negative coefficients beyond 5-day lags. The  
 17 authors' interpretation of these results was that "using single-day exposures may have overestimated

1 the effects on all-cause and cardiovascular mortality, but underestimated the effects on respiratory  
 2 mortality." Thus, the results in part suggest evidence of mortality displacement for all-cause and  
 3 cardiovascular mortality.

**Table 6-42. Estimated percent increase in cause-specific mortality (and 95% CIs) for a 10- $\mu\text{g}/\text{m}^3$  increase in maximum 8-h ozone during June-August, 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)**

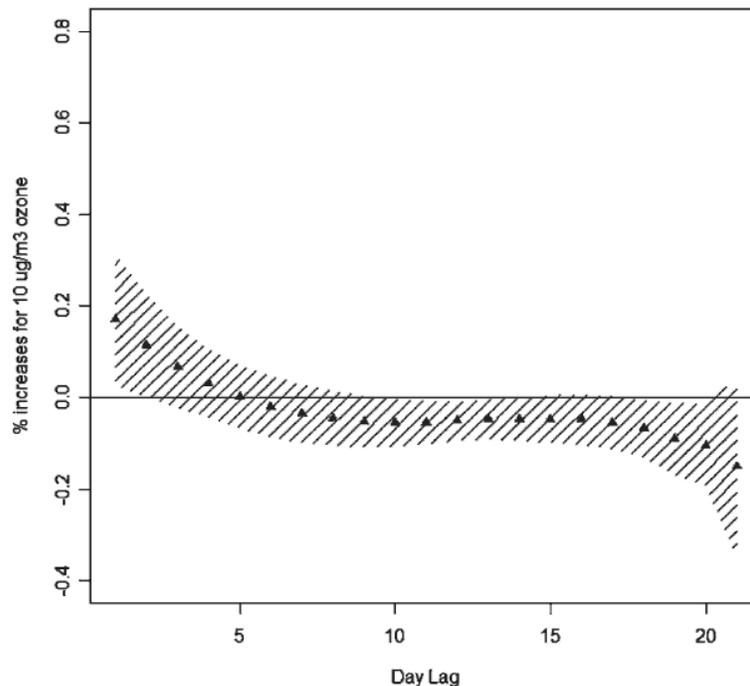
	Fixed effects	Random effects
	Percent increase (95% CI)	Percent increase (95% CI)
Total mortality		
Lag 0	0.28 (0.11 to 0.45)	0.28 (0.07 to 0.48)
Average lags 0-1	0.24 (0.15 to 0.34)	0.22 (0.08 to 0.35)
Sum lags 0-20, unconstrained	0.01 (-0.40 to 0.41)	-0.54 (-1.28 to 0.20)
Sum lags 0-20, penalized	0.01 (-0.41 to 0.42)	-0.56 (-1.30 to 0.19)
Cardiovascular mortality		
Lag 0	0.43 (0.18 to 0.69)	0.37 (0.05 to 0.69)
Average lags 0-1	0.33 (0.19 to 0.48)	0.25 (0.03 to 0.47)
Sum lags 0-20, unconstrained	-0.33 (-0.93 to 0.29)	-0.62 (-1.47 to 0.24)
Sum lags 0-20, penalized	-0.32 (-0.92 to 0.28)	-0.57 (-1.39 to 0.26)
Respiratory mortality		
Lag 0	0.36 (-0.21 to 0.94)	0.36 (-0.21 to 0.94)
Average lags 0-1	0.40 (0.11 to 0.70)	0.40 (0.11 to 0.70)
Sum lags 0-20, unconstrained	3.35 (1.90 to 4.83)	3.35 (1.90 to 4.83)
Sum lags 0-20, penalized	3.66 (2.25 to 5.08)	3.66 (2.25 to 5.08)

Source: Used with permission from BMJ Group, Samoli et al. (2009, [195855](#)).

4 Although the APHENA project (Katsouyanni et al., 2009, [199899](#)) did not specifically  
 5 investigate mortality displacement and therefore did not consider longer lags (e.g., lag > 3 days), the  
 6 study did present O<sub>3</sub> risk estimates for lag 0-1, lag 1, and a distributed lag model of 0-2 days in the  
 7 Canadian, European, and U.S. datasets. Katsouyanni et al. (2009, [199899](#)) found that the results  
 8 somewhat vary across the regions, but, in general, there was no indication that the distributed lag  
 9 model with up to a 2-day lag yielded meaningfully larger O<sub>3</sub> mortality risk estimates than the lag 0-1  
 10 and lag 1 results. For example, for all-cause mortality, using the model with natural splines and  
 11 8 df/year to adjust for seasonal trends, a reported percent excess risk for mortality for a 40-ppb  
 12 increase in 1-h max O<sub>3</sub> concentrations for lag 0-1, lag 1, and the distributed lag model (lag 0-2) was  
 13 2.70% (95% CI: 1.02, 4.40%), 1.42% (95% CI: 0.08, 2.78%), and 3.02% (95% CI: 1.10, 4.89%),  
 14 respectively. Thus, the observed associations appear to occur over a short time period, (i.e., a  
 15 few days).

16 When comparing the studies that explicitly examined the potential for mortality displacement  
 17 in the O<sub>3</sub>-mortality relationship, the results from Samoli et al. (2009, [195855](#)), which provide  
 18 evidence that suggests mortality displacement, are not consistent with those reported by Zanobetti

1 and Schwartz (2008, [101596](#)). However, the shapes of the estimated smooth distributed lag  
 2 associations are similar (Figure 6-34 versus Figure 6-35). A closer examination of these figures  
 3 shows that in the European data beyond a lag of 5 days the estimates remain negative whereas in the  
 4 U.S. data the results remain near zero for the corresponding lags. These observed difference could be  
 5 due the differences in the model specification between the 2 studies, specifically the use of: an  
 6 unconstrained distributed lag model for apparent temperature up to 7 previous days (Zanobetti and  
 7 Schwartz, 2008, [101596](#)) versus a linear term for humidity and an unconstrained distributed lag  
 8 model of temperature up to 3 previous days (Samoli et al., 2009, [195855](#)); and natural cubic splines  
 9 with 2 df per season (Zanobetti and Schwartz, 2008, [101596](#)) versus dummy variables per month per  
 10 year to adjust for season (Samoli et al., 2009, [195855](#)). It is important to note, that these differences  
 11 in model specification may have also influenced the city-to-city variation in risk estimates observed  
 12 in these two studies (i.e., homogenous estimates across cities in Zanobetti and Schwartz (2008,  
 13 [101596](#)) and heterogeneous estimates across cities in Samoli et al. (2009, [195855](#)). Overall, the  
 14 evidence of mortality displacement remains unclear, but Samoli et al. (2009, [195855](#)), Zanobetti and  
 15 Schwartz (2008, [101596](#)), and Katsouyanni et al. (2009, [199899](#)) all suggest that the positive  
 16 associations between O<sub>3</sub> and mortality are observed mainly in the first few days after exposure.



Source: Used with permission from BMJ Group, Samoli et al. (2009, [195855](#)).

**Figure 6-35. Estimated combined smooth distributed lag in 21 European cities during the summer (June-August) months. [The triangles represent the percent increase in all-cause mortality for a 10- $\mu\text{g}/\text{m}^3$  increase in 8-h max ozone concentrations at each lag; the shaded area represents the 95% CIs.**

## Adaptation

1           Controlled human exposure studies have demonstrated an adaptive response to O<sub>3</sub> exposure  
2 for respiratory effects, such as lung function decrements, but this issue has not been examined in the  
3 epidemiologic investigation of mortality effects of O<sub>3</sub>. Zanobetti and Schwartz (2008, [195755](#))  
4 examined if there was evidence of an adaptive response in the O<sub>3</sub>-mortality relationship in 48 U.S.  
5 cities from 1989 to 2000 (i.e., the same data analyzed in Zanobetti and Schwartz (2008, [101596](#))).  
6 The authors examined all-cause mortality using a case-crossover design to estimate the same-day  
7 (i.e., lag 0) effect of O<sub>3</sub>, matched on referent days from every-3rd-day in the same month and year as  
8 the case. Zanobetti and Schwartz (2008, [195755](#)) examined O<sub>3</sub>-mortality associations by: season,  
9 month in the summer season (i.e., May through September), and age categories in the summer  
10 season (Table 6-43). The estimated O<sub>3</sub> mortality risk estimate at lag 0 was found to be highest in the  
11 summer (1.51% [95% CI: 1.14, 1.87%]; lag 0 for a 30-ppb increase in 8-h max O<sub>3</sub> concentrations),  
12 and, within the warm months, the association was highest in July (1.96% [95% CI: 1.42, 2.48%];  
13 lag 0) (Table 6-43). Upon further examination of the summer months, the authors also observed  
14 diminished effects in August (0.84% [95% CI: 0.33, 1.39%]; lag 0). Based on these results, the  
15 authors concluded that the mortality effects of O<sub>3</sub> appear diminished later in the O<sub>3</sub> season.

16           To further evaluate the potential adaptive response observed in Zanobetti and Schwartz (2008,  
17 [195755](#)) the distribution of the O<sub>3</sub> concentrations across the 48 U.S. cities during July and August  
18 was examined. Both July and August were found to have comparable means of 48.6 and 47.9 ppb  
19 with a reported maximum value of 97.9 and 96.0 ppb, respectively. Thus, the observed reduction in  
20 O<sub>3</sub>-related mortality effect estimates in August (0.84%) compared to July (1.96%) appears to support  
21 the existence of an adaptive response. However, unlike an individual's adaptive response to  
22 decrements in lung function from short-term O<sub>3</sub> exposure, an examination of mortality prevents a  
23 direct observation of adaptation. Rather, for mortality the adaptation hypothesis is tested with a tacit  
24 assumption that, whatever the mechanism for O<sub>3</sub>-induced mortality, the risk of death from short-term  
25 O<sub>3</sub> exposure is reduced over the course of the summer months through repeated exposures. This idea  
26 would translate to a smaller population that would die from O<sub>3</sub> exposure towards the end of summer.  
27 This may complicate the interpretation of the distributed lag coefficients with long lag periods  
28 because the decreased coefficients may reflect diminished effects of the late summer, rather than  
29 diminished effects that are constant across the summer. These inter-twined issues need to be  
30 investigated together in future research.

**Table. 6-43. 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**

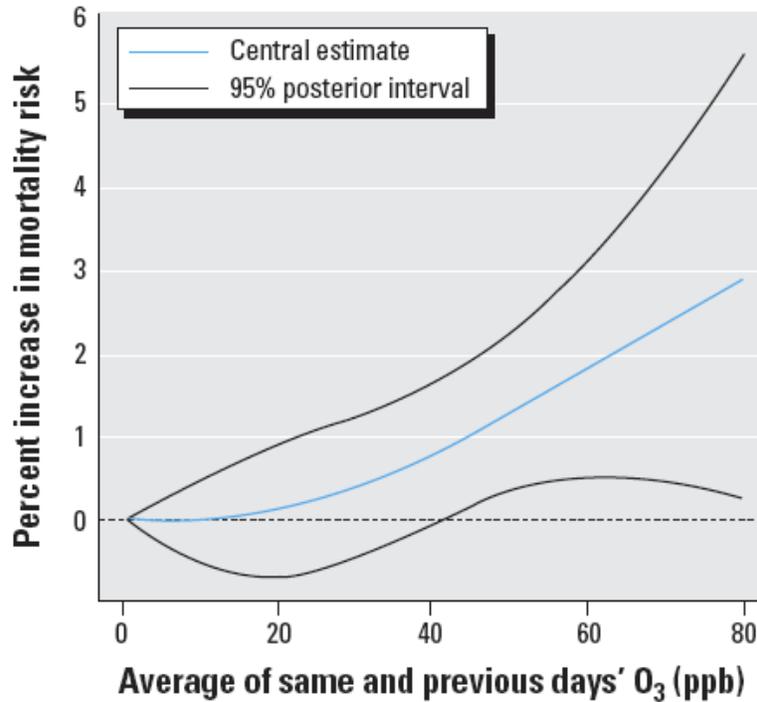
	%	95% CI	
By Season			
Winter	-0.13	-0.56	0.29
Spring	0.35	0.16	0.54
Summer	0.50	0.38	0.62
Fall	0.05	-0.14	0.24
By Month			
May	0.48	0.28	0.68
June	0.46	0.24	0.68
July	0.65	0.47	0.82
August	0.28	0.11	0.46
September	-0.09	-0.35	0.16
By Age Group			
0-20	0.08	-0.42	0.57
21-30	0.10	-0.67	0.87
31-40	0.07	-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: Used with permission from BioMed Central Ltd., Zanobetti and Schwartz (2008, [195755](#)).

### Ozone-Mortality Concentration-Response Relationship and Threshold Analyses

1 Several of the recent studies evaluated have applied a variety of statistical approaches to  
2 examine the shape of the O<sub>3</sub>-mortality C-R relationship and whether a threshold exists. The approach  
3 used by Bell et al. (2006, [087680](#)) consisted of applying four statistical models to the NMMAPS  
4 data, which included 98 U.S. communities for the period 1987-2000. These models included: a linear  
5 analysis (i.e., any change in O<sub>3</sub> concentration can be associated with mortality) (Model 1); a subset  
6 analysis (i.e., examining O<sub>3</sub>-mortality relationship below a specific concentration, ranging from 5 to  
7 60 ppb) (Model 2); a threshold analysis (i.e., assuming that an association between O<sub>3</sub> and mortality  
8 is observed above a specific concentration and not below it, using the threshold values set at an  
9 increment of 5 ppb between 0 to 60 ppb and evaluating a presence of a local minima in AICs  
10 computed at each increment) (Model 3); and nonlinear models using natural cubic splines with  
11 boundary knots placed at 0 and 80 ppb, and interior knots placed at 20 and 40 ppb (Model 4). A two-  
12 stage Bayesian hierarchical model was used to examine these models and O<sub>3</sub>-mortality risk estimates  
13 at the city-level in the first stage analysis and aggregate estimates across cities in the 2nd stage  
14 analysis using the average of 0- and 1-day lagged 24-h avg O<sub>3</sub> concentrations. The results from all of  
15 these models suggest that if a threshold exists it does so well below the current O<sub>3</sub> NAAQS. When  
16 restricting the analysis to all days when the current 8 h standard (i.e., 84 ppb daily 8-h max) is met in

1 each community, Bell et al. (2006, [087680](#)) found there was still a 0.60% (95% PI: 0.30, 0.90%)  
2 increase in mortality per 20-ppb increase in 24-h avg O<sub>3</sub> concentrations at lag 0-1. Figure 6-36 shows  
3 the combined C-R curve obtained using the nonlinear model (Model 4). Although these results  
4 suggest the lack of threshold in the O<sub>3</sub>-mortality relationship, it is difficult to interpret such a curve  
5 because it does not take into consideration the heterogeneity in O<sub>3</sub>-mortality risk estimates across  
6 cities.



Source: Bell et al. (2006, [087680](#)).

**Figure 6-36. Estimated combined C-R curve for ozone and nonaccidental mortality using the nonlinear (spline) model.**

7 The APHENA project (Katsouyanni et al., 2009, [199899](#)) also analyzed the Canadian and  
8 European datasets (the U.S. data were analyzed for PM<sub>10</sub> only) for evidence of a threshold, using the  
9 threshold analysis method (Model 3) applied in Bell et al.'s (2006, [087680](#)) study described above.  
10 There was no evidence of a threshold in the Canadian data (i.e., the pattern of AIC values for each  
11 increment of a potential threshold value varied across cities, most of which showed no local  
12 minima). Likewise, the threshold analysis conducted using the European data also showed no  
13 evidence of a threshold.

14 Additional threshold analyses were conducted using NMMAPS data, by Xia and Tong (2006,  
15 [623157](#)) and Stylianou and Nicolich (2009, [620299](#)). Both studies used a new statistical approach  
16 developed by Xia and Tong (2006, [623157](#)) to examine thresholds in the O<sub>3</sub> mortality C-R  
17 relationship. The approach consisted of an extended GAM model, which accounted for the

1 cumulative and nonlinear effects of air pollution using a weighted cumulative sum for each pollutant,  
2 with the weights (non-increasing further into the past) derived by a restricted minimization method.  
3 The authors did not use the term distributed lag model, but their model has the form of distributed  
4 lag model, except that it allows nonlinear functional forms. Using NMMAPS data for 1987-1994 for  
5 3 U.S. cities (Chicago, Pittsburgh, and El Paso), Xia and Tong (2006, [623157](#)) found that the extent  
6 of cumulative effects of O<sub>3</sub> on mortality were relatively short. While the authors also note that there  
7 was evidence of a threshold effect around 24-h avg concentrations of 25 ppb, the threshold values  
8 estimated in the analysis were sometimes in the range where data density was low. Thus, this  
9 threshold analysis needs to be replicated in a larger number of cities. It should be noted that the  
10 model used in this analysis did not include a smooth function of days to adjust for unmeasured  
11 temporal confounders, and instead adjusted for season using a temperature term. As a result, these  
12 results need to be viewed with caution because some potential temporal confounders (e.g., influenza)  
13 do not always follow seasonal patterns of temperature.

14 Stylianou and Nicolich (2009, [620299](#)) examined the existence of thresholds following an  
15 approach similar to Xia and Tong (2006, [623157](#)) for all-cause, cardiovascular, and respiratory  
16 mortality using data from NMMAPS for nine major U.S. cities (i.e., Baltimore, Chicago, Dallas/Fort  
17 Worth, Los Angeles, Miami, New York, Philadelphia, Pittsburgh, and Seattle) for the years  
18 1987-2000. The authors found that PM<sub>10</sub> and O<sub>3</sub> were the two important predictors of mortality.  
19 Stylianou and Nicolich (2009, [620299](#)) found that the estimated O<sub>3</sub>-mortality risks varied across the  
20 nine cities with the models exhibiting apparent thresholds, in the 10-45 ppb range for O<sub>3</sub>. However,  
21 given the city-to-city variation in risk estimates, combining the city-specific estimates into an overall  
22 estimate complicates the interpretation of a threshold. Unlike the Xia and Tong (2006, [623157](#))  
23 analysis, Stylianou and Nicolich (2009, [620299](#)) included a smooth function of time to adjust for  
24 seasonal/temporal confounding, which could explain the difference in results between the two  
25 studies.

26 In conclusion, the evaluation of the O<sub>3</sub>-mortality C-R relationship did not find any evidence  
27 that supports a threshold for the association between short-term exposure to O<sub>3</sub> and mortality. It was  
28 also demonstrated that the heterogeneity in the O<sub>3</sub>-mortality relationship across cities (or regions)  
29 complicates the interpretation of a combined C-R curve and threshold analysis. Additionally, given  
30 the effect modifiers identified in the mortality analyses that are also expected to vary regionally (e.g.,  
31 temperature, air conditioning prevalence), a national or combined analysis may not be appropriate to  
32 identify whether a threshold exists in the O<sub>3</sub>-mortality C-R relationship.

### **6.6.2.5. Associations of Cause-Specific Mortality and Short-term Ozone Exposure**

33 In the 2006 O<sub>3</sub> AQCD, an evaluation of studies that examined cause-specific mortality found  
34 consistent positive associations between short-term O<sub>3</sub> exposure and cardiovascular mortality, with  
35 less consistent evidence for associations with respiratory mortality. The majority of the evidence for  
36 associations between O<sub>3</sub> exposure and cause-specific mortality were from single-city studies, which  
37 had small daily mortality counts and subsequently limited statistical power to detect associations.

1 New multicity studies evaluated in this review build upon and confirm the associations  
2 between short-term O<sub>3</sub> exposure and cause-specific mortality identified in the 2006 O<sub>3</sub> AQCD  
3 (Figure 6-37; Table 6-44). In APHENA, a multicontinent study that consisted of the NMMAPS,  
4 APHEA2 and Canadian multicity datasets, consistent positive associations were reported for both  
5 cardiovascular and respiratory mortality in all-year analyses when focusing on the natural spline  
6 model with 8 df/year (Section 6.6.2.1). Cardiovascular mortality associations persisted in analyses  
7 restricted to the summer season with evidence for stronger respiratory mortality associations  
8 compared to the all-year analysis results (Figure 6-37; Table 6-44). Additional multicity studies from  
9 the U.S. (Zanobetti and Schwartz, 2008, [101596](#)) and Europe (Samoli et al., 2009, [195855](#); Stafoggia  
10 et al., 2010, [625034](#)) that conducted summer season analyses also found strong associations between  
11 O<sub>3</sub> exposure and cardiovascular and respiratory mortality.

12 Of the studies evaluated, only the APHENA study (Katsouyanni et al., 2009, [199899](#)) and an  
13 Italian multicity study (Stafoggia et al., 2010, [625034](#)) conducted an analysis of the potential for  
14 co-pollutant confounding of the O<sub>3</sub> cause-specific mortality relationship. When focusing on the  
15 natural spline model with 8 df/year and lag 1 results (as discussed in Section 6.6.2.1), the APHENA  
16 study found that O<sub>3</sub> cause-specific mortality risk estimates were fairly robust to the inclusion of  
17 PM<sub>10</sub> in co-pollutant models in the European dataset with more variability in the U.S. and Canadian  
18 datasets (i.e., co-pollutant risk estimates increased and decreased for respiratory and cardiovascular  
19 mortality). In summer season analyses in the U.S. and Europe, the Canadian dataset did not examine  
20 co-pollutant models during the summer season, cardiovascular O<sub>3</sub> mortality risk estimates were  
21 robust in the European dataset and attenuated but remained positive in the U.S. datasets; whereas,  
22 respiratory O<sub>3</sub> mortality risk estimates were attenuated in the European dataset and robust in the U.S.  
23 dataset (Figure 6-37; Table 6-44). Interpretation of these results requires caution; however, due to the  
24 different PM sampling schedules employed in each of these study locations (i.e., primarily every-6th  
25 day in the U.S. and Canadian datasets and every-day in the European dataset). The results of the  
26 summer season analyses from the APHENA study (Katsouyanni et al., 2009, [199899](#)) are consistent  
27 with those from a study of 10 Italian cities during the summer months (Stafoggia et al., 2010,  
28 [625034](#)). Stafoggia et al. (2010, [625034](#)) found that cardiovascular (14.3% [95% CI: 6.7, 22.4%])  
29 and cerebrovascular (8.5% [95% CI: 0.06, 16.3%]) mortality O<sub>3</sub> effect estimates were robust to the  
30 inclusion of PM<sub>10</sub> in co-pollutant models (14.3% [95% CI: 6.7, 23.1%] and 7.3% [95% CI: -1.2,  
31 16.3], respectively), while respiratory mortality O<sub>3</sub> effects estimates (17.6% [95% CI: 1.8, 35.5%])  
32 were attenuated, but remained positive (9.2% [95% CI: -6.9, 28.8%]).

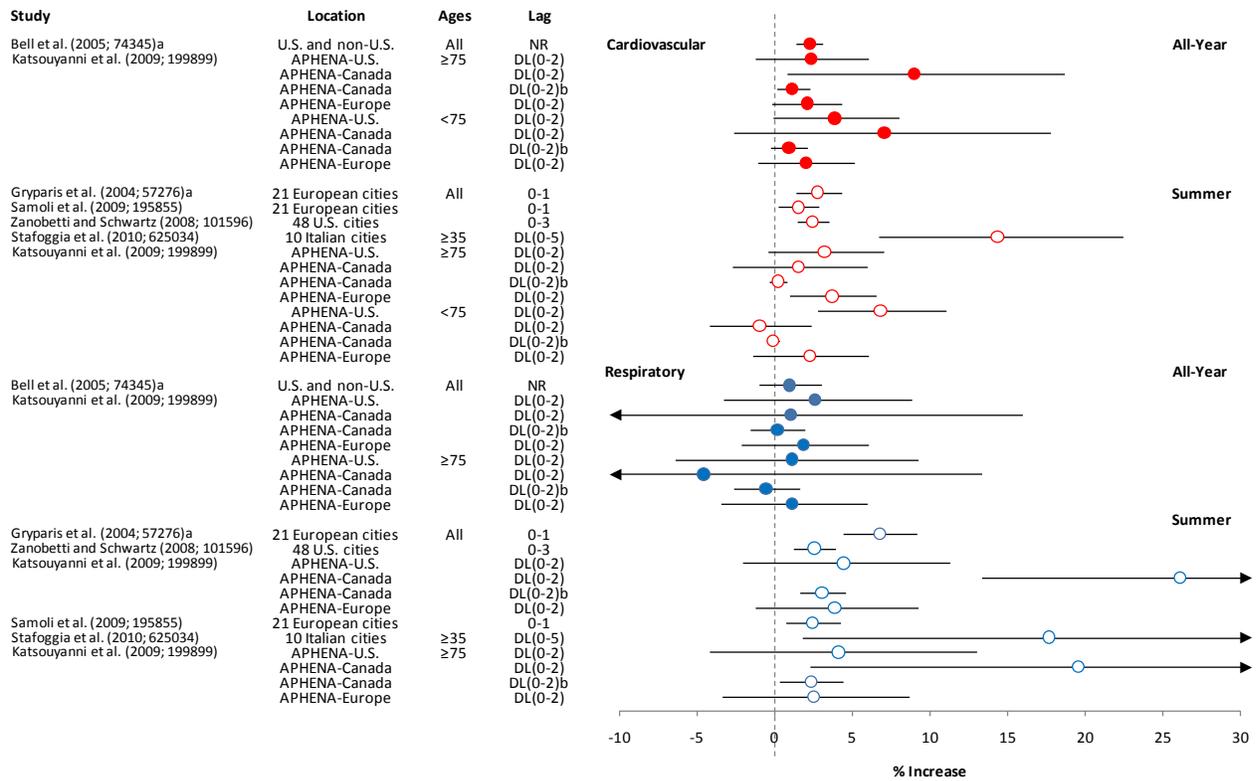


Figure 6-37. Percent increase in cause-specific mortality. Effect estimates are for a 20-ppb increase in 24-h avg; 30 in 8-h max; and 40-ppb increase in 1-h max ozone concentrations. Red = cardiovascular; blue = respiratory; closed circles = all-year analysis; and open circles = summer-only analysis. An “a” represents studies from the 2006 ozone 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 ozone concentrations (Section 6.2.7.2).

**Table 6-44. Corresponding effect estimates for Figure 6-37**

Study	Location	Ages	Lag	Avg Time	% Increase (95% CI)	
<b>Cardiovascular</b>						
All-year						
Bell et al. (2005, <a href="#">074345</a> ) <sup>a</sup>	U.S. and non-U.S.	All	NR	24-h avg	2.23 (1.36,3.08)	
Katsouyanni et al. (2009, <a href="#">199899</a> )	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) <sup>b</sup>		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) <sup>b</sup>		0.87 (-0.35, 2.10)	
	APHENA-Europe		DL(0-2)		1.98 (-1.09, 5.13)	
Summer						
Gryparis et al. (2004, <a href="#">057276</a> ) <sup>a</sup>	21 European cities	All	0-1	8-h max	2.7 (1.29,4.32)	
Samoli et al. (2009, <a href="#">195855</a> )	21 European cities		0-1	8-h max	1.48 (0.18, 2.80)	
Zanobetti and Schwartz (2008, <a href="#">101596</a> )	48 U.S. cities		0-3	8-h max	2.42 (1.45, 3.43)	
Stafoggia et al. (2010, <a href="#">625034</a> )	10 Italian cities	≥ 35	DL(0-5)	8-h max	14.3 (6.65, 22.4)	
Katsouyanni et al. (2009, <a href="#">199899</a> )	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) <sup>b</sup>		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) <sup>b</sup>		-0.13 (-0.55, 0.29)	
	APHENA-Europe		DL(0-2)		2.22 (-1.48, 6.04)	
	<b>Respiratory</b>					
	All-year					
Bell et al. (2005, <a href="#">074345</a> ) <sup>a</sup>	U.S. and non-U.S.	All	NR	24-h avg	0.94 (-1.02, 2.96)	
Katsouyanni et al. (2009, <a href="#">199899</a> )	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) <sup>b</sup>		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) <sup>b</sup>		-0.60 (-2.70, 1.60)	
	APHENA-Europe		DL(0-2)		1.10 (-3.48, 5.95)	
	Summer					
Gryparis et al. (2004, <a href="#">057276</a> ) <sup>a</sup>	21 European cities	All	0-1	8-h max	6.75 (4.38, 9.10)	
Zanobetti and Schwartz (2008, <a href="#">101596</a> )	48 U.S. cities		0-3	8-h max	2.51 (1.14, 3.89)	
Katsouyanni et al. (2009, <a href="#">199899</a> )	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) <sup>b</sup>		3.00 (1.60, 4.50)	
	APHENA-Europe		DL(0-2)		3.83 (-1.33, 9.21)	
Samoli et al. (2009, <a href="#">195855</a> )	21 European cities		0-1	8-h max	2.38 (0.65, 4.19)	
Stafoggia et al. (2010, <a href="#">625034</a> )	10 Italian cities	≥ 35	DL(0-5)	8-h max	17.6 (1.78, 35.5)	
Katsouyanni et al. (2009, <a href="#">199899</a> )	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) <sup>b</sup>		2.30 (0.28, 4.40)	
	APHENA-Europe		DL(0-2)		2.46 (-3.40, 8.62)	

<sup>a</sup>Studies from the 2006 O<sub>3</sub> AQCD.

<sup>b</sup>Risk estimates from APHENA-Canada standardized to an approximate IQR of 5.1 ppb for a 1-h max increase in O<sub>3</sub> concentrations (Section 6.2.7.2).

- 1 Collectively, the results from the new multicity studies provide evidence of associations
- 2 between short-term O<sub>3</sub> exposure and cardiovascular and respiratory mortality with additional
- 3 evidence indicating these associations persist, and in the case of respiratory mortality are
- 4 strengthened, in the summer season. Although co-pollutant analyses of cause-specific mortality are

1 limited, the APHENA study found that O<sub>3</sub> cause-specific mortality risk estimates were fairly robust  
2 to the inclusion of PM<sub>10</sub> in co-pollutant models in the European dataset, which is supported by the  
3 results from Stafoggia et al. (2010, [625034](#)). Additionally, APHENA found that O<sub>3</sub> cause-specific  
4 mortality risk estimates were moderately to substantially sensitive (e.g., increased or attenuated) to  
5 inclusion of PM<sub>10</sub> in the U.S. and Canadian datasets. However, the mostly every-6th-day sampling  
6 schedule for PM<sub>10</sub> in the U.S. and Canadian datasets greatly reduced their sample size and limits the  
7 interpretation of these results.

### 6.6.3. Summary and Causal Determination

8 The evaluation of new multicity studies that examined the association between short-term O<sub>3</sub>  
9 exposure and mortality found evidence which supports the conclusions of the 2006 O<sub>3</sub> AQCD. These  
10 new studies reported consistent positive associations between short-term O<sub>3</sub> exposure and all-cause  
11 (nonaccidental) mortality, with associations being stronger during the warm season, as well as  
12 additional support for associations between O<sub>3</sub> exposure and cardiovascular and respiratory  
13 mortality.

14 New studies further examined potential confounders (e.g., co-pollutants and seasonality) of the  
15 O<sub>3</sub>-mortality relationship. Because the PM-O<sub>3</sub> correlation varies across regions, due to the difference  
16 in PM chemical constituents, interpretation of the combined effect of PM on the relationship  
17 between O<sub>3</sub> and mortality is not straightforward. Unlike previous studies that were limited to  
18 primarily examining the confounding effects of PM<sub>10</sub>, the new studies expanded their analyses to  
19 include multiple PM indices (e.g., PM<sub>10</sub>, PM<sub>2.5</sub>, and PM components). An examination of co-  
20 pollutant models found evidence that associations between O<sub>3</sub> and all-cause mortality were robust to  
21 the inclusion of PM<sub>10</sub> or PM<sub>2.5</sub> (Bell et al., 2007, [093256](#); Katsouyanni et al., 2009, [199899](#);  
22 Stafoggia et al., 2010, [625034](#)), while other studies found evidence for a modest reduction  
23 (~20-30%) when examining PM<sub>10</sub> (Smith et al. (2009, [199750](#)). Additional evidence suggests  
24 potential sensitivity (e.g., increases and attenuation) of O<sub>3</sub> mortality risk estimates to co-pollutants  
25 by age group or cause-specific mortality (e.g., respiratory and cardiovascular) (Katsouyanni et al.,  
26 2009, [199899](#); Stafoggia et al., 2010, [625034](#)). An examination of PM components, specifically  
27 sulfate, found evidence for reductions in O<sub>3</sub>-mortality risk estimates in co-pollutant models (Franklin  
28 and Schwartz, 2008, [156448](#)). Overall, across studies, the potential impact of PM indices on  
29 O<sub>3</sub>-mortality risk estimates tended to be much smaller than the variation in O<sub>3</sub>-mortality risk  
30 estimates across cities. Although some studies suggest that O<sub>3</sub>-mortality risk estimates may be  
31 confounded by PM or its chemical components the interpretation of these results requires caution  
32 due to the limited PM datasets used as a result of the every-3rd- and 6th-day PM sampling schedule.  
33 When examining the potential for seasonal confounding of the O<sub>3</sub>-mortality relationship it was  
34 observed that the extent of smoothing or the methods used for adjustment can influence O<sub>3</sub> risk  
35 estimates because of the opposing seasonal trends of O<sub>3</sub> and mortality when not instituting enough  
36 degrees of freedom to control for temporal/seasonal trends (Katsouyanni et al., 2009, [199899](#)).

1           The multicity studies evaluated in this review also examined the regional heterogeneity  
2 observed in O<sub>3</sub>-mortality risk estimates. These studies provide evidence which suggests generally  
3 higher O<sub>3</sub>-mortality risk estimates in northeastern U.S. cities with some regions showing no  
4 associations between O<sub>3</sub> exposure and mortality (e.g., Southwest, Urban midwest) (Bell and  
5 Dominici, 2008, [193828](#); Smith et al., 2009, [199750](#)). Multicity studies that examined individual-  
6 and community-level characteristics identified characteristics that may explain the observed regional  
7 heterogeneity in O<sub>3</sub>-mortality risk estimates as well as characteristics of populations potentially  
8 susceptible to O<sub>3</sub>-related health effects. An examination of community-level characteristics found an  
9 increase in the O<sub>3</sub>-mortality risk estimates in cities with higher unemployment, percentage of the  
10 population Black/African-American, percentage of the working population that uses public  
11 transportation, lower temperatures, and lower prevalence of central air conditioning (Medina-Ramón  
12 and Schwartz, 2008, [193829](#)). Additionally, a potential interactive, or synergistic, effect on the  
13 O<sub>3</sub>-mortality relationship was observed when examining differences in the O<sub>3</sub>-mortality association  
14 across temperature levels (Ren et al. (2008, [093281](#)). An examination of individual-level  
15 characteristics found evidence that older age, female sex, Black race, having atrial fibrillation, and  
16 out-of hospital deaths, specifically in those individuals with diabetes, are significant effect modifiers  
17 of O<sub>3</sub>-mortality associations (Medina-Ramón and Schwartz, 2008, [193829](#); Stafoggia et al., 2010,  
18 [625034](#)), and may increase susceptibility to O<sub>3</sub>-related health effects. Overall, additional research is  
19 needed to further confirm whether these characteristics, individually or in combination, can explain  
20 the observed regional heterogeneity.

21           Additional studies were evaluated that examined factors, such as multi-day effects, mortality  
22 displacement, adaptation, and whether a threshold exists in the O<sub>3</sub>-mortality relationship, which may  
23 influence the shape of the O<sub>3</sub>-mortality C-R curve. An examination of multiday effects in a U.S. and  
24 European multicity study found conflicting evidence for mortality displacement, but both studies  
25 suggest that the positive associations between O<sub>3</sub> and mortality are observed mainly in the first  
26 few days after exposure (Samoli et al., 2009, [195855](#); Zanobetti and Schwartz, 2008, [101596](#)). A  
27 U.S. multicity study found evidence of an adaptive response to O<sub>3</sub> exposure, with the highest risk  
28 estimates earlier in the O<sub>3</sub> season (i.e., July) and diminished effects later (i.e., August) (Zanobetti and  
29 Schwartz, 2008, [195755](#)). However, the evidence of adaptive effects has an implication for the  
30 interpretation of multi-day effects, and requires further analysis. Analyses that specifically focused  
31 on the O<sub>3</sub>-mortality C-R relationship found no evidence of a threshold, but did observe evidence for  
32 potential differences in the C-R relationship across cities (Bell et al., 2006, [087680](#); Katsouyanni et  
33 al., 2009, [199899](#); Stylianou and Nicolich, 2009, [620299](#)). Collectively, these studies support the  
34 conclusions of the 2006 O<sub>3</sub> AQCD that “if a population threshold level exists in O<sub>3</sub> health effects, it  
35 is likely near the lower limit of ambient O<sub>3</sub> concentrations in the U.S.”

36           In conclusion, the new epidemiologic studies build upon and confirm the associations reported  
37 in the 2006 O<sub>3</sub> AQCD resulting in a body of evidence that is sufficient to conclude that **there is**  
38 **likely to be a causal relationship between short-term O<sub>3</sub> exposure and all-cause mortality.**

## 6.7. Overall Summary

1           The evidence reviewed in this chapter describes the recent findings regarding the health effects  
2 of short-term exposure to ambient O<sub>3</sub> concentrations. Table 6-45 provides an overview of the causal  
3 determinations for each of the health categories evaluated.

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**Table 6-45. Summary of causal determinations for short-term exposures to ozone**

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<b>Health Category</b>	<b>Causal Determination</b>
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
Mortality	Likely to be a causal relationship

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# References

A list of all epidemiologic references considered for inclusion in this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=403](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=403)

A list of all toxicological references considered for inclusion in this chapter can be found at

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A list of all controlled human exposure references considered for inclusion in this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=477](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=477)

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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# Chapter 7. Integrated Health Effects of Long-Term Ozone Exposure

## 7.1. Introduction

1 This chapter reviews, summarizes, and integrates the evidence on relationships between health  
2 effects and long-term exposures to O<sub>3</sub>. Both epidemiologic and toxicological studies provide a basis  
3 for examining long-term O<sub>3</sub> exposure health effects for respiratory effects, cardiovascular effects,  
4 reproductive and developmental effects, central nervous system effects, cancer outcomes, and  
5 mortality.

6 Conclusions from the 2006 O<sub>3</sub> AQCD are summarized briefly at the beginning of each section,  
7 and the evaluation of evidence from recent studies builds upon what was available during the  
8 previous review. For each health outcome (e.g., respiratory disease, lung function), results are  
9 summarized for studies from the specific scientific discipline, i.e., epidemiologic and toxicological  
10 studies. The major sections (i.e. respiratory, cardiovascular, mortality, reproductive/developmental,  
11 cancer) conclude with summaries of the evidence for the various health outcomes within that  
12 category and integration of the findings that lead to conclusions regarding causality based upon the  
13 framework described in Chapter 1. Determination of causality is made for the overall health effect  
14 category, such as respiratory effects, with coherence and plausibility being based on evidence from  
15 across disciplines and also across the suite of related health outcomes, including cause-specific  
16 mortality.

## 7.2. Respiratory Effects

17 Studies reviewed in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) examined evidence for  
18 relationships between long-term O<sub>3</sub> exposure and effects on respiratory health outcomes including  
19 seasonal declines in lung function, increases in inflammation, and development of asthma in children  
20 and adults. The term seasonal was used in these studies as a measure of a long-term exposure of  
21 several months. Animal toxicology data provided a clearer picture indicating that long-term O<sub>3</sub>  
22 exposure may have lasting effects. Chronic exposure studies in animals have reported biochemical  
23 and morphological changes suggestive of irreversible long-term O<sub>3</sub> impacts on the lung. In contrast  
24 to supportive evidence from chronic animal studies, the epidemiologic studies on longer-term lung  
25 function declines, inflammation, and new asthma development remained inconclusive. Several  
26 studies (e.g., Frischer et al., 1999, [001037](#); Horak et al., 2002, [034792](#)) collectively indicated that

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

1 seasonal O<sub>3</sub> exposure was associated with smaller increases in lung function growth in children. For  
2 longer time periods, the definitive analysis in the Child Health Study (CHS) reported by Gauderman  
3 et al. (2004, [056569](#)) provided little evidence that long-term exposure to ambient O<sub>3</sub> at current levels  
4 was associated with significant deficits in the growth rate of lung function in children in contrast to  
5 the effects observed with other pollutants such as acid vapor, NO<sub>2</sub>, and PM<sub>2.5</sub>. Asthmatic children  
6 with GSTM1 null genotype were found to be more susceptible to the impact of O<sub>3</sub> exposure on small  
7 airways function in Mexico (Romieu et al., 2004, [056796](#)). Limited epidemiologic research  
8 examined the relationship between long-term O<sub>3</sub> exposures and inflammation. Inflammatory effects  
9 consistent with known effects of O<sub>3</sub> such as increased eosinophil levels were observed in an Austrian  
10 study (Frischer et al., 2001, [019683](#)). The cross-sectional surveys available for the 2006 O<sub>3</sub> AQCD  
11 detected no associations between long-term O<sub>3</sub> exposures and asthma prevalence, asthma-related  
12 symptoms or allergy to common aeroallergens in children after controlling for covariates.

13 New evidence presented below reports consistent associations between long-term O<sub>3</sub> exposure  
14 and new-onset asthma related to genotype in U.S. cohorts in multi-community studies. Related  
15 studies report coherent relationships between respiratory symptoms among asthmatics and long-term  
16 O<sub>3</sub> exposure. A new line of evidence reports a positive exposure response relationship between first  
17 asthma hospitalization and long-term O<sub>3</sub> exposure. Results from recent studies examining pulmonary  
18 function, inflammation, and allergic responses are also presented.

### 7.2.1. New Onset Asthma

19 Risk for new-onset asthma is related in part to genetic susceptibility, behavioral factors and  
20 environmental exposure (Gilliland et al., 1999, [155792](#)). Complex chronic diseases, such as asthma,  
21 are partially the result of a sequence of biochemical reactions involving exposures to various  
22 environmental agents metabolized by a number of different genes (Conti et al., 2003, [626696](#)).  
23 Understanding the relation between genetic polymorphisms and environmental exposure can help  
24 identify high-risk subgroups in the population and provide better insight into pathway mechanisms  
25 for these complex diseases. Oxidative stress likely underlies these mechanistic hypotheses (Gilliland  
26 et al., 1999, [155792](#)). Susceptibility genes act through modification of disease risk associated with  
27 environmental factors. Epidemiologic investigation of hypotheses of possible mechanisms involving  
28 the gene-environmental (GxE) interaction involves statistical analysis of these interactions for the  
29 risk of new-onset asthma in children being influenced by exposure to air pollution (Gauderman,  
30 2001, [625862](#); Gauderman, 2002, [626945](#); Gilliland et al., 1999, [155792](#)).

31 Evidence for the potential importance of genetic susceptibility and behavioral factors on new  
32 onset asthma are provided by several recent studies (Ercan et al., 2006, [595172](#); Gilliland et al.,  
33 2002, [090970](#); Hanene et al., 2007, [595428](#); Himes et al., 2009, [480112](#); Islam et al., 2008, [097348](#);  
34 Li et al., 2006, [596447](#); Li et al., 2008, [596449](#); Tamer et al., 2004, [199914](#)). Evidence for a gene-  
35 pollution interaction in the pathogenesis of asthma are supported by recent study findings (Gilliland  
36 et al., 2002, [090970](#); Islam et al., 2008, [097348](#); Islam et al., 2009, [196715](#); Lee et al., 2004, [090971](#);  
37 Oryszczyn et al., 2007, [596460](#)).

1 Evidence for associations between long-term exposure to O<sub>3</sub> and new-onset asthma is provided  
2 by new studies from the CHS. Initiated in the early 1990's, the CHS was originally designed to  
3 examine whether ambient pollutants were related to chronic respiratory outcomes in children (Peters  
4 et al., 1999, [087243](#); Peters et al., 1999, [087237](#)). About 10 years later, the CHS inaugurated a series  
5 of genetic studies (Gilliland et al., 1999, [155792](#)) nested within the CHS cohort by obtaining  
6 biological samples from the study subjects (buccal cells). These new studies examined the  
7 relationship between health outcomes, genetic susceptibility, behavioral factors and environmental  
8 exposure.

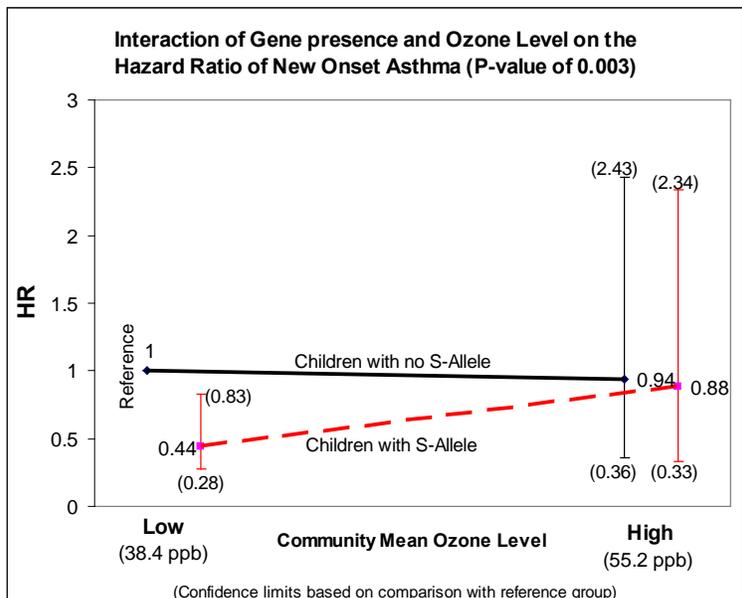
9 First, the hypothesis that the functional polymorphisms of HMOX-1 [(GT)<sub>n</sub> repeat], CAT  
10 (-262C > T -844C > T), and MNSOD (Ala-9Val) are associated with new-onset asthma was  
11 evaluated, and then whether the effects of these variants varied by exposure to O<sub>3</sub> (Islam et al., 2008,  
12 [097348](#)). HMOX1 [heme oxygenase (decycling) 1] is a human gene that encodes for the enzyme  
13 heme oxygenase. Heme oxygenase 1 (HO-1) is an enzyme that catalyzes the metabolism of heme.  
14 The heme iron serves as a source or sink of electrons during electron transfer or redox chemistry, so  
15 the presence of the HMOX1 gene, and therefore the generation of heme oxygenase, protects against  
16 oxidative stress in the body. The authors observed that functional promoter variants in CAT and  
17 HMOX-1 showed ethnicity-specific associations with new-onset asthma and that oxidant gene  
18 protection was restricted to children living in low-O<sub>3</sub> communities.

19 The subjects were obtained from the CHS from 12 communities in southern California.  
20 Children with a history of asthma or wheeze were excluded from this analysis. Analyses were  
21 restricted to children of Hispanic (n = 576) or non-Hispanic white ethnicity (n = 1,125). New-onset  
22 asthma was classified as such for children with no prior history of asthma at study entry who  
23 subsequently reported physician-diagnosed asthma at annual follow-up with the date of onset  
24 assigned to be the midpoint of the interval between the interview date when asthma diagnosis was  
25 first reported and the previous interview date. As a sensitivity analysis, the asthma definition was  
26 restricted to those new-onset asthma cases who also used an inhaler (n = 121). Long-term pollutant  
27 levels were calculated from 1994 through 2003. The effect of ambient air pollution on the  
28 relationship between genetic polymorphism and new-onset asthma was assessed using models where  
29 the community specific average air pollution levels were fitted as a continuous variable together with  
30 the appropriate interaction terms for genes and air pollutants (Berhane et al., 2004, [626732](#)). Cox  
31 proportional hazard regression models were fitted to the data. A stratified analysis for the two  
32 independent fourth-grade cohorts of the study population recruited in 1993 and 1996 were conducted  
33 to assess whether the results could be replicated in independent groups of children.

34 Over the follow-up period, 160 new cases of asthma were diagnosed (Islam et al., 2008,  
35 [097348](#)). The evidence indicated that the effect of variation in the HMOX-1 gene on risk of new-  
36 onset asthma differed by ambient O<sub>3</sub> level. An interaction P value was reported of 0.003 from the  
37 hierarchical two stage Cox proportional hazard model fitting the community-specific O<sub>3</sub> and PM<sub>10</sub>  
38 levels (continuous) and controlling for random effect of the communities. The annual O<sub>3</sub> levels  
39 (10:00 a.m. – 6:00 p.m.) ranged from 46.5 to 64.9 ppb in the six higher O<sub>3</sub> communities (mean =

1 55.2 ppb) and 28.6 to 45.5 ppb in the six lower O<sub>3</sub> communities (mean = 38.4 ppb). Average O<sub>3</sub>  
2 levels showed low correlation with the other monitored pollutants. The interaction indicated a greater  
3 effect (association) of community O<sub>3</sub> level among children with the gene than with children without  
4 the gene. Alleles with 23 or fewer (GT)<sub>n</sub> repeats are categorized as short (S). The S-allele variant of  
5 this protective enzyme is more readily induced than those with more numerous repeats. The largest  
6 protective effect of the (GT)<sub>n</sub> repeat polymorphism of HMOX-1 was observed for children who  
7 were S-allele carriers and resided in low-O<sub>3</sub> communities with Hazard Ratio (HR) of 0.44 (95% CI:  
8 0.23, 0.83). The ratio of HR of S-allele carriers who resided in high O<sub>3</sub> communities (HR 0.88; [95%  
9 CI: 0.33, 2.34]) was twofold greater than in those who resided in the low-O<sub>3</sub> communities (HR 0.44).  
10 The non-parallelism of the two lines in Figure 7-1 illustrates the interaction: Children with the S-  
11 allele have protection against the onset of asthma; however, in high- O<sub>3</sub> communities, this protection  
12 is attenuated. The results from sensitivity analyses on the two fourth-grade cohorts, and the inhaler  
13 definition for asthma were both consistent with the main results. An analysis related to children's  
14 participation in sports or time spent outdoors produced the same outcome. No significant interactions  
15 were observed between PM<sub>10</sub> or other pollutants and the HMOX -1 gene. A potential concern for not  
16 adjusting for multiple testing was considered by the authors as not a factor in this analysis because  
17 the selection of the genes was based on a priori hypotheses defined by a well-studied biological  
18 pathway. Thus in this cohort in southern California, Islam et al. (2008, [097348](#)) related new-onset  
19 asthma to O<sub>3</sub> exposure in genetically susceptible children.

20 Related to the findings in Islam et al. (2008, [097348](#)) discussed above, Islam et al. (2009,  
21 [196715](#)) examined whether GSTP1, GSTM1, exercise and O<sub>3</sub> exposure have interrelated effects on  
22 the pathogenesis of asthma. A modifying role of air pollution on the association between Ile105Val  
23 and asthma in a cohort of children had been observed (Lee et al., 2004, [090971](#)), but the study did  
24 not examine O<sub>3</sub> specifically or consider exercise. A primary conclusion that the authors (Islam et al.,  
25 2009, [196715](#)) reported was that the common functional variants of GSTP1 and GSTM1 null  
26 genotypes modulate the risk of new onset asthma during adolescence. Children who had the GSTM1  
27 null genotype were at 1.6-fold (95% CI: 1.2, 2.2) increased risk of developing new onset asthma  
28 compared with those without the null genotype. Further, the CHS investigators examined the  
29 complex interrelationship of antioxidant defenses with asthma risk with increasing doses of O<sub>3</sub>,  
30 resulting from increasing ventilation associated with vigorous exercise characterized by the number  
31 of team sports played. In an earlier analysis, McConnell et al. (2002, [023150](#)) had reported that the  
32 risk of new onset asthma was associated with outdoor exercise, especially in high O<sub>3</sub> communities  
33 but did not consider genetic variants. The plausibility of a causal association is strengthened by the  
34 observation by Islam et al. (2009, [196715](#)) that the risk of participation in team sports was related to  
35 increased genetic susceptibility to oxidative stress. The sixfold increased risk of asthma (HR 6.15,  
36 [95% CI: 2.2, 7.4]) for children who were homozygous for Ile105, participated in three or more team  
37 sports and lived in high-O<sub>3</sub> communities demonstrates the potential importance of a combination of  
38 genetic variability, O<sub>3</sub> exposure and behavior on asthma risk.



Source: Used with permission from American Thoracic Society, Islam et al. (2008, [097348](#)).

**Figure 7-1. Interaction of gene presence and ozone level on the Hazard Ratio (HR) of new-onset asthma in the 12 Children's Health Study communities. An interaction P-value of 0.003 was obtained from the hierarchical two stage Cox proportional hazard model fitting the community specific ozone and controlling for random effect of the communities. The interaction indicates there is a greater effect (association) of community ozone level on children with the gene than with children without the gene. The HRs are off-set as opposed to overlapping in the figure to allow clearer presentation of the results.**

1 Epidemiologic evidence of associations of arginase variants with asthma are limited (Li et al.,  
 2 2006, [596447](#)). Asthmatic subjects have higher arginase activity than nonasthmatic subjects (Morris  
 3 et al., 2004, [674145](#)). NO is a mediator of nitrosative stress synthesized from L-arginine by nitric  
 4 oxide synthases. In the CHS, Salam et al. (2009, [596644](#)) examined whether arginase variants  
 5 (ARG1 and ARG2 genes) were associated with asthma and whether atopy and exposures to smoking  
 6 and air pollution influence the associations. The modifying effect of O<sub>3</sub> and atopy on the association  
 7 between haplotypes and asthma were evaluated using likelihood ratio tests with appropriate  
 8 interaction terms. They found that both ARG1 and ARG2 genetic loci were associated with  
 9 childhood-onset asthma. The effect of the ARG1 haplotype varied by the child's history of atopy and  
 10 ambient O<sub>3</sub>. Among atopic children living in high O<sub>3</sub> communities, those carrying the ARG1  
 11 halotype had reduced asthma risk (OR per ARG1h4 halotype copy: 0.12; [95% CI: 0.04, 0.43];  
 12 P heterogeneity across atopy/O<sub>3</sub> categories = 0.008).

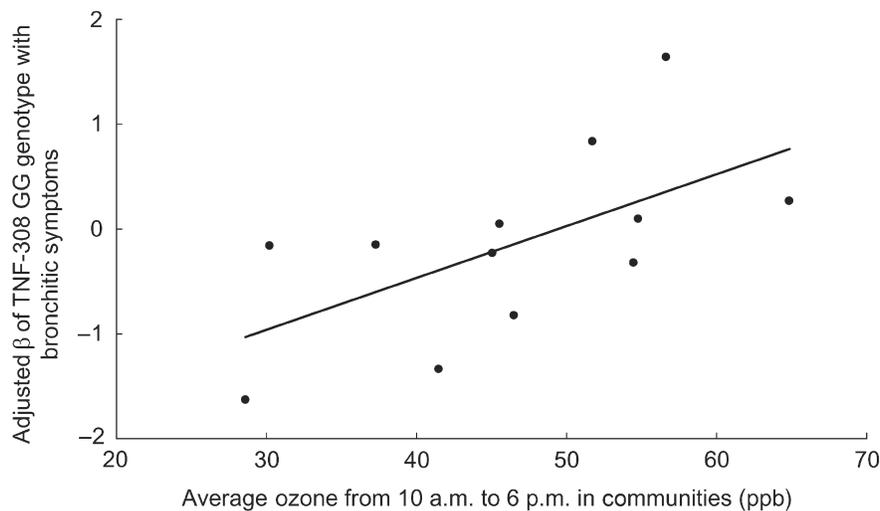
13 Further, the CHS presents results examining the relationship of new onset asthma with traffic-  
 14 related pollution near homes and schools (McConnell et al., 2010, [625501](#)). Asthma risk increased  
 15 with modeled traffic-related pollution exposure from roadways near homes and near schools. The  
 16 HR was 0.76 (95% CI: 0.38, 1.54) across the range of ambient O<sub>3</sub> exposure in the communities. With

1 adjustment for school and residential non-freeway traffic-related exposure, the estimated HR for O<sub>3</sub>  
2 was 1.01 (95% CI: 0.49, 2.11). Gene variants were not evaluated in this study.

3 Some cross-sectional studies reviewed in the 2006 O<sub>3</sub> AQCD observed positive relationships  
4 between chronic exposure to O<sub>3</sub> and prevalence of asthma and asthmatic symptoms in school  
5 children (Ramadour et al., 2000, [013259](#); Wang et al., 1999, [008105](#)) while others (Charpin et al.,  
6 1999, [015152](#); Kuo et al., 2002, [036310](#)) did not. Recent studies provide additional evidence.

7 In a cross-sectional nationwide study of 32,672 Taiwanese school children, Hwang et al.  
8 (2005, [089454](#)) assessed the effects of air pollutants on the risk of asthma. The study population was  
9 recruited from elementary and middle schools within 1 km of air monitoring stations. The risk of  
10 asthma was related to O<sub>3</sub> in the one-pollutant model. The addition of other pollutants, in two-  
11 pollutant and three-pollutant models, increased the O<sub>3</sub> risk estimates. The prevalence of childhood  
12 asthma was assessed in Portugal by contrasting the risk of asthma between a high O<sub>3</sub> rural area and  
13 an area with low O<sub>3</sub> levels (Sousa et al., 2008, [619959](#); Sousa et al., 2009, [619956](#); Sousa et al.,  
14 2011, [676712](#)). The locations were selected to provide a difference in O<sub>3</sub> levels without the  
15 confounding effects of other pollutants. Both evaluation for asthma symptoms and FEV<sub>1</sub> suggested  
16 that O<sub>3</sub> increased asthma prevalence. Clark et al. (2010, [594440](#)) investigated the effect of exposure  
17 to ambient air pollution in utero and during the first year of life on risk of subsequent incidence  
18 asthma diagnosis up to 3-4 years of age in a population-based nested case-control study for all  
19 children born in southwestern British Columbia in 1999 and 2000 (n=37,401; including 3,482 [9.3%]  
20 with asthma). Air pollution exposure for each subject was estimated based on their residential  
21 address history using regulatory monitoring data, land use regression modeling, and proximity to  
22 stationary pollutant sources. Daily values from the three closest monitors within 50 km were used to  
23 calculate exposures. Traffic-related pollutants were associated with the highest risk. Ozone was  
24 inversely correlated with the primary traffic-related pollutants (r = -0.7 to -0.9). The low reliability of  
25 asthma diagnosis in infants makes this study difficult to interpret (Martinez et al., 1995, [046150](#)). In  
26 a cross-sectional analysis, Akinbamia et al. (2010, [378580](#)) examined the association between  
27 chronic exposure to outdoor pollutants (12-month average levels by county) and asthma outcomes in  
28 a national sample of children ages 3-17 years living in U.S. metropolitan areas (National Health  
29 Interview Survey, N = 34,073). A 5-ppb increase in estimated 8-h max O<sub>3</sub> concentration (annual  
30 average) yielded a positive association for both currently having asthma and for having at least 1  
31 asthma attack in the previous year; while the adjusted odds ratios for other pollutants were not  
32 statistically significant. Models in which pollutant value ranges were divided into quartiles produced  
33 comparable results. Multi-pollutant models produced similar results. The median value for 12-month  
34 average O<sub>3</sub> levels was 39.5 ppb and the IQR was 35.9-43.7 ppb. The adjusted odds for current  
35 asthma for the highest quartile (49.9-59.5 ppb) of estimated O<sub>3</sub> exposure was 1.56 (95% CI: 1.15,  
36 2.10) with a positive dose-response relationship apparent from the lowest quartile to the highest.  
37 Thus, this cross-sectional analysis and Hwang et al. (2005, [089454](#)) provides further evidence  
38 relating O<sub>3</sub> exposure and the risk of asthma.

1 The occurrence of bronchitic symptoms among children with asthma was investigated in the  
 2 CHS examining the role of gene-environment interactions and long-term O<sub>3</sub> exposure. Lee et al.  
 3 (2009, [199915](#)) studied associations of TNF-308 genotype with bronchitis symptoms among  
 4 asthmatic children and investigated whether associations vary with ambient O<sub>3</sub> exposure since  
 5 increased airway TNF may be related to inflammation. Asthmatic children with the GG genotype  
 6 had a lower prevalence of bronchitic symptoms compared with children carrying at least one A-allele  
 7 (e.g., GA or AA). Low-versus high-O<sub>3</sub> strata were defined as less than or greater than 50- ppb O<sub>3</sub>  
 8 average. Asthmatic children with TNF-308 GG genotype had a significantly reduced risk of  
 9 bronchitic symptoms with low-O<sub>3</sub> exposure (OR: 0.53; [95% CI: 0.31, 0.91]). The risk was not  
 10 reduced in children living in high-O<sub>3</sub> communities (OR: 1.42; [95% CI: 0.75, 2.70]). The difference  
 11 in genotypic effects between low- and high-O<sub>3</sub> environments was statistically significant among  
 12 asthmatics (P for interaction = 0.01), but insignificant among non-asthmatic children. By using  
 13 dummy variables in each community, Lee et al. (2009, [199915](#)) calculated the effect of TNF-308 GG  
 14 genotype on the occurrence of bronchitic symptoms among children with asthma. Figure 7-2  
 15 presents adjusted O<sub>3</sub> community-specific beta-coefficients plotted against ambient O<sub>3</sub> concentration,  
 16 using weights proportional to the inverse variance. They further report that they found no substantial  
 17 differences in the effect of the GG genotype in asthmatic children in relation to exposure to PM<sub>10</sub>,  
 18 PM<sub>2.5</sub>, NO<sub>2</sub>, acid vapor or second-hand smoke exposure. These results suggest a role of gene-  
 19 environment interactions such as long-term O<sub>3</sub> exposure on the occurrence of bronchitic symptoms  
 20 among children with asthma.



Source: Used with permission from John Wiley & Sons A/S, Lee et al. (2009, [199915](#)).

**Figure 7-2. Ozone modifies the effect of TNF G-308A genotype on bronchitic symptoms among children with asthma in the CHS. Using dummy variables in each of the 12 communities, betas were calculated of TNF-308 GG genotype on the occurrence of bronchitic symptoms among children with asthma.**

1 The French Epidemiology study on Genetics and Environment of Asthma (EGEA)  
2 investigated the relationship between ambient air pollution and asthma severity in a cohort in five  
3 French cities (Paris, Lyon, Marseille, Montpellier, and Grenoble) (Rage et al., 2009, [196720](#)). In this  
4 cross-sectional study, asthma severity over the past 12 months was assessed among 328 adult  
5 asthmatics using two methods: (1) a four-class severity score that integrated clinical events and type  
6 of treatment; and (2) a five-level asthma score based only on symptoms. Two measures of exposure  
7 were also assessed: (1 [first method]) closest monitor data from 1991 to 1995 where a total of 93%  
8 of the subjects lived within 10 km of a monitor, but where 70% of the O<sub>3</sub> concentrations were back-  
9 extrapolated values; and (2 [second method]) a validated spatial model that used geostatistical  
10 interpolations and then assigned air pollutants to the geocoded residential addresses of all  
11 participants and individually assigned exposure to ambient air pollution estimates. Higher asthma  
12 severity scores were significantly related to both the 8-h avg O<sub>3</sub> during April-September and the  
13 number of days with 8-h O<sub>3</sub> averages above 55 ppb. Both exposure assessment methods and severity  
14 score methods resulted in very similar findings. Effect estimates of O<sub>3</sub> were similar in three-pollutant  
15 models. No PM data were available. Since these estimates were not sensitive to the inclusion of  
16 ambient NO<sub>2</sub> in the three-pollutant models, the authors viewed the findings not to be explained by  
17 particles which usually have substantial correlations between PM and NO<sub>2</sub>. Ozone concentrations by  
18 the first method for annual levels, nearest monitor were 8-hours (n = 210); mean (+SD) 30.25 (+9.7);  
19 IQR: 21-36.5 (+15.5) ppb. The second exposure approach yielded summer (n = 308); mean (+SD)  
20 levels of 31.5 (+5.2); IQR of 28.5-33.9 (+5.5) ppb. Effect estimates for O<sub>3</sub> in three-pollutant models  
21 including O<sub>3</sub>, SO<sub>2</sub>, and NO<sub>2</sub> yielded OR for O<sub>3</sub>-days of 2.74 (95% CI: 1.68, 4.48) per IQR days of  
22 10-28 (+18) ppb. The effect estimates for SO<sub>2</sub> and NO<sub>2</sub> in the three-pollutant model were 1.33 (95%  
23 CI: 0.85, 2.11) and 0.94 (95% CI: 0.68, 1.29) respectfully. Taking into account duration of residence  
24 did not change the result. This study suggests that a higher asthma severity score is related to long-  
25 term O<sub>3</sub> exposure.

26 The interrelationships between variants in catalase (CAT) and myeloperoxidase (MPO) genes,  
27 ambient pollutants, and acute respiratory illness were investigated in a national U.S. cohort (Wenten  
28 et al., 2009, [597084](#)). Health information, air pollution, and incident respiratory-related school  
29 absences were ascertained in January-June 1996 for 1,136 Hispanic and non-Hispanic white U.S.  
30 elementary schoolchildren as part of the prospective Air Pollution and Absence Study, a population  
31 based cohort study conducted as part of the CHS. A related earlier study (Gilliland et al., 2001,  
32 [013232](#)), which was discussed in the 2006 O<sub>3</sub> AQCD, examined the effects of ambient air pollution  
33 on school absenteeism due to respiratory illness without a genetic aspect to the study. In a new study  
34 Wenten et al. (2009, [597084](#)) hypothesized that variation in the level or function of these enzymes  
35 would modulate respiratory illness risk, especially under high levels of oxidative stress. The joint  
36 effect of these two genes on respiratory illness was examined. Risk of respiratory-related school  
37 absences was elevated for children with the CAT (G/G) and MPO (G/A or A/A) genes (relative risk =  
38 1.35, [95% CI: 1.03, 1.77]; P-interaction = 0.005). To assess effects of long-term average levels of  
39 O<sub>3</sub> on acute effects, communities were divided into high and low exposure groups by median levels

1 (46.9 ppb O<sub>3</sub>). The epistatic effect of CAT and MPO variants was evident in communities exhibiting  
2 high ambient O<sub>3</sub> levels (P-interaction = 0.03). The association of respiratory-illness absences with  
3 functional variants in CAT and MPO that differ by air pollution levels illustrates the need to consider  
4 genetic epistasis in assessing gene-environment interactions. In high O<sub>3</sub> communities, CAT/MPO  
5 genotypes that resulted in decreased oxidative stress were associated with a decreased risk of  
6 respiratory related school absences compared with the CAT/MPO wild-type genotype (RR = 0.42,  
7 [95% CI: 0.20, 0.89]).

## 7.2.2. Asthma Hospital Admissions and ED Visits

8 The studies on O<sub>3</sub>-related hospital discharges and emergency department (ED) visits for  
9 asthma and respiratory disease that were available in the 2006 O<sub>3</sub> AQCD mainly looked at the daily  
10 time metric. New studies evaluated long-term O<sub>3</sub> exposure metrics providing a new line of evidence  
11 that suggests a positive exposure-response relationship between first asthma hospital admission and  
12 long-term O<sub>3</sub> exposure.

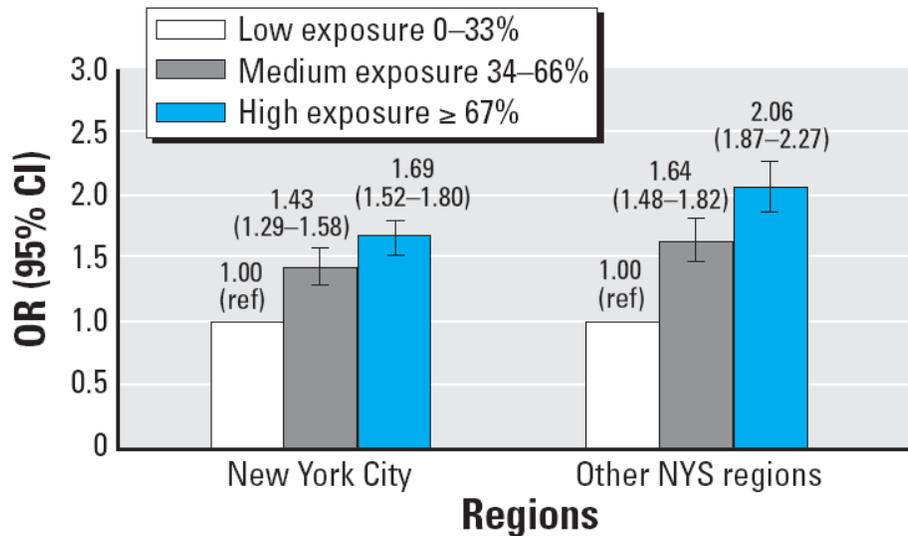
13 An ecologic study (Moore et al., 2008, [196685](#)) evaluated time trends in associations between  
14 declining warm-season O<sub>3</sub> concentrations and hospitalization for asthma in children in California's  
15 South Coast Air Basin who ranged in age from birth to 19 years. Quarterly average concentrations  
16 from 195 spatial grids, 10×10 km, were used. Ozone was the only pollutant associated with  
17 increased hospital admissions over the study period. A linear relation was observed for asthma  
18 hospital discharges (Moore et al., 2008, [196685](#)). A matched case-control study (Karr et al., 2007,  
19 [090719](#)) was conducted of infant bronchiolitis (ICD 9, code 466.1) hospitalization and two measures  
20 of long-term pollutant exposure (the month prior to hospitalization and the lifetime average) for O<sub>3</sub>  
21 in the South Coast Air Basin of southern California among 18,595 infants born between 1995 and  
22 2000. Ozone was associated with reduced risk in the single-pollutant model, but this relation did not  
23 persist in multi-pollutant models.

24 In a cross-sectional study, Meng et al. (2010, [594252](#)) examined associations between air  
25 pollution and asthma morbidity in the San Joaquin Valley in California by using the 2001 California  
26 Health Interview Survey data from subjects ages 1 to 65+ who reported physician-diagnosed asthma  
27 (n = 1502). Subjects were assigned annual average concentrations for O<sub>3</sub> based on residential ZIP  
28 code and the closest air monitoring station within 8 km but did not have data on duration of residence.  
29 Multi-pollutant models for O<sub>3</sub> and PM did not differ substantially from single-pollutant estimates,  
30 indicating that pollutant multi-collinearity is not a problem in these analyses. The authors reported  
31 increased asthma-related ED visits or hospitalizations for O<sub>3</sub> (OR 1.49; [95% CI: 1.05, 2.11] per  
32 10 ppb) for all ages. Positive associations were obtained for symptoms but 95% CIs included null  
33 values. Associations for symptoms for adults (ages 18 +) were observed (OR 1.40; [95% CI: 1.02,  
34 1.91] per 10 ppb).

35 Associations between air pollution and poorly controlled asthma among adults in Los Angeles  
36 and San Diego Counties, were investigated using the California Health Interview Survey data  
37 collected between November 2000 and September 2001 (Meng et al., 2007, [093275](#)). Each

1 respondent was assigned an annual average concentration measured at the nearest station within  
2 5 miles of the residential cross-street intersection. Poorly controlled asthma was defined as having  
3 daily or weekly asthma symptoms or at least one ED visit or hospitalization because of asthma  
4 during the past 12 months. This cross-sectional study reports an OR of 3.34 (95% CI: 1.01, 11.09)  
5 for poorly controlled asthma when comparing those 65 years of age and older above the 90th  
6 percentile (28.7 ppb) level to those below that level. Multi-pollutant analysis produced similar  
7 results.

8 Evidence associating long-term O<sub>3</sub> exposure to first asthma hospital admission in a  
9 concentration-response relationship is provided in a retrospective cohort study (Lin et al., 2008,  
10 [196680](#)). This study investigated the association between chronic exposure to O<sub>3</sub> and childhood  
11 asthma admissions (defined as a principal diagnosis of ICD9, code 493) by following a birth cohort  
12 of 1,204,396 eligible births born in New York State during 1995-1999 to first asthma admission or  
13 until 31 December 2000. There were 10,429 (0.87%) children admitted to the hospital for asthma  
14 between 1 and 6 years of age. The asthma hospitalization rate in New York State in 1993 was 2.87  
15 per 1,000 (Lin et al., 1999, [377917](#)). Three indicators (all 8-h max from 10:00 a.m. to 6:00 p.m.)  
16 were used to define chronic O<sub>3</sub> exposure: (1) mean concentration during the follow-up period  
17 (41.06 ppb); (2) mean concentration during the O<sub>3</sub> season (50.62 ppb); and (3) proportion of follow-  
18 up days with O<sub>3</sub> levels >70 ppb. In this study the authors aimed to predict the risk of having asthma  
19 admissions in a birth cohort, but the time to the first admission in children that is usually analyzed in  
20 survival models was not their primary interest. The effects of co-pollutants were assessed and  
21 controlled for using the Air Quality Index (AQI). Interaction terms were used to assess potential  
22 effect modifications. A positive association between chronic exposure to O<sub>3</sub> and childhood asthma  
23 hospital admissions was observed indicating that children exposed to high O<sub>3</sub> levels over time are  
24 more likely to develop asthma severe enough to be admitted to the hospital. The various factors were  
25 examined and differences were found for younger children (1-2 years), poor neighborhoods,  
26 Medicaid/self-paid births, geographic region and others. As shown in Figure 7-3, positive  
27 concentration-response relationships were observed. Asthma admissions were significantly  
28 associated with increased O<sub>3</sub> levels for all chronic exposure indicators (ORs, 1.16-1.68). When  
29 estimating the O<sub>3</sub> effect using the exceedance proportion, an increase was observed (OR 1.68; [95%  
30 CI: 1.64, 1.73]) in hospital admissions with an IQR (2.51%) increase in O<sub>3</sub>. A proportional hazards  
31 model for the New York City data was run as a sensitivity analysis and it yielded similar results  
32 between asthma admissions and chronic exposure to O<sub>3</sub> ( HR from the Cox model: HR: 1.14, [95%  
33 CI: 1.124, 1.155] is similar to OR from the logistic model: 1.16 (95% CI: 1.15, 1.17) (Lin, personal  
34 communication, 2010, [676733](#)). Thus, this study provides evidence associating long-term O<sub>3</sub>  
35 exposure to first asthma hospital admission in a concentration-response relationship.



Source: Lin et al. (2008, [196680](#));(Lin, personal communication, 2010, [676733](#)).

**Figure 7-3. Ozone-asthma concentration-response relationship using the mean concentration during the entire follow-up period 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.**

OR’s 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.

### 7.2.3. Pulmonary Structure and Function

1 The definitive 8-year follow-up analysis of the first cohort of the CHS (Gauderman et al.,  
 2 2004, [056569](#)) provided little evidence that long-term exposure to ambient O<sub>3</sub> at current levels was  
 3 associated with significant deficits in the growth rate of lung function in children. A later CHS study  
 4 (Islam et al., 2007, [090697](#)) examined relationships between air pollution, lung function, and new  
 5 onset asthma and reported no substantial differences in the effect of lung function between “high-”  
 6 and “low-” O<sub>3</sub> communities. Ozone concentrations from the least to most polluted communities  
 7 (mean annual average of 8-h avg O<sub>3</sub>) ranged from 30 to 65 ppb, whereas the ranges observed for the  
 8 other pollutants had four- to eightfold differences in concentrations. In a more recent CHS study,  
 9 Breton et al. (2011, [687660](#)) hypothesized that genetic variation in genes on the glutathione  
 10 metabolic pathway may influence the association between ambient air pollutant exposures and lung  
 11 function growth in children. They investigated whether genetic variation in glutathione genes GSS,  
 12 GSR, GCLC, and GCLM was associated with lung function growth in healthy children using data  
 13 collected on 2,106 children over an 8-year time-period as part of the Children’s Health Study. Breton  
 14 et al. (2011, [687660](#)) found that variation in the GSS locus was associated with differences in  
 15 susceptibility of children for lung function growth deficits associated with NO<sub>2</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>,

1 elemental carbon, organic carbon, and O<sub>3</sub>. The negative effects of air pollutants were largely  
2 observed within participants who had a particular GSS haplotype. The effects ranged from -124.2 to  
3 -149.1 mL for FEV<sub>1</sub>, -92.9 to -126.7 mL for FVC and -193.9 to -277.9 mL/s for MMEF for all  
4 pollutants except O<sub>3</sub>, for which some positive associations were reported: 25.9 mL for FEV<sub>1</sub>; 0.1 mL  
5 for FVC, and 166.5 mL/s for MMEF. Ozone did show larger decreases in lung function in children  
6 without this haplotype, when compared to the other pollutants with values of -76.6 mL for FEV<sub>1</sub>,  
7 -17.2 mL for FVC, and -200.3 mL/s for MMEF, but only MMEF was statistically significant.

8 As discussed in the 2006 O<sub>3</sub> AQCD, a study of freshman students at the University of  
9 California, Berkeley reported that lifetime exposure to O<sub>3</sub> was associated with decreased measures of  
10 small airways (<2 mm) function (FEF<sub>75</sub> and FEF<sub>25-75</sub>) (Tager et al., 2005, [087538](#)). There was an  
11 interaction with the FEF<sub>25-75</sub>/FVC ratio, a measure of intrinsic airway size. Subjects with a large ratio  
12 were less likely to have decreases in FEF<sub>75</sub> and FEF<sub>25-75</sub> for a given estimated lifetime exposure to  
13 O<sub>3</sub>. Kinney and Lippmann (2000, [011913](#)) examined 72 nonsmoking adults (mean age 20 years)  
14 from the second-year class of students at the U.S. Military Academy in West Point, NY, and reported  
15 results that appear to be consistent with a seasonal decline in lung function that may in part be due to  
16 O<sub>3</sub> exposures. Ilhorst et al. (2004, [055608](#)) examined 2,153 children with a median age of 7.6 years  
17 and reported summer pulmonary function results which indicated that significantly lower FVC and  
18 FEV<sub>1</sub> increases were associated with higher O<sub>3</sub> exposures in the summer, but not in the winter. Semi-  
19 annual mean O<sub>3</sub> concentrations ranged from 22 to 54 ppb during the summer and 4 to 36 ppb during  
20 the winter. However, over a 3.5-year period Ilhorst et al. (2004, [055608](#)) found no associations  
21 between increases in lung function and mean summer O<sub>3</sub> levels for FVC and FEV<sub>1</sub>, in contrast to the  
22 significant seasonal effects. Frischer et al. (1999, [001037](#)) showed results similar to the Ilhorst et al.  
23 (2004, [055608](#)) study.

24 Mortimer et al. (2008, [122163](#); 2008, [187280](#)) examined the association of prenatal and  
25 lifetime exposures to air pollutants with pulmonary function and allergen sensitization in a subset of  
26 asthmatic children (ages 6-11) included in the Fresno Asthmatic Children's Environment Study  
27 (FACES). Monthly means of pollutant levels for the years 1989-2000 were created and averaged  
28 separately across several important developmental time-periods, including: the entire pregnancy,  
29 each trimester, the first 3 years of life, the first 6 years of life, and the entire lifetime. In the first  
30 analysis (Mortimer et al., 2008, [122163](#)), negative effects on pulmonary function were found for  
31 exposure to PM<sub>10</sub>, NO<sub>2</sub>, and CO during key neonatal and early life developmental periods. The  
32 authors did not find a negative effect of exposure to O<sub>3</sub> within this cohort. In the second analysis  
33 (Mortimer et al., 2008, [187280](#)), sensitization to at least one allergen was associated, in general, with  
34 higher levels of CO and PM<sub>10</sub> during the entire pregnancy and second trimester, and higher PM<sub>10</sub>  
35 during the first 2 years of life. Lower exposure to O<sub>3</sub> during the entire pregnancy or second trimester  
36 was associated with an increased risk of allergen sensitization. Although the pollutant metrics across  
37 time periods were correlated, the strongest associations with the outcomes were observed for  
38 prenatal exposures. Though it may be difficult to disentangle the effect of prenatal and postnatal  
39 exposures, the models from this group of studies suggest that each time period of exposure may

1 contribute independently to different dimensions of school-aged children's pulmonary function. For  
2 4 of the 8 pulmonary-function measures (FVC, FEV<sub>1</sub>, PEF, FEF<sub>25-75</sub>), prenatal exposures were more  
3 influential on pulmonary function than early-lifetime metrics, while, in contrast, the ratio of  
4 measures (FEV<sub>1</sub>/FVC and FEF<sub>25-75</sub>/FVC) were most influenced by postnatal exposures. When  
5 lifetime metrics were considered alone, or in combination with the prenatal metrics, the lifetime  
6 measures were not associated with any of the outcomes. This suggests that the timing of the O<sub>3</sub>  
7 exposure may be more important than the overall dose, and prenatal exposures are not just markers  
8 for lifetime or current exposures.

9 Latzin et al. (2009, [195721](#)) examined whether prenatal exposure to air pollution was  
10 associated with lung function changes in the newborn. Tidal breathing, lung volume, ventilation  
11 inhomogeneity and eNO were measured in 241 unsedated, sleeping neonates (age = 5 weeks).  
12 Consistent with the previous studies, no association was found for prenatal exposure to O<sub>3</sub> and lung  
13 function.

14 In a cross-sectional study of adults, Qian et al. (2005, [093283](#)) examined the association of  
15 long-term exposure to O<sub>3</sub> and PM<sub>10</sub> with pulmonary function from data of 10,240 middle-aged  
16 subjects who participated in the Atherosclerosis Risk in Communities (ARIC) study in four U.S.  
17 communities. A surrogate for long-term O<sub>3</sub> exposure from daily data was determined at the  
18 individual level. Ozone was significantly and negatively associated with measures of pulmonary  
19 function.

20 To determine the extent to which long-term exposure to outdoor air pollution accelerates adult  
21 decline in lung function, Forbes et al. (2009, [595425](#)) studied the association between chronic  
22 exposure to outdoor air pollution and lung function in approximately 42,000 adults aged 16 and  
23 older who were representatively sampled cross-sectionally from participants in the Health Survey for  
24 England (1995, 1996, 1997, and 2001). FEV<sub>1</sub> was not associated with O<sub>3</sub> concentrations. In contrast  
25 to the results for PM<sub>10</sub>, NO<sub>2</sub>, and SO<sub>2</sub>, combining the results of all the survey years showed that a  
26 5-ppb difference in O<sub>3</sub> was counter-intuitively associated with a higher FEV<sub>1</sub> by 22 mL.

27 In a prospective cohort study consisting of school-age, non-asthmatic children in Mexico City  
28 (n = 3,170) who were 8 years of age at the beginning of the study, Rojas-Martinez et al. (2007,  
29 [091064](#)) evaluated the association between long-term exposure to O<sub>3</sub>, PM<sub>10</sub> and NO<sub>2</sub> and lung  
30 function growth every 6 months from April 1996 through May 1999. Exposure data were provided  
31 by 10 air quality monitor stations located within 2 km of each child's school. Over the study period,  
32 8-h O<sub>3</sub> concentrations ranged from 60 ppb (SD, ±25) in the northeast area of Mexico City to 90 ppb  
33 (SD, ±34) in the southwest, with an overall mean of 69.8 ppb. In multi-pollutant models, an IQR  
34 increase in mean O<sub>3</sub> concentration of 11.3 ppb was associated with an annual deficit in FEV<sub>1</sub> of  
35 12 mL in girls and 4 mL in boys. Single-pollutant models showed an association between ambient  
36 pollutants (O<sub>3</sub>, PM<sub>10</sub> and NO<sub>2</sub>) and deficits in lung function growth. While the estimates from  
37 co-pollutant models were not substantially different than single pollutant models, independent effects  
38 for pollutants could not be estimated accurately because the traffic-related pollutants were correlated.  
39 To reduce exposure misclassification, microenvironmental and personal exposure assessments were

1 conducted in a randomly selected subsample of 60 children using passive O<sub>3</sub> samplers. Ozone  
2 concentrations were correlated ( $p < 0.05$ ) with the measurements obtained from the fixed-site air  
3 monitoring stations.

4 In the 2006 O<sub>3</sub> AQCD, few studies had investigated the effect of chronic O<sub>3</sub> exposure on  
5 pulmonary function. The strongest evidence was for seasonal effects of extended O<sub>3</sub> exposures on  
6 lung function in children, i.e., reduced lung function growth being associated with higher ambient O<sub>3</sub>  
7 levels. Longer-term studies, investigating the association of chronic O<sub>3</sub> exposure on yearly lung  
8 function such as the CHS, were inconclusive. Thus for new studies for pulmonary function, in one  
9 study where O<sub>3</sub> and other pollutant levels were higher (90 ppb at high end of the range) than those in  
10 the CHS, a relationship between O<sub>3</sub> concentration and pulmonary function declines was observed in  
11 school-aged children. Two studies of adult cohorts provide mixed results where long-term exposures  
12 were at the high end of the range with levels of 49.5 ppb in one study and 27 ppb IQR in the other.  
13 Thus there is little new evidence to build upon the very limited studies from the 2006 O<sub>3</sub> AQCD.

### 7.2.3.1. Evidence from Toxicological Studies

14 As reviewed in the 1996 and 2006 O<sub>3</sub> AQCDs (U.S. EPA, (1996, [017831](#)), (2006, [088089](#))),  
15 considerable controversy surrounds the extrapolation of data generated by rodent toxicology studies  
16 to the understanding of adverse health effects observed in humans, as documented by epidemiology  
17 and controlled exposure studies. Chief among these data extrapolation issues are the differences  
18 between rodent and human respiratory physiology, cellular makeup, dosimetry, and morphometry.  
19 Unique among the six NAAQS criteria pollutants, however, O<sub>3</sub>-inhalation studies have been  
20 performed in non-human primates whose respiratory system most closely resembles that of the  
21 human. A long series of studies have used non-human primates to examine the effect of O<sub>3</sub> alone or  
22 in combination with an inhaled allergen, house dust mite antigen, on morphology and lung function.  
23 These studies, by Plopper and colleagues, have demonstrated changes in pulmonary function and  
24 airway morphology in adult and infant non-human primates repeatedly exposed to environmentally  
25 relevant concentrations of O<sub>3</sub>. (Carey et al., 2007, [195752](#); Chang MM-J; Wu et al., 1998, [011983](#);  
26 Chen et al., 2003, [035576](#); Duan et al., 1993, [086326](#); Duan et al., 1996, [080791](#); Evans et al., 2003,  
27 [048167](#); Evans et al., 2004, [596379](#); Fanucchi et al., 2000, [012284](#); Fanucchi et al., 2006, [096491](#);  
28 Fujinaka et al., 1985, [040278](#); Harkema et al., 1987, [041496](#); Harkema et al., 1987, [040816](#);  
29 Harkema et al., 1993, [039794](#); Hatch et al., 1994, [076120](#); Hyde et al., 1989, [094057](#); Hyde et al.,  
30 1999, [015124](#); Joad et al., 2000, [012984](#); Joad et al., 2006, [596390](#); Joad et al., 2008, [596391](#); Larson  
31 et al., 2004, [057062](#); Lee et al., 1998, [054473](#); Moffatt et al., 1987, [040841](#); Plopper and Schelegle,  
32 1997, [656713](#); Plopper et al., 1991, [042617](#); Plopper et al., 1998, [087203](#); Schelegle et al., 2003,  
33 [053778](#); Tran et al., 2004, [628626](#); Tucker et al., 1993, [056406](#); Wilson et al., 1984, [040044](#); Wu et  
34 al., 1999, [012089](#)).

35 Since the 1996 and 2006 O<sub>3</sub> AQCDs, the initial observations in adult non-human primates  
36 have been expanded in a series of experiments using infant rhesus monkeys repeatedly exposed to  
37 0.5 ppm O<sub>3</sub> starting at 1 month of age (Plopper et al., 2007, [596412](#)). Many of the observations

1 found in adult monkeys have also been noted in infant rhesus monkeys, although a direct comparison  
2 of the degree of adverse effects between adult and infant monkeys has not been reported. In terms of  
3 pulmonary function changes, after several episodic exposures of infant monkeys to O<sub>3</sub> (each cycle:  
4 5 days of 0.5 ppm O<sub>3</sub> at 8 h/day, followed by 9 days of filtered air exposures), they observed more  
5 than a doubling in the baseline airway resistance, which was accompanied by a small increase in  
6 airway responsiveness to inhaled histamine (Schelegle et al., 2003, [053778](#)), although neither  
7 measurement was statistically different from filtered air control values. Exposure of animals to  
8 inhaled house dust mite antigen alone also produced small but not statistically significant changes in  
9 baseline airway resistance and airway responsiveness, whereas the combined exposure to both (O<sub>3</sub> +  
10 antigen) produced statistically significant and greater than additive changes in both functional  
11 measurements. This non-human primate evidence, of an O<sub>3</sub>-induced change in airway  
12 responsiveness, supports the biologic plausibility of long-term exposure to O<sub>3</sub> contributing to the  
13 adverse effects of asthma in children. To understand which conducting airways and inflammatory  
14 mechanisms are involved in O<sub>3</sub>-induced airway hyperresponsiveness in the infant rhesus monkey, a  
15 follow-up study examined airway responsiveness ex vivo in lung slices (Joad et al., 2006, [596390](#)).  
16 Using video microscopy to morphometrically evaluate the response of bronchi and respiratory  
17 bronchioles to methacholine, (a bronchoconstricting agent commonly used to evaluate airway  
18 responsiveness in asthmatics), the investigators observed differential effects for the two airway sizes.  
19 While episodic exposure to O<sub>3</sub> alone (0.5 ppm) had little effect on ex vivo airway responsiveness in  
20 bronchi and respiratory bronchioles, exposure to dust mite antigen alone produced airway  
21 hyperresponsiveness in the large bronchi, whereas O<sub>3</sub> + antigen produced significant increases in  
22 airway hyperresponsiveness only in the respiratory bronchioles. These results suggest that ozone's  
23 effect on airway responsiveness occurs predominantly in the smaller bronchioles.

24 The functional changes in the conducting airways of infant rhesus monkeys exposed to either  
25 O<sub>3</sub> alone or O<sub>3</sub> + antigen were accompanied by a number of cellular and morphological changes,  
26 including a significant fourfold increase in eosinophils, (a cell type important in allergic asthma), in  
27 the bronchoalveolar lavage of infant monkeys exposed to O<sub>3</sub> alone. Thus, these studies demonstrate  
28 both functional and cellular changes in the lung of infant monkeys after cyclic exposure to 0.5 ppm  
29 O<sub>3</sub>. This concentration, while higher than those used in controlled human exposure studies, provides  
30 relevant information to understanding the adverse effects of ambient O<sub>3</sub> exposure on the respiratory  
31 tract of humans. No concentration-response data, however, are available from these non-human  
32 primate studies.

33 In addition to these functional and cellular changes, significant structural changes in the  
34 respiratory tract have been observed in infant rhesus monkeys exposed to O<sub>3</sub>. During normal  
35 respiratory tract development, conducting airways increase in diameter and length in the infant  
36 rhesus monkey. Exposure to O<sub>3</sub> alone (5 days of 0.5 ppm O<sub>3</sub> at 8 h/day, followed by 9 days of  
37 filtered air exposures for 11 cycles), however, markedly affected the growth pattern of distal  
38 conducting airways (Fanucchi et al., 2006, [096491](#)). Whereas the first alveolar outpocketing  
39 occurred at airway generation 13 or 14 in filtered air-control infant monkeys, the most proximal

1 alveolarized airways occurred at an average of 10 airway generations in O<sub>3</sub>-exposed monkeys.  
2 Similarly, the diameter and length of the terminal and respiratory bronchioles were significantly  
3 decreased in O<sub>3</sub>-exposed monkeys. Importantly, the O<sub>3</sub>-induced structural pathway changes persisted  
4 after recovery in filtered air for 6 months after cessation of the O<sub>3</sub> exposures. These structural effects  
5 were accompanied by significant increases in mucus goblet cell mass, alterations in smooth muscle  
6 orientation in the respiratory bronchioles, epithelial nerve fiber distribution, and basement membrane  
7 zone morphometry. These latter effects are significant because of their potential contribution to  
8 airway obstruction and airway hyperresponsiveness which are central features of asthma.

9 As noted above, a significant increase in airway responsiveness to inhaled histamine occurred  
10 in infant rhesus monkeys exposed to O<sub>3</sub> + house dust mite antigen, but not to O<sub>3</sub> alone (Schelegle et  
11 al., 2003, [053778](#)). To study the underlying mechanisms of this airway hyperresponsiveness, these  
12 investigators evaluated the effect of exposure to O<sub>3</sub> alone and in combination with (+) antigen on  
13 non-specific airway responsiveness to methacholine at different airway generations. After exposure  
14 to filtered air, O<sub>3</sub>, antigen, or O<sub>3</sub> + antigen, the bronchi and respiratory bronchioles of 6-month-old  
15 monkeys were challenged ex vivo with methacholine. Exposure to O<sub>3</sub> alone had no significant effect  
16 on airway responsiveness to methacholine in either airway, whereas O<sub>3</sub> + antigen produced a  
17 significant increase in airway responsiveness in the respiratory bronchioles but not the larger  
18 bronchi.

19 Because many cellular and biochemical factors are known to contribute to allergic asthma, the  
20 effect of exposure to O<sub>3</sub> alone or O<sub>3</sub> + antigen on immune system parameters was also examined in  
21 infant rhesus monkeys. Mast cells, which contribute to asthma via the release of potent proteases,  
22 were elevated in animals exposed to antigen alone but O<sub>3</sub> alone had little effect on mast cell numbers  
23 and the response of animals exposed to O<sub>3</sub> + antigen was not different from that of animals exposed  
24 to antigen alone; thus suggesting that mast cells played little role in the interaction between O<sub>3</sub> and  
25 antigen in this model of allergic asthma (Van Winkle et al., 2010, [670301](#)). Increases in CD4+ and  
26 CD8+ lymphocytes were observed at 6 months of age in the blood and bronchoalveolar lavage fluid  
27 of infant rhesus monkeys exposed to O<sub>3</sub> + antigen but not in monkeys exposed to either agent alone  
28 (Miller et al., 2009, [596406](#)). Activated lymphocytes (i.e., CD25+ cells) were morphometrically  
29 evaluated in the airway mucosa and significantly increased in infant monkeys exposed to antigen  
30 alone or O<sub>3</sub> + antigen. Although O<sub>3</sub> alone had no effect on CD25+ cells, it did alter the anatomic  
31 distribution of CD25+ cells within the airways. Ozone had only a small effect on these sets of  
32 immune cells and did not produce a strong interaction with an inhaled allergen in this non-human  
33 primate model; more mechanistic studies are necessary to understand a concentration-response effect  
34 of O<sub>3</sub> on allergic asthma.

35 In addition to alterations in the immune system, nervous system interactions with epithelial  
36 cells are thought to play a contributing role to airway hyperresponsiveness. As noted in the 2006 O<sub>3</sub>  
37 AQCD, exposure of infant rhesus monkeys altered the normal development of neural innervation in  
38 the epithelium of the conducting airways (Larson et al., 2004, [057062](#)). Whereas, a significant  
39 reduction in airway innervation occurred after exposure to O<sub>3</sub> alone, a significantly greater reduction

1 occurred in monkeys exposed to O<sub>3</sub> + antigen. This reduction in overall airway innervation was  
2 accompanied, however, by an increase in the abundance of protein gene product 9.5, a nonspecific  
3 neural marker. Significant increases in protein gene product 9.5 were still observed in O<sub>3</sub> alone- and  
4 O<sub>3</sub> + antigen-exposed infant monkeys after a 6-month recovery protocol (Kajekar et al., 2007,  
5 [567661](#)). Thus, in addition to structural, immune, and inflammatory effects, exposure to O<sub>3</sub> produces  
6 alterations in airway innervation which may contribute to O<sub>3</sub>-induced exacerbation of asthma.

7 While the infant rhesus monkey studies examined the effect of long-term O<sub>3</sub> exposure on  
8 functional and morphologic development of the lung during early life, a small number of rodent  
9 studies have examined the role of age in the response to O<sub>3</sub>. In mice, age-related differences in  
10 O<sub>3</sub>-induced inflammation and the immediate-early gene response were observed. Johnston and  
11 colleagues (2006, [097439](#)) demonstrated that the lung damage produced by O<sub>3</sub> occurred through  
12 distinct (compared to inhaled endotoxin), early gene expression responses. Whereas c-fos and c-jun  
13 mRNA levels were elevated in a concentration-dependent manner (1 and 2.5 ppm O<sub>3</sub> for 4 hours) in  
14 the lungs of C57BL/6 mice at 4, 10, and 56 days of age, the relative abundance of mRNA for TLR-4  
15 (which has been shown to play a role in the pulmonary response to inhaled O<sub>3</sub> (Hollingsworth et al.,  
16 2010, [635786](#); Kleeberger et al., 2001, [016163](#))), was induced in the lungs of 10- and 56-day old but  
17 not 4-day-old mice. Similar age-related differences in response were observed with inhaled  
18 endotoxin, thus suggesting that the murine lung responds differently throughout the postnatal stage  
19 of development. A study by Vancza et al. (2009, [596419](#)) also demonstrated age-related differences  
20 in the pulmonary response of mice to O<sub>3</sub>. Significantly greater inflammatory changes were observed  
21 in neonatal (15 to 16 days old) compared to adult (15 week old) mice. Because this increase in  
22 neonatal response was seen only in a subset of the 8 inbred mouse strains exposed to 0.8 ppm O<sub>3</sub> for  
23 5 hours, this strain-dependency suggests that genetic host factors play a role in age-related  
24 differences in response to O<sub>3</sub>. Thus, these rodent studies suggest that the response to O<sub>3</sub> in the  
25 neonatal period is dependent on which postnatal day(s) the exposure occurs, as would be expected in  
26 a rapidly developing mammalian lung.

27 Collectively, evidence from animal studies strongly suggests that chronic O<sub>3</sub> exposure is  
28 capable of damaging the distal airways and proximal alveoli, resulting in lung tissue remodeling -  
29 leading to apparent irreversible changes. Compromised pulmonary function and structural changes  
30 due to persistent inflammation may exacerbate the progression and development of chronic lung  
31 disease. These findings offer some insight into potential biological mechanisms for the suggested  
32 association between seasonal O<sub>3</sub> exposure and reduced lung function development in children as  
33 observed in epidemiologic studies.

#### 7.2.4. Pulmonary Inflammation, Injury, and Oxidative Stress

34 The 2006 O<sub>3</sub> AQCD stated that the extensive human clinical and animal toxicological  
35 evidence, together with the limited epidemiologic evidence available, suggests a causal role for O<sub>3</sub> in  
36 inflammatory responses in the airways. Though the majority of recent studies focus on short-term

1 exposures, several epidemiologic and toxicology studies of long-term exposure add to observations  
2 of O<sub>3</sub>-induced inflammation and injury.

3 Inflammatory markers and peak expiratory pulmonary function were examined in 37 allergic  
4 children with physician-diagnosed mild persistent asthma in a highly polluted urban area in Italy and  
5 then again 7 days after relocation to a rural location with significantly lower pollutant levels  
6 (Renzetti et al., 2009, [199834](#)). The authors observed a fourfold decrease in nasal eosinophils and a  
7 statistically significant decrease in fractional exhaled nitric oxide along with an improvement in  
8 lower airway function. Several pollutants were examined, including PM<sub>10</sub>, NO<sub>2</sub>, and O<sub>3</sub>, though  
9 pollutant-specific results were not presented. These results are consistent with studies showing that  
10 traffic-related exposures are associated with increased airway inflammation and reduced lung  
11 function in children with asthma and contribute to the notion that this negative influence may be  
12 rapidly reversible. Exhaled NO (eNO) has been shown to be a useful biomarker for airway  
13 inflammation in large population-based studies (Linn et al., 2009, [597363](#)). Thus, while the time  
14 scale of 7 days between examinations for eNO needs to be evaluated for appropriateness, the results  
15 suggest that inflammatory responses are reduced when O<sub>3</sub> levels are decreased.

16 Chest radiographs (CXR) of 249 children in Mexico City who were chronically exposed to O<sub>3</sub>  
17 and PM<sub>2.5</sub> were analyzed by Calderón-Garcidueñas et al. (2006, [091253](#)). They reported an  
18 association between chronic exposures to O<sub>3</sub> and other pollutants and a significant increase in  
19 abnormal CXR's and lung CTs suggestive of a bronchiolar, peribronchiolar, and/or alveolar duct  
20 inflammatory process, in clinically healthy children with no risk factors for lung disease. These CXR  
21 and CT results should be viewed with caution because it is difficult to attribute effects to air  
22 pollution exposure.

23 In a cross-sectional study, Wood et al. (2009, [597085](#)) examined the association of outdoor air  
24 pollution with respiratory phenotype (PiZZ type) in alpha 1-Antitrypsin deficiency ( $\alpha$ -ATD) from the  
25 U.K.  $\alpha$ -ATD registry. In total, 304 PiZZ subjects underwent full lung function testing and  
26 quantitative high-resolution computed tomography to identify the presence and severity of COPD –  
27 emphysema. Mean annual air pollution data for 2006 was matched to the location of patients' houses  
28 and used in regression models to identify phenotypic associations with pollution controlling for  
29 covariates. Relative trends in O<sub>3</sub> levels were assessed to validate use of a single year's data to  
30 indicate long-term exposure and validation; data showed good correlations between modeled and  
31 measured data (Stedman and Kent, 2008, [110057](#)). Regression models showed that estimated higher  
32 exposure to O<sub>3</sub> exposure was associated with worse gas transfer and more severe emphysema, albeit  
33 accounting for only a small proportion of the lung function variability. This suggests that a gene-  
34 specific group demonstrates a long-term O<sub>3</sub> exposure effect.

35 The similarities of non-human primates to humans make them attractive models in which to  
36 study the effects of O<sub>3</sub> on the respiratory tract. The nasal mucous membranes, which protect the more  
37 distal regions of the respiratory tract, are susceptible to injury from O<sub>3</sub>. Carey et al. (2007, [195752](#))  
38 conducted a study of O<sub>3</sub> exposure in infant rhesus macaques, whose nasal airways closely resemble  
39 that of humans. Monkeys were exposed either acutely for 5 days (8 h/day) to 0.5 ppm O<sub>3</sub>, or

1 episodically for several biweekly cycles alternating 5 days of 0.5 ppm O<sub>3</sub> with 9 days of filtered air  
2 (0 ppm O<sub>3</sub>), designed to mimic human exposure (70 days total). All monkeys acutely exposed to O<sub>3</sub>  
3 had moderate to marked necrotizing rhinitis, with focal regions of epithelial exfoliation, numerous  
4 infiltrating neutrophils, and some eosinophils. The distribution, character, and severity of lesions in  
5 episodically exposed monkeys were similar to that of acutely exposed animals. Neither group  
6 exhibited mucous cell metaplasia proximal to the lesions, a protective adaptation observed in adult  
7 monkeys exposed continuously to 0.3 ppm O<sub>3</sub> in another study (Harkema et al., 1987, [040816](#)). A  
8 90-day exposure of rats to 0.8 ppm O<sub>3</sub> (8 h/day) elicited significantly elevated pro-inflammatory  
9 eicosanoids PGE<sub>2</sub> and 12-HETE in BAL, but cytokine profiles did not differ from those of filtered  
10 air-exposed rats (Schmelzer et al., 2006, [112994](#)).

### 7.2.5. Allergic Responses

11 The association of air pollutants with childhood respiratory allergies was examined in the U.S.  
12 using the 1999-2005 National Health Interview Survey of approximately 70,000 children, and  
13 ambient air pollution data from the U.S. EPA, with monitors within 20 miles of each child's  
14 residential block (Parker et al., 2009, [192359](#)). The authors examined the associations between the  
15 reporting of respiratory allergy or hay fever and summer exposure to O<sub>3</sub>, controlling for  
16 demographic and geographic factors. Increased respiratory allergy/hay fever was associated with  
17 increased O<sub>3</sub> levels (adjusted OR per 10 ppb = 1.20; [95% CI: 1.15, 1.26]). These associations  
18 persisted after stratification by urban-rural status, inclusion of multiple pollutants, and definition of  
19 exposure by differing exposure radii; smaller samples within 5 miles of monitors were remarkably  
20 similar to the primary results. No associations between the other pollutants and the reporting of  
21 respiratory allergy/hay fever were apparent. Ramadour et al. (2000, [013259](#)) reported no relationship  
22 between O<sub>3</sub> levels and rhinitis symptoms and hay fever. Hwang et al. (2006, [088971](#)) report the  
23 prevalence of allergic rhinitis (adjusted OR per 10 ppb = 1.05; [95% CI: 0.98, 1.12]) in a large cross-  
24 sectional study in Taiwan. In a large cross-sectional study in France, Penard-Morand et al. (2005,  
25 [087951](#)) reported a positive relationship between lifetime allergic rhinitis and O<sub>3</sub> exposure in a two-  
26 pollutant model with NO<sub>2</sub>. These studies related positive outcomes of allergic response and O<sub>3</sub>  
27 exposure but with variable strength for the effect estimates. Nasal eosinophils, which participate in  
28 allergic disease, were observed to decrease by fourfold in 37 atopic, mildly asthmatic children 7 days  
29 after relocation from a highly polluted urban area in Italy to a rural location with significantly lower  
30 pollutant levels (Renzetti et al., 2009, [199834](#)).

31 Total IgE levels were related to air pollution levels in 369 adult asthmatics in five French  
32 centers using generalized estimated equations (GEE) as part of the EGEA study described earlier  
33 (Rage et al., 2009, [196719](#)). Geostatistical models were performed on 4×4 km grids to assess  
34 individual outdoor air pollution exposure that was assigned to subject's home address. Ozone  
35 concentrations were positively related to total IgE levels and an increase of 5 ppb of O<sub>3</sub> resulted in an  
36 increase of 20.4% (95% CI: 3.0, 40.7) in total IgE levels. Nearly 75% of the subjects were atopic.  
37 Two-pollutant models for O<sub>3</sub> with NO<sub>2</sub> were decreased by 25% while NO<sub>2</sub> was decreased by 57%.

1 Associations were not sensitive to adjustment for covariates or the season of IgE measurements.  
2 These cross-sectional results suggest that exposure to O<sub>3</sub> may increase total IgE in adult asthmatics.  
3 No toxicological studies of long-term exposure are available, but short-term exposure studies  
4 in rodents and non-human primates demonstrate allergic skewing of immune responses and  
5 enhanced IgE production. Due to the persistent nature of these responses, the short-term  
6 toxicological evidence lends biological plausibility to the limited epidemiologic findings of an  
7 association between long-term O<sub>3</sub> exposure and allergic outcomes.

### 7.2.6. Host Defense

8 Short-term exposures to O<sub>3</sub> cause decreases in host defenses against infectious lung disease in  
9 animal models. However, acute O<sub>3</sub>-induced suppression of alveolar phagocytosis and immune  
10 functions observed in animals appears to be transient and attenuated with continuous or repeated  
11 exposures. Chronic exposures (weeks, months) of 0.1 ppm do not cause greater effects on infectivity  
12 than short exposures, due to defense parameters becoming reestablished with prolonged exposures,  
13 although chronic exposure has been shown to slow alveolar clearance. In an older study (Jakab and  
14 Bassett, 1990, [042196](#)), no detrimental effects were seen with a 120-day exposure to 0.5 ppm O<sub>3</sub> on  
15 acute lung injury from influenza virus administered immediately before O<sub>3</sub> exposure started. But  
16 there were O<sub>3</sub>-enhanced postinfluenzal alveolitis and lung parenchymal changes. No new evidence  
17 has become available to address the effects of long-term exposure on host defense mechanisms.

### 7.2.7. Respiratory Mortality

18 A limited number of epidemiologic studies have assessed the relationship between long-term  
19 exposure to O<sub>3</sub> and mortality. The 2006 O<sub>3</sub> AQCD concluded that an insufficient amount of evidence  
20 existed “to suggest a causal relationship between chronic O<sub>3</sub> exposure and increased risk for  
21 mortality in humans” (U.S. EPA, 2006, [088089](#)). Though total and cardio-pulmonary mortality were  
22 considered in these studies, respiratory mortality was not specifically considered. In the most recent  
23 follow-up analysis of the ACS cohort (Jerrett et al., 2009, [194160](#)), cardiopulmonary deaths were  
24 subdivided into respiratory and cardiovascular, separately, as opposed to combined in the Pope et al.  
25 (2002, [024689](#)) work. A 10-ppb increment in exposure to O<sub>3</sub> elevated the risk of death from  
26 respiratory causes and this effect was robust to the inclusion of PM<sub>2.5</sub>. The association between  
27 increased O<sub>3</sub> concentrations and increased risk of death from respiratory causes was insensitive to  
28 the use of a random-effects survival model allowing for spatial clustering within the metropolitan  
29 area and state of residence, and to adjustment for several ecologic variables considered individually.

### 7.2.8. Summary and Causal Determination

30 The epidemiologic studies reviewed in the 2006 O<sub>3</sub> AQCD detected no associations between  
31 long-term O<sub>3</sub> exposures and asthma-related symptoms, asthma prevalence, or allergy to common  
32 aeroallergens among children after controlling for covariates. Little evidence was available to relate

1 long-term exposure to current ambient O<sub>3</sub> concentrations to deficits in the growth rate of lung  
 2 function in children. Additionally, limited evidence was available evaluating the relationship  
 3 between long-term O<sub>3</sub> levels and pulmonary inflammation and other endpoints. From toxicological  
 4 studies, it appeared that O<sub>3</sub>-induced inflammation tapered off during long-term exposures, but that  
 5 hyperplastic and fibrotic changes remained elevated and in some cases even worsened after a  
 6 postexposure period in clean air. Episodic exposures were also known to cause more severe  
 7 pulmonary morphologic changes than continuous exposure (U.S. EPA, 2006, [088089](#)).

8 The new epidemiologic evidence base consists of studies using a variety of designs and  
 9 analysis methods evaluating the relationship between long-term measures of exposure to ambient O<sub>3</sub>  
 10 and measures of respiratory morbidity conducted by different research groups in different locations.  
 11 See Table 7-1 for O<sub>3</sub> concentrations associated with selected studies. The positive results from  
 12 various designs and locations support an association between long-term O<sub>3</sub> concentrations and  
 13 respiratory morbidity.

14 New studies examined the relationship between long-term O<sub>3</sub> exposure and new onset asthma  
 15 in children. Studies have provided evidence for a relationship between different genetic variants  
 16 (HMOX, GST, ARG) that, in combination with O<sub>3</sub> exposure, are related to new onset asthma (Islam  
 17 et al., 2008, [097348](#); Islam et al., 2009, [196715](#); Salam et al., 2009, [596644](#)). These studies involve  
 18 two separate cohorts in the CHS. These prospective cohort studies represent strong evidence because  
 19 they are methodologically rigorous epidemiology studies. The studies were conducted in 12  
 20 California communities. The stratified analysis for the two independent fourth-grade cohorts of the  
 21 study population recruited in 1993 and 1996 yielded consistent results and provides replication in  
 22 independent groups of children. Also, no meaningful interactions were observed between other air  
 23 pollutants such as PM<sub>10</sub> and genes.

**Table 7-1. Summary of selected key new studies examining annual ozone exposure and respiratory health effects**

<b>Study; Health Effect; Location</b>	<b>Mean Annual O<sub>3</sub> Concentration (ppb)</b>	<b>O<sub>3</sub> Range (ppb) Percentiles</b>
Islam et al.(2008, <a href="#">097348</a> ); new-onset asthma; CHS	55.2 high vs. 38.4 low communities 10:00 a.m. to 6:00 p.m.	See left
Islam et al. (2009, <a href="#">196715</a> ); new-onset asthma; CHS	55.2 high vs. 38.4 low communities 10:00 a.m. to 6:00 p.m.	See left
Salam et al. (2009, <a href="#">596644</a> ); childhood onset asthma; CHS	O <sub>3</sub> greater than or less than 50 ppb	See left
Lin et al. (2008, <a href="#">196680</a> ); first asthma hospital admission; New York State - 10 regions	Range of mean O <sub>3</sub> concentrations over the 10 New York Regions 37.51 to 47.78	See left
Moore et al. (2008, <a href="#">196685</a> ); asthma hospital admissions; South Coast Basin	Median 87.8 ppb	Range 28.6 to 199.9 ppb
Meng et al. (2010, <a href="#">594252</a> ); asthma ED visits or hospitalizations; San Joaquin Valley, CA	Median 30.3 ppb	25-75% range 27.1 to 34.0
Lee et al. (2009, <a href="#">199915</a> ); bronchitic symptoms in asthmatic children; CHS	Above and below 50 ppb	See left
Rage et al. (2009, <a href="#">196719</a> ); asthma severity; five French cities	Mean 30 ppb	25th-75th 21-36 ppb

1 Studies using a cross-sectional design provide support for a relationship between long-term O<sub>3</sub>  
2 exposure and health effects in asthmatics. A long-term O<sub>3</sub> exposure study relates bronchitic  
3 symptoms to TNF-308 genotype asthmatic children with ambient O<sub>3</sub> exposure in the CHS (Lee et al.,  
4 2009, [199915](#)). A study relating asthma severity to long-term O<sub>3</sub> exposure in five French cities  
5 provides additional support to the notion that effects on asthma are related to long-term O<sub>3</sub> exposure  
6 (Rage et al., 2009, [196720](#)). For the respiratory health of the general U.S. population, risk of  
7 respiratory-related school absences was elevated for children with the CAT and MPO variant genes  
8 related to communities with high ambient O<sub>3</sub> levels (Wenten et al., 2009, [597084](#)).

9 Chronic O<sub>3</sub> exposure was related to first childhood asthma hospital admissions in a positive  
10 concentration-response relationship in a New York State birth cohort (Lin et al., 2008, [196680](#)). A  
11 separate hospitalization cross-sectional study in San Joaquin Valley in California reports similar  
12 findings (Meng et al., 2010, [594252](#)). Another study relates asthma hospital admissions to quarterly  
13 average O<sub>3</sub> in the South Coast Air Basin of California (Moore et al., 2008, [196685](#)).

14 Information from toxicological studies indicates that long term exposure to O<sub>3</sub> during gestation  
15 or development can result in irreversible morphological changes in the lung, which in turn can  
16 influence pulmonary function. Studies by Plopper and colleagues have demonstrated changes in  
17 pulmonary function and airway morphology in adult and infant non-human primates repeatedly  
18 exposed to environmentally relevant concentrations of O<sub>3</sub> (Fanucchi et al., 2006, [096491](#); Harkema  
19 et al., 1987, [041496](#); Joad et al., 2006, [596390](#); Schelegle et al., 2003, [053778](#)). This non-human  
20 primate evidence of an O<sub>3</sub>-induced change in airway responsiveness supports the biologic  
21 plausibility of long term exposure to O<sub>3</sub> contributing to the adverse effects of asthma in children.  
22 Results from epidemiologic studies examining long-term O<sub>3</sub> exposure and pulmonary function  
23 effects are inconclusive with some new studies relating effects at higher exposure levels. The results  
24 from the CHS still remain as the definitive line of evidence. Other cross-sectional studies provide  
25 mixed results.

26 The 2006 O<sub>3</sub> AQCD states that the extensive human clinical and animal toxicological  
27 evidence, together with the limited epidemiologic evidence available, suggests a causal role for O<sub>3</sub> in  
28 inflammatory responses in the airways. Though the majority of recent studies focus on short-term  
29 exposures, several epidemiologic and toxicology studies of long-term exposure add to observations  
30 of O<sub>3</sub>-induced inflammation and injury. Toxicological studies in rodents and non-human primates  
31 indicate that chronic O<sub>3</sub> exposure causes structural changes in the respiratory tract, and simulated  
32 seasonal exposure studies suggest that such exposures might have cumulative impacts. The strongest  
33 epidemiologic evidence for a relationship between long-term O<sub>3</sub> exposure and respiratory morbidity  
34 is provided by new studies that demonstrate associations between long-term measures of O<sub>3</sub>  
35 exposure and new-onset asthma in children and increased respiratory symptom effects in asthmatics.  
36 While there are currently a limited number of studies in this data base, these U.S. multi-community  
37 prospective cohort studies are methodologically rigorous epidemiology studies. Asthma risk is

1 related to the important relationships between genetic variability, environmental O<sub>3</sub> exposure, and  
2 behavior. These relationships are complex. The genes, evaluated in these studies, are both key  
3 candidates in the oxidative stress pathway and have been shown to play an important role in asthma  
4 development. Reduced risk for asthma development is reported in some studies in children living in  
5 low- O<sub>3</sub> communities. Ozone levels in the studies (10:00 a.m. to 6:00 p.m.) ranged from 28.6 to  
6 45.5 ppb in low O<sub>3</sub> communities (mean = 38.4 ppb) and from 46.5 to 64.9 ppb in high O<sub>3</sub>  
7 communities (mean = 55.2 ppb). Other studies in the new data base provide coherent evidence for  
8 long-term O<sub>3</sub> exposure and respiratory morbidity effects such as first asthma hospitalization and  
9 respiratory symptoms in asthmatics. Studies considering other pollutants provide data suggesting  
10 that the effects related to O<sub>3</sub> are independent from potential effects of the other pollutants. Some  
11 studies provide evidence for a positive concentration-response relationship. The above discussion of  
12 the recent epidemiologic and toxicological data base provides a compelling case to support the  
13 hypothesis that a relationship exists between long-term exposure to ambient O<sub>3</sub> and measures of  
14 respiratory morbidity. The 2006 O<sub>3</sub> AQCD concluded the evidence was suggestive but inconclusive  
15 at that time. The new epidemiological data base, combined with toxicological studies in rodents and  
16 non-human primates, provides biologically plausible evidence that **there is likely to be causal**  
17 **relationship between long-term exposure to O<sub>3</sub> and respiratory morbidity.**

## 7.3. Cardiovascular Effects

### 7.3.1. Cardiovascular Disease

#### 7.3.1.1. Cardiovascular Epidemiology

18 Long-term exposure to O<sub>3</sub> and its effects on cardiovascular morbidity were not considered in  
19 the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). However, recent studies have assessed the chronic  
20 effects of O<sub>3</sub> exposure on cardiovascular morbidity (Chen et al., 2007, [145956](#); Chuang et al., 2011,  
21 [670846](#); Forbes et al., 2009, [190351](#)). The association between O<sub>3</sub> exposure and markers of lipid  
22 peroxidation and antioxidant capacity was examined among 120 nonsmoking healthy college  
23 students, aged 18-22 years, from the University of California, Berkeley (Feb-Jun 2002) (Chen et al.,  
24 2007, [145956](#)). By design, students were chosen that had experienced different geographic levels of  
25 O<sub>3</sub> over their lifetimes and during recent summer vacation in either greater Los Angeles (LA) or the  
26 San Francisco Bay Area (SF). A marker of lipid peroxidation, 8-isoprostane (8-iso-PGF) in plasma,  
27 was assessed. This marker is formed continuously under normal physiological conditions but has  
28 been found at elevated concentrations in response to environmental exposures. A marker of overall  
29 antioxidant capacity, ferric reducing ability of plasma (FRAP), was also measured. The lifetime O<sub>3</sub>  
30 exposure estimates (estimated monthly average, ppb) did not show much overlap between the two  
31 geographic areas [median (range): LA, 42.9 (28.5-65.3); SF, 26.9 (17.6-33.5)]. Estimated lifetime O<sub>3</sub>  
32 exposure was related to 8-iso-PGF [ $\beta = 0.025$  (pg/mL)/8-h ppb O<sub>3</sub>,  $p = 0.0007$ ]. For the 17-ppb

1 cumulative lifetime O<sub>3</sub> exposure difference between LA and SF participants, there was a  
2 17.41-pg/mL (95% CI: 15.43, 19.39) increase in 8-iso-PGF. No evidence of association was  
3 observed between lifetime O<sub>3</sub> exposure and FRAP [ $\beta$  = -2.21 (pg/mL)/8-h ppb O<sub>3</sub>, p = 0.45]. The  
4 authors note that O<sub>3</sub> was highly correlated with PM<sub>10-2.5</sub> and NO<sub>2</sub> in this study population; however,  
5 their inclusion in the O<sub>3</sub> models did not substantially modify the magnitude of the associations with  
6 O<sub>3</sub>. Because the lifetime exposure results were supported by shorter-term exposure results from  
7 analyses considering O<sub>3</sub> concentrations up to 30 days prior to sampling, the authors conclude that  
8 persistent exposure to O<sub>3</sub> can lead to sustained oxidative stress and increased lipid peroxidation.  
9 However, because there was not much overlap in lifetime O<sub>3</sub> exposure estimates between LA and SF,  
10 it is possible that the risk estimates involving the lifetime O<sub>3</sub> exposures could be confounded by  
11 unmeasured factors related to other differences between the two cities.

12 Forbes et al. (2009, [190351](#)) used the annual average exposures to assess the relationship  
13 between chronic ambient air pollution and levels of fibrinogen and C-reactive protein (CRP) in a  
14 cross-sectional study conducted in England. Data were collected from the Health Survey of England  
15 for 1994, 1998, and 2003. The sampling strategy was designed to obtain a representative sample of  
16 the English population; however, due to small group sizes, only data from white ethnic groups were  
17 analyzed. For analyses, the annual concentrations of O<sub>3</sub> were averaged for the year of data collection  
18 and the previous year with the exception of 1994 (because pollutant data were not available for  
19 1993). Median O<sub>3</sub> concentrations were 26.7 ppb, 25.4 ppb, and 28 ppb for 1994, 1998, and 2003,  
20 respectively. Year specific adjusted effect estimates were created and combined in a meta-analysis.  
21 No evidence of association was observed for O<sub>3</sub> and levels of fibrinogen or CRP (e.g., the combined  
22 estimates for the percent change in fibrinogen and CRP for a 10 ppb increase in O<sub>3</sub> were -0.28 [95%  
23 CI: -2.43, 1.92] and -3.05 [95% CI: -16.10, 12.02], respectively). Further research will be important  
24 for understanding the effects, if any, of chronic O<sub>3</sub> exposure on cardiovascular morbidity risk.

25 A study was performed in Taiwan to examine the association between long-term O<sub>3</sub>  
26 concentrations and blood pressure and blood markers using the Social Environment and Biomarkers  
27 of Aging Study (SEBAS) (Chuang et al., 2011, [670846](#)). Individuals included in the study were  
28 54 years of age and older. The mean annual O<sub>3</sub> concentration during the study period was 22.95 ppb  
29 (SD 6.76 ppb). Positive associations were observed between O<sub>3</sub> concentrations and both systolic and  
30 diastolic blood pressure [changes in systolic and diastolic blood pressure were 21.51mmHg (95% CI:  
31 16.90, 26.13) and 20.56 mmHg (95% CI: 18.14, 22.97) per 8.95 ppb increase in O<sub>3</sub>, respectively].  
32 Increased O<sub>3</sub> concentrations were also associated with increased levels of total cholesterol, fasting  
33 glucose, hemoglobin A1c, and neutrophils. No associations were observed between O<sub>3</sub>  
34 concentrations and triglyceride and IL-6 levels. The observed associations were reduced when other  
35 pollutants were added to the models.

### 7.3.1.2. Long-Term Cardiovascular Toxicology

36 Three new studies have investigated the cardiovascular effects of long-term exposure to O<sub>3</sub> in  
37 animal models. In addition to the short-term effects described in Section 6.3.1, a recent study found

1 that ApoE<sup>-/-</sup> mice (6-14 weeks old) exposed to O<sub>3</sub> (0.5 ppm) for 8 weeks (5 days/week, 8 h/day) had  
2 enhanced aortic atherosclerotic lesion area compared to air exposed controls (Chuang et al., 2009,  
3 [197202](#)). Chuang et al. (2009, [197202](#)) not only provided evidence for increased atherogenesis in  
4 susceptible mice, but also reported an elevated vascular inflammatory and redox state in wild-type  
5 mice and infant primates (Section 6.3.1). This study is compelling in that it identifies biochemical  
6 and cellular events responsible for transducing the airway epithelial reactions of O<sub>3</sub> into  
7 proinflammatory responses that are apparent in the extrapulmonary vasculature (Cole and Freeman,  
8 2009, [597507](#)).

9 Another recent study provides further evidence for increased vascular inflammation and  
10 oxidation and long term effects in the extrapulmonary space. Rats episodically exposed to O<sub>3</sub>  
11 (0.4 ppm) for 16 weeks (5 h/day, 1 day/week) presented marked increases in gene expression of  
12 biomarkers of oxidative stress, thrombosis, vasoconstriction, and proteolysis (Kodavanti et al., In  
13 Press, [666323](#)). Ozone exposure upregulated aortic mRNA expression of heme oxygenase-1 (HO-1),  
14 tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor  
15 (vWf), thrombomodulin, endothelial nitric oxide synthase (eNOS), endothelin-1 (ET-1), matrix  
16 metalloprotease-2 (MMP-2), matrix metalloprotease-3 (MMP-3), and tissue inhibitor of matrix  
17 metalloprotease-2 (TIMP-2). In addition, O<sub>3</sub> exposure depleted some cardiac mitochondrial  
18 phospholipid fatty acids (C16:0 and C18:1), which may be the result of oxidative modifications. The  
19 authors speculate that oxidatively modified lipids and proteins produced in the lung and heart  
20 promote vascular pathology through activation of lectin-like oxidized-low density lipoprotein  
21 receptor-1 (LOX-1). Activated LOX-1 induces expression of a number of the biomarkers induced by  
22 O<sub>3</sub> exposure and is considered pro-atherogenic. Both LOX-1 mRNA and protein were increased in  
23 mouse aorta after O<sub>3</sub> exposure. This study provides a possible pathway and further support to the  
24 observed O<sub>3</sub> induced atherosclerosis.

25 Vascular occlusion resulting from atherosclerosis can block blood flow through vessels  
26 causing ischemia. The restoration of blood flow or reperfusion can cause injury to the tissue from  
27 subsequent inflammation and oxidative damage. Ozone exposure (0.8 ppm for 28 or 56 days)  
28 enhanced the sensitivity to myocardial ischemia-reperfusion (I/R) injury in Sprague-Dawley rats  
29 while increasing oxidative stress levels and pro-inflammatory mediators and decreasing production  
30 of anti-inflammatory proteins (Perepu et al., 2010, [385020](#)). Both long- and short-term O<sub>3</sub> exposure  
31 decreased the left ventricular developed pressure, rate of change of pressure development, and rate  
32 of change of pressure decay and increased left ventricular end diastolic pressure in isolated perfused  
33 hearts. In this ex vivo heart model, O<sub>3</sub> induced oxidative stress by decreasing SOD enzyme activity  
34 and increasing malondialdehyde levels. Ozone also elicited a proinflammatory state evident by an  
35 increase in TNF- $\alpha$  and a decrease in the anti-inflammatory cytokine IL-10. The authors conclude that  
36 O<sub>3</sub> exposure will result in a greater I/R injury.

### 7.3.2. Cardiac Mortality

1 A limited number of epidemiologic studies have assessed the relationship between long-term  
2 exposure to O<sub>3</sub> and mortality. The 2006 O<sub>3</sub> AQCD concluded that an insufficient amount of evidence  
3 existed “to suggest a causal relationship between chronic O<sub>3</sub> exposure and increased risk for  
4 mortality in humans” (U.S. EPA, 2006, [088089](#)). Though total and cardio-pulmonary mortality were  
5 considered in these studies, cardiovascular mortality was not specifically considered. In the most  
6 recent follow-up analysis of the ACS cohort (Jerrett et al., 2009, [194160](#)), cardiopulmonary deaths  
7 were subdivided into respiratory and cardiovascular, separately, as opposed to combined in the Pope  
8 et al. (2002, [024689](#)) work. A 10-ppb increment in exposure to O<sub>3</sub> elevated the risk of death from the  
9 cardiopulmonary, cardiovascular, and ischemic heart disease. Inclusion of PM<sub>2.5</sub> as a co-pollutant  
10 attenuated the association with exposure to O<sub>3</sub> for all of the cardiovascular endpoints to become null.

### 7.3.3. Summary and Causal Determination

11 Previous AQCDs did not address the cardiovascular effects of long-term O<sub>3</sub> exposure due to  
12 limited data availability. The evidence remains limited; however the emerging data is supportive of a  
13 role for O<sub>3</sub> in chronic cardiovascular diseases. Few epidemiologic studies have investigated  
14 cardiovascular morbidity after long-term O<sub>3</sub> exposure, and the majority only assessed cardiovascular  
15 disease related biomarkers. A study on O<sub>3</sub> and cardiovascular mortality reported no association after  
16 adjustment for PM<sub>2.5</sub> levels. Further epidemiologic studies on cardiovascular morbidity and mortality  
17 after long-term exposure have not been published.

18 Toxicological evidence on long-term O<sub>3</sub> exposure is also limited but three strong toxicological  
19 studies have been published since the previous AQCD. These studies provide evidence for O<sub>3</sub>  
20 enhanced atherosclerosis and I/R injury, corresponding with development of a systemic oxidative,  
21 proinflammatory environment. Although questions exist for how O<sub>3</sub> inhalation causes systemic  
22 effects, a recent study proposes a mechanism for development of vascular pathology that involves  
23 activation of LOX-1 by O<sub>3</sub> oxidized lipids and proteins. This activation may also be responsible for  
24 O<sub>3</sub> induced changes in genes involved in proteolysis, thrombosis, and vasoconstriction. Taking into  
25 consideration the positive toxicological studies reported, the generally limited body of evidence **is**  
26 **suggestive of a causal relationship between relevant long-term exposures to O<sub>3</sub> and**  
27 **cardiovascular effects.**

## 7.4. Reproductive and Developmental Effects

28 Although the body of literature is growing, the research focusing on adverse birth outcomes is  
29 limited when compared to the numerous studies that have examined the more well-established health  
30 effects of air pollution. Among this small number of studies, various measures of birth weight and  
31 fetal growth, such as low birth weight (LBW), small for gestational age (SGA), and intrauterine

1 growth restriction (IUGR), and preterm birth (<37-week gestation; [PTB]) have received more  
2 attention in air pollution research, while congenital malformations are less studied.

3 Infants and fetal development processes may be particularly vulnerable to O<sub>3</sub> exposure, and  
4 although the physical mechanisms are not fully understood, several hypotheses have been proposed  
5 involving direct effects on fetal health, altered placenta function, or indirect effects on the mother's  
6 health (Bracken et al., 2003, [156288](#); Clifton et al., 2001, [156360](#); Maisonet et al., 2004, [156725](#);  
7 Schatz et al., 1990, [156073](#); Sram et al., 2005, [087442](#)). Study of these outcomes can be difficult  
8 given the need for detailed exposure data and potential residential movement of mothers during  
9 pregnancy. Air pollution epidemiologic studies reviewed in the 2006 O<sub>3</sub> AQCD examined impacts on  
10 birth-related endpoints, including intrauterine, perinatal, postneonatal, and infant deaths; premature  
11 births; intrauterine growth retardation; very low birth weight (weight <1,500 grams) and low birth  
12 weight (weight <2,500 grams); and birth defects. However, in the limited number of studies that  
13 investigated O<sub>3</sub>, no associations were found between O<sub>3</sub> and birth outcomes, with the possible  
14 exception of birth defects.

15 Two recent articles have reviewed methodological issues relating to the study of outdoor air  
16 pollution and adverse birth outcomes (Ritz and Wilhelm, 2008, [156914](#); Slama et al., 2008, [156985](#)).  
17 Some of the key challenges to interpretation of these study results include the difficulty in assessing  
18 exposure as most studies use existing monitoring networks to estimate individual exposure to  
19 ambient air pollution; the inability to control for potential confounders such as other risk factors that  
20 affect birth outcomes (e.g., smoking); evaluating the exposure window (e.g., trimester) of  
21 importance; and limited evidence on the physiological mechanism of these effects (Ritz and  
22 Wilhelm, 2008, [156914](#); Slama et al., 2008, [156985](#)). Although early animal studies (Kavlock et al.,  
23 1980, [094043](#)) found that exposure to O<sub>3</sub> in the late gestation of pregnancy in rats led to some  
24 abnormal reproductive performances for neonates, to date human studies have reported inconsistent  
25 results for the association of ambient O<sub>3</sub> on birth outcomes.

### 7.4.1. Effects on Sperm

26 A limited amount of research has been conducted to examine the association between air  
27 pollution and male reproductive outcomes, specifically semen quality. To date, the epidemiologic  
28 studies have considered various exposure durations before semen collection that encompass either  
29 the entire period of spermatogenesis (i.e., 90 days) or key periods of sperm development that  
30 correspond to epididymal storage, development of sperm motility, and spermatogenesis. In an  
31 analysis conducted as part of the Teplice Program, 18-year-old men residing in the heavily polluted  
32 district of Teplice in the Czech Republic were found to be at greater risk of having abnormalities in  
33 sperm morphology and chromatin integrity than men of similar age residing in Prachatice, a less  
34 polluted district (Selevan et al., 2000, [012578](#); Sram et al., 1999, [078127](#)). A follow-up longitudinal  
35 study conducted on a subset of the same men from Teplice revealed associations between total  
36 episodic air pollution and abnormalities in sperm chromatin (Rubes et al., 2005, [078091](#)). A  
37 limitation of these studies is that they did not identify specific pollutants and their concentrations.

1 More recent epidemiologic studies conducted in the U.S. have also reported associations  
2 between ambient air pollution and sperm quality for individual air pollutants, including O<sub>3</sub> and  
3 PM<sub>2.5</sub>. In a repeated measures study in Los Angeles, CA, Sokol et al. (2006, [098539](#)) reported a  
4 reduction in average sperm concentration during three exposure windows (0-9, 10-14, and  
5 70-90 days before semen collection) associated with high ambient levels of O<sub>3</sub> in healthy sperm  
6 donors. This effect persisted under a joint additive model for O<sub>3</sub>, CO, NO<sub>2</sub> and PM<sub>10</sub>. The authors did  
7 not detect a reduction in sperm count. Hansen et al. (2010, [594438](#)) investigated the effect of  
8 exposure to O<sub>3</sub> and PM<sub>2.5</sub> on sperm quality in three southeastern counties (Wake County, NC; Shelby  
9 County, TN; Galveston County, TX). Outcomes included sperm concentration and count,  
10 morphology, DNA integrity and chromatin maturity. Overall, the authors found both protective and  
11 adverse effects, although some results suggested adverse effects on sperm concentration, count and  
12 morphology. There was evidence of an association between decreased sperm concentration and  
13 count with O<sub>3</sub>, though these associations were not statistically significant.

14 The biological mechanisms linking ambient air pollution to decreased sperm quality have yet  
15 to be determined, though O<sub>3</sub>-induced oxidative stress, inflammatory reactions, and the induction of  
16 the formation of circulating toxic species have been suggested as possible mechanisms (Sokol et al.,  
17 2006, [098539](#)). Decremental effects on testicular morphology have been demonstrated in  
18 toxicological studies with histological evidence of O<sub>3</sub>-induced depletion of germ cells in testicular  
19 tissue and decreased seminiferous tubule epithelial layer. Jedlinska-Krakowska et al. (2006, [195640](#))  
20 demonstrated histopathological evidence of impaired spermatogenesis (round spermatids/  
21 spermatocytes, giant spermatid cells, and focal epithelial desquamation with denudation to the  
22 basement membrane). The exposure protocol used five month old adult rats exposed to O<sub>3</sub> as adults  
23 (0.5 ppm, 5 h/day for 50 days). This degeneration could be rescued by vitamin E administration,  
24 indicating an antioxidant effect. Vitamin C administration had no effect at low doses of ascorbic acid  
25 and exacerbated the O<sub>3</sub>-dependent damage at high doses, as would be expected as vitamin C can be a  
26 radical generator instead of an antioxidant at higher doses. In summary, this study provided  
27 toxicological evidence of impaired spermatogenesis with O<sub>3</sub> exposure that was rescued with certain  
28 antioxidant supplementation.

29 Overall, there is limited epidemiologic evidence for an association with O<sub>3</sub> concentration and  
30 decreased sperm concentration. A recent toxicological study provides limited evidence for a possible  
31 biological mechanism (histopathology showing impaired spermatogenesis) for such an association.

## 7.4.2. Effects on Reproduction

32 Evidence suggests that exposure to air pollutants during pregnancy is associated with adverse  
33 birth outcomes, which has been attributed to the increased susceptibility of the fetus due to  
34 physiologic immaturity. Gametes (i.e., ova and sperm) may be even more vulnerable, especially  
35 outside of the human body, as occurs with assisted reproduction. Smokers require twice the number  
36 of in vitro fertilization (IVF) attempts to conceive as non-smokers (Feichtinger et al., 1997, [625251](#)),  
37 suggesting that a preconception exposure can be harmful to pregnancy. A recent study used an

1 established national-scale, log-normal kriging method to spatially estimate daily mean  
2 concentrations of criteria pollutants at addresses of women undergoing their first IVF cycle and at  
3 their IVF labs from 2000 to 2007 in the northeastern U.S. (Legro et al., 2010, [597377](#)). Increasing O<sub>3</sub>  
4 concentration at the patient's address was significantly associated with an increased chance of live  
5 birth during ovulation induction (OR 1.13, [95% CI: 1.05, 1.22] per 10 ppb increase), but with  
6 decreased odds of live birth when exposed from embryo transfer to live birth (OR 0.79, [95% CI:  
7 0.69, 0.90] per 10 ppb increase). After controlling for NO<sub>2</sub> in a co-pollutant model, however, O<sub>3</sub> was  
8 no longer significantly associated with IVF failure. The results of this study suggest that exposure to  
9 O<sub>3</sub> during ovulation was beneficial (perhaps due to early conditioning to O<sub>3</sub>), whereas later exposure  
10 to O<sub>3</sub> (e.g., during gestation) was detrimental, and reduced the likelihood of a live birth.

11 In toxicological studies, reproductive success in rats appears unaffected by O<sub>3</sub> exposure.  
12 Ozone administration (continuous 0.4, 0.8 or 1.2 ppm O<sub>3</sub>) to CD-1 mouse dams during the majority  
13 of pregnancy (PD7-17, which excludes the pre-implantation period), led to no adverse effects on  
14 reproductive success (proportion of successful pregnancies, litter size, sex ratio, frequency of still  
15 birth, or neonatal mortality) (Bignami et al., 1994, [076063](#)). There was a nearly statistically  
16 significant increase in pregnancy duration (0.8 and 1.2 ppm O<sub>3</sub>). Initially, dam body weight (0.8 and  
17 1.2 ppm), water consumption (0.4, 0.8 and 1.2 ppm O<sub>3</sub>) and food consumption (0.4, 0.8 and 1.2 ppm)  
18 during pregnancy were decreased with O<sub>3</sub> exposure but these deficits dissipated a week or two after  
19 the initial exposure (Bignami et al., 1994, [076063](#)). The anorexigenic effect of O<sub>3</sub> exposure on the  
20 pregnant dam appears to dissipate with time; the dams seem to adapt to the O<sub>3</sub> exposure. In males,  
21 data exist showing morphological evidence of altered spermatogenesis in O<sub>3</sub> exposed animals  
22 (Jedlinska-Krakowska et al. (2006, [195640](#)). Some evidence suggests that O<sub>3</sub> may affect  
23 reproductive success when combined with other chemicals. Kavlock et al. (1979, [039228](#)) showed  
24 that O<sub>3</sub> acted synergistically with sodium salicylate to increase the rate of pup resorptions after  
25 midgestational exposure (1.0 ppm O<sub>3</sub>, GD9-12). At low doses of O<sub>3</sub> exposure, toxicological studies  
26 show reproductive effects to include a transient anorexigenic effect of O<sub>3</sub> on gestational weight gain,  
27 and a synergistic effect of O<sub>3</sub> on salicylate-induced pup resorptions; other fecundity, pregnancy and  
28 gestation related outcomes appear unaffected by O<sub>3</sub> exposure. Collectively, there is very little  
29 epidemiologic evidence for the effect of O<sub>3</sub> on reproductive success, and the reproductive success in  
30 rats appears to be unaffected in toxicological studies of O<sub>3</sub> exposure.

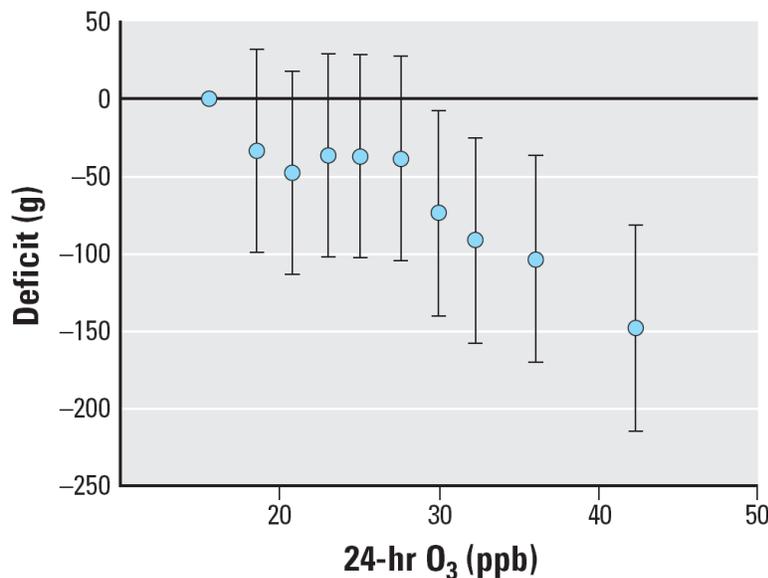
### 7.4.3. Birth Weight

31 With birth weight routinely collected in vital statistics and being a powerful predictor of infant  
32 mortality, it is the most studied outcome within air pollution-birth outcome research. Air pollution  
33 researchers have analyzed birth weight as a continuous variable and/or as a dichotomized variable in  
34 the form of LBW (<2,500 g [5 lbs, 8 oz]).

35 Birth weight is primarily determined by gestational age and intrauterine growth, but also  
36 depends on maternal, placental and fetal factors as well as on environmental influences. In both  
37 developed and developing countries, LBW is the most important predictor for neonatal mortality and

1 is a significant determinant of postneonatal mortality and morbidity. Recent studies report that  
2 infants who are smallest at birth have a higher incidence of diseases and disabilities, which continue  
3 into adulthood (Hack and Fanaroff, 1999, [625952](#)).

4 The strongest evidence for an effect of O<sub>3</sub> on birth weight comes from the Children’s Health  
5 Study conducted in southern California. In this study, Salam et al. (2005, [087885](#)) report that  
6 maternal exposure to O<sub>3</sub> averaged over the entire pregnancy was associated with reduced birth  
7 weight for 24-h avg (39.3 g decrease [95% CI: -55.8, -22.8] in birth weight per 10 ppb and 8-h avg  
8 (19.2-g decrease [95% CI: -27.7, -10.7] in birth weight per 10 ppb) O<sub>3</sub> concentrations. This effect  
9 was stronger for concentrations averaged over the second and third trimesters. PM<sub>10</sub>, NO<sub>2</sub> and CO  
10 concentrations averaged over the entire pregnancy were not statistically significantly associated with  
11 birth weight, though CO concentrations in the first trimester and PM<sub>10</sub> concentrations in the third  
12 trimester were associated with a decrease in birth weight. Additionally, the authors observed a  
13 concentration-response relationship of birth weight with 24-h avg O<sub>3</sub> concentrations averaged over  
14 the entire pregnancy that was clearest above the 30-ppb level (see Figure 7-4). Relative to the lowest  
15 decile of 24-h avg O<sub>3</sub>, estimates for the next 5 lowest deciles were approximately -40 g to -50 g, with  
16 no clear trend and with 95% confidence bounds that included zero. The highest four deciles of O<sub>3</sub>  
17 exposure showed an approximately linear decrease in birth weight, and all four 95% CIs excluded  
18 zero, and ranged from mean decreases of 74 grams to decreases of 148 grams.



Source: Salam et al. (2005, [087885](#))

**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. □ Deficits are plotted against the decile-group-specific median ozone exposure. Error bars represent 95% CIs. Indicator variables for each decile of ozone exposure (except the least-exposed group) were included in a mixed model.**

1 Several additional studies conducted in the U.S. and Canada also investigated the association  
2 between ambient O<sub>3</sub> concentrations and birth weight and found little evidence for an association.  
3 Morello-Frosch et al. (2010, [670076](#)) estimated ambient O<sub>3</sub> concentrations throughout pregnancy  
4 and for each trimester in the neighborhoods of women who delivered term singleton births between  
5 1996 and 2006 in California. A 10-ppb increase in O<sub>3</sub> averaged across the entire pregnancy was  
6 associated with a 5.7-g decrease (95% CI: -6.6, -4.9) in birth weight when exposures were calculated  
7 using monitors within 10 km of the maternal address at date of birth. When the distance from the  
8 monitor was restricted to 3 km, the decrease in birth weight associated with a 10-ppb increase in O<sub>3</sub>  
9 increased to 8.9 g (95% CI: -10.6, -7.1). These results persisted in co-pollutant models and in models  
10 that stratified by trimester of exposure, SES, and race. Chen et al. (2002, [024945](#)) used 8-h avg O<sub>3</sub>  
11 concentrations to create exposure variables based on average maternal exposure for each trimester.  
12 Ozone was not found to be related to birth weight in single-pollutant models, though the O<sub>3</sub> effect  
13 during the third trimester was borderline significant in a co-pollutant model with PM<sub>10</sub>. Wilhelm and  
14 Ritz (2005, [088668](#)) extended previous analyses of term LBW (Ritz and Yu, 1999, [086976](#); Ritz et  
15 al., 2000, [012068](#)) to include the period 1994-2000. The authors examined varying residential  
16 distances from monitoring stations to see if the distance affected risk estimation, exploring the  
17 possibility that effect attenuation may result from local pollutant heterogeneity inadequately captured  
18 by ambient monitors. As in their previous studies, the authors observed associations between  
19 elevated concentrations of CO and PM<sub>10</sub> both early and late in pregnancy and risk of term LBW.  
20 After adjusting for CO and/or PM<sub>10</sub> the authors did not observe associations between O<sub>3</sub> and term  
21 LBW in any of their models. Brauer et al. (2008, [156292](#)) evaluated the impacts of air pollution (CO,  
22 NO<sub>2</sub>, NO, O<sub>3</sub>, SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>) on birth weight for the period 1999-2002 using spatiotemporal  
23 residential exposure metrics by month of pregnancy in Vancouver, BC. Quantitative results were not  
24 presented for the association between O<sub>3</sub> and LBW, though the authors observed associations that  
25 were largely protective. Dugandzic et al. (2006, [088681](#)) examined the association between LBW  
26 and ambient levels of air pollutants by trimester of exposure among a cohort of term singleton births  
27 from 1988-2000. Though there was some indication of an association with SO<sub>2</sub> and PM<sub>10</sub>, there were  
28 no effects for O<sub>3</sub>.

29 Similarly, studies conducted in Australia, Latin America, and Asia report limited evidence for  
30 an association between ambient O<sub>3</sub> and measures of birth weight. In Sydney, Australia, Mannes et al.  
31 (2005, [087895](#)) found that O<sub>3</sub> concentrations in the second trimester of pregnancy had small adverse  
32 effects on birth weight (7.5-g decrease; [95 % CI: -13.8, 1.2] per 10 ppb), though this effect  
33 disappeared when the analysis was limited to births with a maternal address within 5 km of a  
34 monitoring station (87.7-g increase; [95% CI: 10.5, 164.9] per 10 ppb). Hansen et al. (2007, [090703](#))  
35 reported that trimester and monthly specific exposures to all pollutants were not statistically  
36 significantly associated with a reduction in birth weight in Brisbane, Australia. In Sao Paulo, Brazil,  
37 Gouveia et al. (2004, [055613](#)) found that O<sub>3</sub> exhibited a small inverse relation with birth weight over  
38 the third trimester (6.0-g decrease; [95% CI: -30.8, 18.8] per 10 ppb). Lin et al. (2004, [089503](#))  
39 reported a positive, though not statistically significant, exposure-response relationship for O<sub>3</sub> during

1 the entire pregnancy in a Taiwanese study. In a study performed in Korea, Ha et al. (2001, [019390](#))  
 2 reported no O<sub>3</sub> effect during the first trimester of pregnancy, but they found that during the third  
 3 trimester of pregnancy O<sub>3</sub> was associated with LBW (RR 1.05 [95% CI: 1.02, 1.08] per 10 ppb).

**Table 7-2. Brief summary of epidemiologic studies of birth weight**

Study	Location Sample Size	Mean O <sub>3</sub> (ppb)	Exposure assessment	Effect Estimate (95% CI)
Salam et al. (2005, <a href="#">087885</a> )	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, <a href="#">670076</a> )	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)
Chen et al. (2002, <a href="#">024945</a> )	northern Nevada, US (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, <a href="#">088668</a> )	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, <a href="#">156292</a> )	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, <a href="#">088681</a> )	Nova Scotia, Canada (n=74,284)	24-h avg: 21	Nearest Monitor (within 25 km)	T1: 0.97 (0.81, 1.18) T2: 1.06 (0.87, 1.27) T3: 1.01 (0.83-1.24)
Mannes et al. (2005, <a href="#">087895</a> )	Sydney, Australia (n=138,056)	1-h max: 31.6	City-wide 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, <a href="#">090703</a> )	Brisbane, Australia (n=26,617)	8 h max: 26.7	City-wide 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, <a href="#">055613</a> )	Sao Paulo, Brazil (n=179,460)	1-h max: 31.5	City-wide 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. (2004, <a href="#">089503</a> )	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) <sup>^</sup> T1: 1.02 (0.85, 1.22) <sup>^</sup> T2: 0.93 (0.78, 1.12) <sup>^</sup> T3: 1.05 (0.87, 1.26) <sup>^</sup>
Ha et al. (2001, <a href="#">019390</a> )	Seoul, Korea (n=276,763)	8-h avg: 22.4-23.3 <sup>*</sup>	City-wide avg	T1: 0.87 (0.81, 0.94) <sup>+</sup> T3: 1.05 (1.02, 1.08) <sup>+</sup>

\*Median

# Change in birthweight per 10 ppb change in O<sub>3</sub>

<sup>^</sup>Odds ratios of LBW; Highest quartile of exposure compared to lowest quartile of exposure

<sup>+</sup>Relative risk of LBW per 10 ppb change in O<sub>3</sub>

T1 = First Trimester, T2 = Second Trimester, T3 = Third Trimester

NR: No quantitative results reported

4 Table 7-2 provides a brief overview of the epidemiologic studies of birth weight. In summary,  
 5 only the Children's Health Study conducted in southern California (Salam et al., 2005, [087885](#))  
 6 provides strong evidence for an effect of ambient O<sub>3</sub> on birth weight. The study by Morello-Frosch

1 et al. (2010, [670076](#)), also conducted in California, provides support for the results of the Children's  
2 Health Study. Additional studies conducted in the U.S., Canada, Australia, Latin America, and Asia  
3 provide limited and inconsistent evidence to support the effect reported in the Children's Health  
4 Study. The toxicological literature on the effect of O<sub>3</sub> on birth weight is sparse. In some studies, the  
5 reporting of birth weight may be avoided because birth weight can be confounded by decreased litter  
6 size resulting from an increased rate of pup resorption (aborted pups) in O<sub>3</sub> exposed dams. In one  
7 toxicological study by Haro and Paz (1993, [044194](#)), no differences in litter size were observed and  
8 decreased birth weight in pups from dams who were exposed to 1ppm O<sub>3</sub> during pregnancy was  
9 reported.

#### 7.4.4. Preterm Birth

10 Preterm birth (PTB) is a syndrome (Romero et al., 2006, [625253](#)) that is characterized by  
11 multiple etiologies. It is therefore unusual to be able to identify an exact cause for each PTB. In  
12 addition, PTB is not an adverse outcome in itself, but an important determinant of health status (i.e.,  
13 neonatal morbidity and mortality). Although some overlap exists for common risk factors, different  
14 etiologic entities related to distinct risk factor profiles and leading to different neonatal and  
15 postneonatal complications are attributed to PTB and measures of fetal growth. Although both  
16 restricted fetal growth and PTB can result in LBW, prematurity does not have to result in LBW or  
17 growth restricted babies.

18 A major issue in studying environmental exposures and preterm birth is selecting the relevant  
19 exposure period, since the biological mechanisms leading to preterm birth and the critical periods of  
20 vulnerability are poorly understood (Bobak, 2000, [011448](#)). Exposures proximate to the birth may be  
21 most relevant if exposure causes an acute effect. However, exposure occurring in early gestation  
22 might affect placentation, with results observable later in pregnancy, or cumulative exposure during  
23 pregnancy may be the most important determinant. The studies reviewed have dealt with this issue in  
24 different ways. Many have considered several exposure metrics based on different periods of  
25 exposure. Often the time periods used are the first month (or first trimester) of pregnancy and the  
26 last month (or 6 weeks) prior to delivery. Using a time interval prior to delivery introduces an  
27 additional problem since cases and controls are not in the same stage of development when they are  
28 compared. For example, a preterm infant delivered at 36 weeks is a 32-week fetus 4 weeks prior to  
29 birth, while an infant born at term (40 weeks) is a 36-week fetus 4 weeks prior to birth.

30 Recently, investigators have examined the association of PTB with both short- and long-term  
31 exposure periods. Time-series studies have been used to examine the association between air  
32 pollution concentrations during the days immediately preceding birth. An advantage of these time-  
33 series studies is that this approach can remove the influence of covariates that vary across individuals  
34 over a short period of time. Retrospective cohort and case-control studies have been used to examine  
35 long-term exposure periods, often averaging air pollution concentrations over months or trimesters  
36 of pregnancy.

1           Reported studies fail to show consistency in pollutants and periods during pregnancy where an  
2 effect occurs. For example, while some studies find the strongest effects associated with exposures  
3 early in pregnancy, others report effects when the exposure is limited to the second or third trimester.  
4 However, the effect of air pollutant exposure during pregnancy on PTB has a biological basis. There  
5 is an expanding list of possible mechanisms that may explain the association between O<sub>3</sub> exposure  
6 and PTB. These include: decreased in utero oxygen supply leading to a reduction of oxygen carrying  
7 capacity; changes in blood viscosity and disturbances of uterine blood flow; genetic mutations in  
8 first trimester leading to placental abnormalities; complex vascular alterations leading to placental  
9 abnormalities; disrupted implantation and placentation and suboptimal placental function; acute or  
10 sustained inflammatory response; disturbances of the pituitary-adrenocortico-placental system; and  
11 increased maternal susceptibility to infections.

12           Many studies of PTB compare exposure in quartiles, using the lowest quartile as the reference  
13 (or control) group. No studies use a truly unexposed control group. If exposure in the lowest quartile  
14 confers risk, than it may be difficult to demonstrate additional risk associated with a higher quartile.  
15 Thus negative studies must be interpreted with caution.

16           Preterm birth occurs both naturally (*idiopathic preterm*), and as a result of medical  
17 intervention (*iatrogenic preterm*). Ritz et al. (2000, [012068](#); 2007, [096146](#)) excluded all births by  
18 Cesarean section to limit their studies to idiopathic preterm. No other studies attempted to  
19 distinguish the type of preterm birth, although air pollution exposure maybe associated with only one  
20 type. This is a source of potential effect misclassification.

21           A number of air pollution-birth outcome studies have investigated the possible association  
22 between PTB and maternal exposure to O<sub>3</sub>. Most recently, Darrow et al. (2009, [195818](#)) used vital  
23 record data to construct a retrospective cohort of 476,489 births occurring between 1994 and 2004 in  
24 5 central counties of metropolitan Atlanta. Using a time-series approach, the authors examined  
25 aggregated daily counts of preterm birth in relation to ambient levels of CO, NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>,  
26 PM<sub>2.5</sub> and speciated PM measurements. This study investigated 3 gestational windows of exposure:  
27 the first month of gestation, the final week of gestation, and the final 6 weeks of gestation. The  
28 authors did not observe associations of preterm birth with O<sub>3</sub>.

29           A number of U.S. studies were conducted in southern California, and report somewhat  
30 inconsistent results. Ritz et al. (2000, [012068](#)) evaluated the effect of air pollution (CO, NO<sub>2</sub>, O<sub>3</sub>,  
31 PM<sub>10</sub>) exposure during pregnancy on the occurrence of PTB in a cohort of 97,518 neonates born in  
32 southern California between 1989 and 1993. The authors averaged pollutant measures taken at the  
33 closest air-monitoring station over distinct periods, such as 1, 2, 4, 6, 8, 12, and 26 weeks before  
34 birth and the whole pregnancy period. Additionally, they calculated average exposures for the first  
35 and second months of pregnancy. The authors found no consistent effects for O<sub>3</sub> over any of the  
36 pregnancy periods in single or multi-pollutant models. Wilhelm and Ritz (2005, [088668](#)) extended  
37 previous analyses of PTB (Ritz and Yu, 1999, [086976](#); Ritz et al., 2000, [012068](#)) in California to  
38 include 1994-2000. The authors examined varying residential distances from monitoring stations to  
39 see if the distance affected risk estimation, because effect attenuation may result from local pollutant

1 heterogeneity inadequately captured by ambient monitors. The authors analyzed the association  
2 between O<sub>3</sub> exposure during varying periods of pregnancy and PTB, finding a positive association  
3 between O<sub>3</sub> levels in both the first trimester of pregnancy (RR 1.23 [95% CI: 1.06, 1.42] per 10 ppb  
4 increase in 24-h avg O<sub>3</sub>) and the first month of pregnancy (results for first trimester exposure were  
5 similar, but slightly smaller, quantitative results not presented) in models containing all pollutants.  
6 No association was observed between O<sub>3</sub> in the 6 weeks before birth and preterm delivery. Finally,  
7 Ritz et al. (2007, [096146](#)) conducted a case-control survey nested within a birth cohort and assessed  
8 the extent to which residual confounding and exposure misclassification impacted air pollution effect  
9 estimates. The authors calculated mean exposure levels for three gestational periods: the entire  
10 pregnancy, the first trimester, and the last 6 weeks before delivery. Though positive associations  
11 were observed for CO and PM<sub>2.5</sub>, no consistent patterns of increase in the odds of preterm birth for  
12 O<sub>3</sub> or NO<sub>2</sub> were observed.

13 One study conducted in Canada evaluated the impacts of air pollution (including CO, NO<sub>2</sub>,  
14 NO, O<sub>3</sub>, SO<sub>2</sub>, PM<sub>2.5</sub>, and PM<sub>10</sub>) on preterm births (1999-2002) using spatiotemporal residential  
15 exposure metrics by month of pregnancy in Vancouver, BC (Brauer et al., 2008, [156292](#)). The  
16 authors did not observe consistent associations with any of the pregnancy average exposure metrics  
17 except for PM<sub>2.5</sub> for PTB. The O<sub>3</sub> associations were largely protective, and no quantitative results  
18 were presented for O<sub>3</sub>. Additionally, Lee et al. (2008, [195720](#)) used time-series techniques to  
19 investigate the short-term associations of O<sub>3</sub> and PTB in London, England. In addition to exposure  
20 on the day of birth, cumulative exposure up to 1 week before birth was investigated. The risk of  
21 preterm birth did not increase with exposure to the levels of ambient air pollution experienced by  
22 this population.

23 Conversely, two studies conducted in Australia and one from China do provide evidence for an  
24 association between ambient O<sub>3</sub> and PTB. Hansen et al. (2006, [089818](#)) reported that exposure to O<sub>3</sub>  
25 during the first trimester was associated with an increased risk of PTB (OR 1.38, [95% CI:  
26 1.14, 1.69] per 10 ppb increase). Although the test for trend was significant due to the strong effect  
27 in the highest quartile, there was not an obvious exposure-response pattern across the quartiles of O<sub>3</sub>  
28 during the first trimester. The effect estimate was diminished and lost statistical significance when  
29 PM<sub>10</sub> was included in the model (OR 1.23, [95% CI: 0.97, 1.59] per 10 ppb increase). Maternal  
30 exposure to O<sub>3</sub> during the 90 days prior to birth showed a weak, positive association with PTB (OR  
31 1.09, [95% CI: 0.85, 1.39] per 10 ppb increase). Jalaludin et al. (2007, [156601](#)) found that O<sub>3</sub> levels  
32 in the month and three months preceding birth had a statistically significant association with PTB.  
33 Ozone levels in the first trimester of pregnancy were associated with increased risks for PTBs (OR  
34 1.15 [95% CI: 1.05, 1.24] per 10 ppb increase in 1-h max O<sub>3</sub> concentration), and remained a  
35 significant predictor of preterm birth in co-pollutant models (ORs between 1.07 and 1.10). ORs  
36 increased for first month of pregnancy when restricted to within 5 km of a monitoring station (OR  
37 1.60, [95% CI: 1.27, 2.03]), but did not show a cumulative effect for first 3 months of pregnancy  
38 (OR 0.81, [95% CI: 0.67, 0.98]). Jiang et al. (2007, [093029](#)) examined the acute effect of air  
39 pollution on preterm birth, including risk in relation to levels of pollutants for a single day exposure

1 window with lags from 0 to 6 days before birth. An increase of 10 ppb of the 8-week average of O<sub>3</sub>  
 2 corresponded to 9.47 % (95% CI: 0.70, 18.7%) increase in PTBs. Increases in PTB were also  
 3 observed for PM<sub>10</sub>, SO<sub>2</sub>, and NO<sub>2</sub>. The authors did not observe any significant acute effect of  
 4 outdoor air pollution on PTB among the 1-day acute time windows examined in the week before  
 5 birth.

6 Little data is available from toxicological studies; one study reported a nearly statistically  
 7 significant increase in pregnancy duration in mice when exposed to 0.8 or 1.2 ppm O<sub>3</sub>. This  
 8 phenomenon was most likely due to the anorexigenic effect of relatively high O<sub>3</sub> concentrations  
 9 (Bignami et al., 1994, [076063](#)).

**Table 7-3. Brief summary of epidemiologic studies of PTB**

Study	Location Sample Size	Mean O <sub>3</sub> (ppb)	Exposure assessment	Effect Estimate# (95% CI)
Darrow et al. (2009, <a href="#">195818</a> )	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, <a href="#">012068</a> )	California, US (n=97,158)	8 h: 36.9	<2 mi of monitor	First month: NR Last 6 weeks: NR
Wilhelm and Ritz (2005, <a href="#">088668</a> )	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, <a href="#">096146</a> )	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, <a href="#">156292</a> )	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. (2008, <a href="#">195720</a> )	London, UK	24-h avg: NR	1 monitor	Lag 0: 1.00 (1.00, 1.01)
Hansen et al. (2006, <a href="#">089818</a> )	Brisbane, Australia (n=28,200)	8-h max: 26.7	City-wide avg	T1: 1.39 (1.15, 1.70) T3: 1.09 (0.88, 1.39)
Jalaludin et al. (2007, <a href="#">156601</a> )	Sydney, Australia (n=123,840)	1-h max: 30.9	City-wide avg and <5 km from monitor	First month: 1.604 (1.268, 2.030)* T1: 0.807 (0.668, 0.976)* T3: 1.011 (0.910, 1.124)* Last month: 0.984 (0.906, 1.069)*
Jiang et al. (2007, <a href="#">093029</a> )	Shanghai, China (n=3,346 preterm births)	8-h avg: 32.7	City-wide 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)

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#Relative risk of PTB per 10 ppb change in O<sub>3</sub>.  
\*Relative risk of PTB per 1 ppb change in O<sub>3</sub>.  
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

1 Table 7-3 provides a brief overview of the epidemiologic studies of PTB. In summary, the  
2 evidence is consistent when examining shorter-term, late-pregnancy exposure to O<sub>3</sub> and reports no  
3 association with PTB. However when long-term exposure to O<sub>3</sub> early in pregnancy is examined the  
4 results are inconsistent. Studies conducted in the U.S., Canada, and England find no association with  
5 O<sub>3</sub> and PTB, while studies conducted in Australia and China report an O<sub>3</sub> effect on PTB.

### 6

#### 7.4.5. Fetal Growth

7 Low birth weight has often been used as an outcome measure because it is easily available and  
8 accurately recorded on birth certificates. However, LBW may result from either short gestation, or  
9 inadequate growth in utero. Most of the studies investigating air pollution exposure and LBW  
10 limited their analyses to term infants to focus on inadequate growth. A number of studies were  
11 identified that specifically addressed growth restriction in utero by identifying infants who failed to  
12 meet specific growth standards. Usually these infants had birth weight less than the 10th percentile  
13 for gestational age, using an external standard. Many of these studies have been previously  
14 discussed, since they also examined other reproductive outcomes (i.e., LBW or PTB).

15 A limitation of environmental studies that use birth weight as a proxy measure of fetal growth  
16 is that patterns of fetal growth during pregnancy cannot be assessed. This is particularly important  
17 when investigating pollutant exposures during early pregnancy as birth weight is recorded  
18 many months after the exposure period. The insult of air pollution may have a transient effect on  
19 fetal growth, where growth is hindered at one point in time but catches up at a later point. For  
20 example, maternal smoking during pregnancy can alter the growth rate of individual body segments  
21 of the fetus at variable developmental stages, as the fetus experiences selective growth restriction  
22 and augmentation (Lampl and Jeanty, 2003, [625252](#)).

23 Fetal growth is influenced by maternal, placental, and fetal factors. The biological mechanisms  
24 by which air pollutants may influence the developing fetus remain largely unknown. Several  
25 mechanisms have been proposed, including maternal susceptibility to infection, oxidative stress,  
26 hematological factors such as blood viscosity, and the direct effect of specific pollutants on fetal  
27 development or on DNA and its transcription. Air pollution may affect maternal respiratory function  
28 or general health, which may in turn impair uteroplacental and umbilical blood flow, transplacental  
29 glucose, and total insulin, all of which are important determinants of fetal growth. Additionally,  
30 certain changes resulting in fetal growth retardation may occur in early pregnancy (around the time  
31 of implantation) caused by an abnormal reaction between the trophoblast and uterine tissues. A  
32 defective trophoblast invasion, resulting in suboptimal placentation and maternal hemodynamic  
33 maladaptation can alter growth and development of the fetus. Inhalation of air pollution can cause  
34 inflammatory responses and oxidative stress, and both of these reactions can interfere with normal

1 intrauterine growth via vascular dysfunction in the placenta and damaged DNA. Also, pro-  
2 inflammatory cytokines can limit trophoblast invasion during the early stages of pregnancy,  
3 restricting fetal growth. Poor placental vascularity is caused partly by dysregulation of gene  
4 expression in key angiogenic factors in early pregnancy, and if ambient air pollution is associated  
5 with poor placental function it may partly be caused by perturbed DNA transcription early in  
6 pregnancy.

7 The terms small-for-gestational-age (SGA), which is defined as a birth weight <10th percentile  
8 for gestational age (and often sex and/or race), and intrauterine growth retardation (IUGR) are often  
9 used interchangeably. However, this definition of SGA does have limitations. For example, using it  
10 for IUGR may overestimate the percentage of “growth-restricted” neonates as it is unlikely that 10%  
11 of neonates have growth restriction (Wollmann, 1998, [193812](#)). On the other hand, when the 10th  
12 percentile is based on the distribution of live births at a population level, the percentage of SGA  
13 among PTB is most likely underestimated (Hutcheon and Platt, 2008, [193795](#)). Nevertheless, SGA  
14 represents a statistical description of a small neonate, whereas the term IUGR is reserved for those  
15 with clinical evidence of abnormal growth. Thus all IUGR neonates will be SGA, but not all SGA  
16 neonates will be IUGR (Wollmann, 1998, [193812](#)). In the following section the terms SGA and  
17 IUGR are referred to as each cited study used the terms.

18 Over the past decade a number of studies examined various metrics of fetal growth restriction.  
19 Salam et al. (2005, [087885](#)) assessed the effect of increasing O<sub>3</sub> concentrations on IUGR in a  
20 population of infants born in California from 1975-1987 as part of the Children’s Health Study. The  
21 authors reported that maternal O<sub>3</sub> exposures averaged over the entire pregnancy and during the third  
22 trimester were associated with increased risk of IUGR. A 10-ppb difference in 24-h maternal O<sub>3</sub>  
23 exposure during the third trimester increased the risk of IUGR by 11% (95% CI: 0, 20%). Brauer et  
24 al. (2008, [156292](#)) evaluated the impacts of air pollution (CO, NO<sub>2</sub>, NO, O<sub>3</sub>, SO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub>) on  
25 SGA (1999-2002) using spatiotemporal residential exposure metrics by month of pregnancy in  
26 Vancouver, BC. The O<sub>3</sub> associations were largely protective (OR= 0.87, [95% CI: 0.81, 0.93] for a  
27 10 ppb increase in inverse distance weighted SGA), and no additional quantitative results were  
28 presented for O<sub>3</sub>. Liu et al. (2007, [090429](#)) examined the association between IUGR among singleton  
29 term live births and SO<sub>2</sub>, NO<sub>2</sub>, CO, O<sub>3</sub>, and PM<sub>2.5</sub> in 3 Canadian cities for the period 1985-2000. No  
30 increase in the risk of IUGR in relation to exposure to O<sub>3</sub> averaged over each month and trimester of  
31 pregnancy was noted.

32 Three studies conducted in Australia provide evidence for an association between ambient O<sub>3</sub>  
33 and fetal growth restriction. Hansen et al. (2007, [090703](#)) examined SGA among singleton, full-term  
34 births in Brisbane, Australia in relation to ambient air pollution (bsp, PM<sub>10</sub>, NO<sub>2</sub>, O<sub>3</sub>) during  
35 pregnancy. They also examined head circumference and crown-heel length in a subsample of term  
36 neonates. Trimester specific exposures to all pollutants were not statistically significantly associated  
37 with a reduction in head circumference or an increased risk of SGA. When monthly specific  
38 exposures were examined, the authors observed an increased risk of SGA associated with exposure  
39 to O<sub>3</sub> during month 4 (OR 1.11 [95% CI: 1.00, 1.24] per 10 ppb increase). In a subsequent study,

1 Hansen et al. (2008, [190273](#)) examined the possible associations between fetal ultrasonic  
2 measurements and ambient air pollution (PM<sub>10</sub>, O<sub>3</sub>, NO<sub>2</sub>, SO<sub>2</sub>) during early pregnancy. This study  
3 had two strengths: (1) fetal growth was assessed during pregnancy as opposed to at birth; and (2)  
4 there was little delay between exposures and fetal growth measurements, which reduces potential  
5 confounding and uses exposures that are concurrent with the observed growth pattern of the fetus.  
6 Fetal ultrasound biometric measurements were recorded for biparietal diameter (BPD), femur length,  
7 abdominal circumference, and head circumference. To further improve exposure assessment, the  
8 authors restricted the samples to include only scans from women for whom the centroid of their  
9 postcode was within 14 km of an air pollution monitoring site. Ozone during days 31-60 was  
10 associated with decreases in all of the fetal growth measurements, and a 1.78 mm reduction in  
11 abdomen circumference per 10 ppb increase in O<sub>3</sub> concentration, though this effect did not persist in  
12 co-pollutant models. The change in ultrasound measurements associated with O<sub>3</sub> during days 31-60  
13 of gestation indicated that increasing O<sub>3</sub> concentration decreased the magnitude of ultrasound  
14 measurements for women living within 2 km of the monitoring site. The relationship decreased  
15 toward the null as the distance from the monitoring sites increased. When assessing effect  
16 modification due to SES, there was some evidence of effect modification for most of the  
17 associations, with the effects of air pollution stronger in the highest SES quartile. In the third study,  
18 Mannes et al. (2005, [087895](#)) estimated the effects of pollutant (PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, CO and O<sub>3</sub>)  
19 exposure in the first, second and third trimesters of pregnancy and risk of SGA in Sydney, Australia.  
20 Citywide average air pollutant concentrations in the last month, third trimester, and first trimester of  
21 pregnancy had no effect on SGA. Concentrations of O<sub>3</sub> in the second trimester of pregnancy had  
22 small but adverse effects on SGA (OR 1.10 [95% CI: 1.00, 1.14] per 10 ppb increment). This effect  
23 disappeared when the analysis was limited to births with a maternal address within 5 km of a  
24 monitoring station (OR 1.00 [95% CI: 0.60, 1.79] per 10 ppb increment).

25 Very little information from toxicological studies is available to address effects on fetal  
26 growth. However, there is evidence to suggest that prenatal exposure to O<sub>3</sub> can affect postnatal  
27 growth. A few studies reported that mice or rats exposed developmentally (gestationally ±  
28 lactationally) to O<sub>3</sub> had deficits in body weight gain in the postpartum period (Bignami et al., 1994,  
29 [076063](#); Haro and Paz, 1993, [044194](#); Kavlock et al., 1980, [094043](#)).

30 Table 7-4 provides a brief overview of the epidemiologic studies of fetal growth restriction. In  
31 summary, the evidence is inconsistent when examining exposure to O<sub>3</sub> and fetal growth restriction.  
32 Similar to PTB, studies conducted in Australia have reported an effect of O<sub>3</sub> on fetal growth, whereas  
33 studies conducted in other areas have not found such an effect. This may be due to the restriction of  
34 births to those within 2-14 km of a monitoring station, as was done in the Australian studies.

**Table 7-4. Brief summary of epidemiologic studies of fetal growth**

Study	Location (Sample Size)	Mean O <sub>3</sub> (ppb)	Exposure assessment	Effect Estimate (95% CI)
Salam et al. (2005, <a href="#">087885</a> )	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, <a href="#">156292</a> )	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. (2007, <a href="#">090429</a> )	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, <a href="#">090703</a> )	Brisbane, Australia (n=26,617)	8-h max: 26.7	City-wide 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, <a href="#">190273</a> )	Brisbane, Australia (n=15,623)	8-h avg: 24.8	Within 2 km of monitor	M1: -0.32 (-1.56, 0.91)* M2: -0.58 (-1.97, 0.80)* M3: 0.26 (-1.07, 1.59)* M4: 0.11 (-0.98, 1.21)*
Mannes et al. (2005, <a href="#">087895</a> )	Sydney, Australia (n=138,056)	1-h max: 31.6	City-wide 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)

#Relative risk of fetal growth restriction per 10 ppb change in O<sub>3</sub>.

\*Mean change in fetal ultrasonic measure of head circumference recorded between 13 and 26 weeks gestation for a 10-ppb increase in maternal exposure to O<sub>3</sub> 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. Birth Defects

1 Despite the growing body of literature evaluating the association between ambient air  
2 pollution and various adverse birth outcomes, relatively few studies have investigated the effect of  
3 temporal variations in ambient air pollution on birth defects. Heart defects and oral clefts have been  
4 the focus of the majority of these recent studies, given the higher prevalence than other birth defects  
5 and associated mortality.

6 Mechanistically, air pollutants could be involved in the etiology of birth defects via  
7 hemodynamic events, anoxic events, oxidative stress, and toxicity to certain cell populations during  
8 development. One potential etiologic pathway may include the neural crest cell population. Normal  
9 migration and differentiation of neural crest cells are important for heart development and are  
10 particularly sensitive to toxic insults. They respond by undergoing apoptosis, in part because they  
11 lack antioxidative stress proteins. Ozone is a very reactive molecule and a strong oxidizing agent that  
12 can generate superoxides, hydrogen peroxide, and hydroxyl radicals, contributing to oxidative stress

1 Several studies have been conducted examining the relationship between O<sub>3</sub> exposure during  
2 pregnancy and birth defects. The earliest of these studies was conducted in southern California (Ritz  
3 et al., 2002, [023227](#)). This study evaluated the effect of air pollution on the occurrence of cardiac  
4 and orofacial birth defects in neonates and fetuses delivered in southern California in 1987-1993.  
5 Maternal exposure estimates were based on data from the fixed site closest to the mother's ZIP code  
6 area. When using a case-control design where cases were matched to 10 randomly selected controls,  
7 results showed increased risks for aortic artery and valve defects (OR 1.56 [95% CI: 1.16, 2.09] per  
8 10 ppb O<sub>3</sub>), pulmonary artery and valve anomalies (OR 1.34 [95% CI: 0.96, 1.87] per 10 ppb O<sub>3</sub>),  
9 and conotruncal defects (OR 1.36 [95% CI: 0.91, 2.03] per 10 ppb O<sub>3</sub>) in a dose-response manner  
10 with second-month O<sub>3</sub> exposure. These associations were not observed for orofacial defects. The  
11 average effect sizes and patterns of second-month O<sub>3</sub> exposure were similar for these defects and  
12 varied only slightly from single- to multi-pollutant models, or when the models were adjusted for  
13 other potential confounding factors. Additionally, the authors reported an OR of 1.13 (95% CI: 0.90,  
14 1.40) per 10 ppb during the second trimester for cleft lip with or without cleft palate.

15 A study conducted in Texas (Gilboa et al., 2005, [087892](#)) looked at a similar period of  
16 exposure but reported no association with most of the birth defects studied (O<sub>3</sub> concentration was  
17 studied using quartiles with the lowest representing <18 ppb and the highest representing 31 ppb).  
18 The authors found slightly elevated odds ratios for pulmonary artery and valve defects. They also  
19 detected an inverse association between O<sub>3</sub> exposure and isolated ventricular septal defects. For cleft  
20 lip with or without cleft palate, the authors reported an OR of 1.09 (95% CI: 0.70, 1.69) for the  
21 fourth quartile contrasted with the first quartile of exposure during 3-8 weeks of pregnancy. Overall,  
22 this study did not provide strong evidence that air pollution increases the risk of cardiac defects or  
23 oral clefts.

24 A recent study conducted in Atlanta, GA examined O<sub>3</sub> exposure during the third through  
25 seventh week of pregnancy and reported no association with risk of cardiovascular malformations  
26 (mean long-term average of 8-h O<sub>3</sub> concentrations excluding November through February ranged by  
27 5-year groups from 39.8 to 43.3 ppb) (Strickland et al., 2009, [190324](#)).

28 Hwang and Jaakola (2008, [193794](#)) conducted a population-based case-control study to  
29 investigate exposure to ambient air pollution and the risk of cleft lip with or without cleft palate in  
30 Taiwan. The risk of cleft lip with or without cleft palate was increased in relation to O<sub>3</sub> levels in the  
31 first gestational month (OR 1.17 [95% CI: 1.01, 1.36] per 10 ppb) and second gestational month  
32 (OR 1.22 [95% CI: 1.03, 1.46] per 10 ppb), but was not related to any of the other pollutants. In  
33 three-pollutant models, the effect estimates for O<sub>3</sub> exposure were stable for the four different  
34 combinations of pollutants and were all statistically significant.

35 Marshall et al. (2010, [597374](#)) compared estimated exposure to ambient pollutants during  
36 early pregnancy among mothers of children with oral cleft defects to that among mothers of controls.  
37 The authors observed no consistent elevated associations between any of the air pollutants examined  
38 and cleft malformations, though there was a weak association between cases of cleft palate only and  
39 increasing O<sub>3</sub> concentrations. This association increased when cases and controls were limited to

1 those with residences within 10 km of the closest O<sub>3</sub> monitor (OR 2.2 [95% CI: 1.0, 4.9], comparing  
 2 highest quartile [>33 ppb] to lowest quartile [<15 ppb]).

3 A limited number of toxicological studies have examined birth defects in animals exposed  
 4 gestationally to O<sub>3</sub>. Kavlock et al. (1979, [039228](#)) exposed pregnant rats to O<sub>3</sub> for precise periods  
 5 during organogenesis. No significant teratogenic effects were found in rats exposed 8 hr/day to  
 6 concentrations of O<sub>3</sub> varying from 0.44 to 1.97 ppm during early (days 6-9), mid (days 9-12), or late  
 7 (days 17 to 20) gestation, or the entire period of organogenesis (days 6-15). Earlier research found  
 8 eyelid malformation following gestational and postnatal exposure to 0.2 ppm O<sub>3</sub> (Veninga, 1967,  
 9 [040746](#)).

10 Table 7-5 provides a brief overview of the epidemiologic studies of birth defects. Results from  
 11 these studies are not entirely consistent. This inconsistency could be due to the absence of true  
 12 associations between O<sub>3</sub> and risks of cardiovascular malformations and oral cleft defects; it could  
 13 also be due to differences in populations, pollution levels, outcome definitions, or analytical  
 14 approaches. The lack of consistency of associations between O<sub>3</sub> and cardiovascular malformations or  
 15 oral cleft defects might be due to issues relating to statistical power or measurement error.

**Table 7-5. Brief summary of epidemiologic studies of birth defects**

Study	Outcomes Examined	Location (Sample Size)	Mean O <sub>3</sub> (ppb)	Exposure Assessment	Exposure Window
Ritz et al. (2002, <a href="#">023227</a> )	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, <a href="#">087892</a> )	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 Jaakola (2008, <a href="#">193794</a> )	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, <a href="#">190324</a> )	Cardiac Defects	Atlanta, GA (n=3,338 cases)	8-h max: 39.8-43.3	Weighted City-wide avg	Weeks 3-7 of gestation
Marshall et al. (2010, <a href="#">597374</a> )	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

#### 7.4.7. Developmental Respiratory Effects

16 The issue of prenatal exposure has assumed increasing importance, since ambient air pollution  
 17 exposures of pregnant women have been shown to lead to adverse pregnancy outcomes, as well as to  
 18 respiratory morbidity and mortality in the first year of life. Growth and development of the  
 19 respiratory system take place mainly during the prenatal and early postnatal periods. This early  
 20 developmental phase is thought to be very important in determining long-term lung growth. Studies  
 21 have recently examined this emerging issue, and several were included in Sections 7.2.1 and 7.2.3,  
 22 and are included here because they included both prenatal and post-natal exposure periods.

23 Mortimer et al. (2008, [122163](#); 2008, [187280](#)) examined the association of prenatal and  
 24 lifetime exposures to air pollutants with pulmonary function and allergen sensitization in a subset of

1 asthmatic children (ages 6-11) included in the Fresno Asthmatic Children's Environment Study  
2 (FACES). Monthly means of pollutant levels for the years 1989-2000 were created and averaged  
3 separately across several important developmental time-periods, including the entire pregnancy, each  
4 trimester, the first 3 years of life, the first 6 years of life, and the entire lifetime. The 8-h avg O<sub>3</sub>  
5 concentrations were approximately 50 ppb for each of the exposure metrics (estimated from figure).  
6 In the first analysis (Mortimer et al., 2008, [122163](#)), negative effects on pulmonary function were  
7 found for exposure to PM<sub>10</sub>, NO<sub>2</sub>, and CO during key neonatal and early life developmental periods.  
8 The authors did not find a negative effect of exposure to O<sub>3</sub> among this cohort. In the second  
9 analysis (Mortimer et al., 2008, [187280](#)), sensitization to at least one allergen was associated, in  
10 general, with higher levels of CO and PM<sub>10</sub> during the entire pregnancy and second trimester and  
11 higher PM<sub>10</sub> during the first 2 years of life. Lower exposure to O<sub>3</sub> during the entire pregnancy or  
12 second trimester was associated with an increased risk of allergen sensitization. Although the  
13 pollutant metrics across time periods are correlated, the strongest associations with the outcomes  
14 were observed for prenatal exposures. Though it may be difficult to disentangle the effect of prenatal  
15 and postnatal exposures, the models from this group of studies suggest that each time period of  
16 exposure may contribute independently to different dimensions of school-aged children's pulmonary  
17 function. For 4 of the 8 pulmonary-function measures (FVC, FEV<sub>1</sub>, PEF, FEF<sub>25-75</sub>), prenatal  
18 exposures were more influential on pulmonary function than early-lifetime metrics, while, in  
19 contrast, the ratio of measures (FEV<sub>1</sub>/FVC and FEF<sub>25-75</sub>/FVC) were most influenced by postnatal  
20 exposures. When lifetime metrics were considered alone, or in combination with the prenatal  
21 metrics, the lifetime measures were not associated with any of the outcomes, suggesting the timing  
22 of the exposure may be more important than the overall dose and prenatal exposures are not just  
23 markers for lifetime or current exposures.

24 Clark et al. (2010, [594440](#)) investigated the effect of exposure to ambient air pollution in utero  
25 and during the first year of life on risk of subsequent asthma diagnosis (incident asthma diagnosis up  
26 to age 3-4) in a population-based nested case-control study. Air pollution exposure for each subject  
27 based on their residential address history was estimated using regulatory monitoring data, land use  
28 regression modeling, and proximity to stationary pollution sources. An average exposure was  
29 calculated for the duration of pregnancy (~15 ppb; transformed from μg/m<sup>3</sup>) and the first year of life  
30 (~14 ppb; transformed from μg/m<sup>3</sup>). In contrast to the Mortimer et al. studies (2008, [122163](#); 2008,  
31 [187280](#)), the effect estimates for first-year exposure were generally larger than for in utero  
32 exposures. However, similar to the Mortimer et al. studies, the observed associations with O<sub>3</sub> were  
33 largely protective. Because of the relatively high correlation between in utero and first-year  
34 exposures for many pollutants, it was difficult to discern the relative importance of the individual  
35 exposure periods.

36 Latzin et al. (2009, [195721](#)) examined whether prenatal exposure to air pollution was  
37 associated with lung function changes in the newborn. Tidal breathing, lung volume, ventilation  
38 inhomogeneity and eNO were measured in 241 unsedated, sleeping neonates (age= 5 weeks). The  
39 median of the 24-h avg O<sub>3</sub> concentrations averaged across the post-natal period was ~44 ppb

1 (transformed from  $\mu\text{g}/\text{m}^3$ ). Consistent with the previous studies, no association was found for  
2 prenatal exposure to  $\text{O}_3$  and lung function.

3 The new toxicological literature since the 2006  $\text{O}_3$  AQCD (U.S. EPA, 2006, [088089](#)), covering  
4 respiratory changes related to developmental  $\text{O}_3$  exposure, reports ultrastructural changes in  
5 bronchiole development, alterations in placental and pup cytokines, and increased pup airway hyper-  
6 reactivity. These studies are detailed below. Older studies are discussed where new information is not  
7 available.

8 Fetal rat lung bronchiole development is triphasic, comprised of the glandular phase  
9 (measured at GD18), the canalicular phase (GD20), and the saccular phase (GD21). The  
10 ultrastructural lung development in fetuses of pregnant rats exposed to 1-ppm  $\text{O}_3$  (12 h/day, out to  
11 either GD18, GD20 or GD21) was examined by electron microscopy during these three phases. In  
12 the glandular phase, bronchiolar columnar epithelial cells in fetuses of dams exposed to  $\text{O}_3$  had  
13 cytoplasmic damage and swollen mitochondria. Bronchial epithelium at the canalicular phase in  $\text{O}_3$   
14 exposed pups had delayed maturation in differentiation, i.e., glycogen abundance in secretory cells  
15 had not diminished as it should with this phase of development. Congruent with this finding, delayed  
16 maturation of tracheal epithelium following early neonatal  $\text{O}_3$  exposure (1 ppm, 4-5 h/day for  
17 first week of life) in lambs has been previously reported (Mariassy et al., 1989, [042246](#); Mariassy et  
18 al., 1990, [042311](#)). Also at the canalicular phase, atypical cells were seen in the bronchiolar lumen of  
19  $\text{O}_3$  exposed rat fetuses. Finally, in the saccular phase, mitochondrial degradation was present in the  
20 non-ciliated bronchiolar cells of rats exposed in utero to  $\text{O}_3$ . In conclusion,  $\text{O}_3$  exposure of pregnant  
21 rats produced ultra-structural damage to near-term fetal bronchiolar epithelium (López et al., 2008,  
22 [197786](#)).

23 Exposure of laboratory animals to multiple airborne pollutants can differentially affect pup  
24 physiology. One study showed that exposure of C57BL/6 mouse dams to 0.48 mg PM intratracheally  
25 twice weekly for 3 weeks during pregnancy augmented  $\text{O}_3$ -induced airway hyper-reactivity in  
26 juvenile offspring. Maternal PM exposure also significantly increased placental cytokines above  
27 vehicle-instilled controls. Pup postnatal  $\text{O}_3$  exposure (1 ppm 3 h/day, every other day, thrice weekly  
28 for 4 weeks) induced significantly increased cytokine levels (IL- $1\beta$ , TNF- $\alpha$ , KC, and IL-6) in whole  
29 lung versus postnatal air exposed groups; this was further exacerbated with gestational PM exposure  
30 (Auten et al., 2009, [200760](#)).

31 A series of experiments using infant rhesus monkeys repeatedly exposed to 0.5 ppm  $\text{O}_3$   
32 starting at one-month of age have examined the effect of  $\text{O}_3$  alone or in combination with an inhaled  
33 allergen on morphology and lung function (Plopper et al., 2007, [596412](#)). Exposure to  $\text{O}_3$  alone or  
34 allergen alone produced small but not statistically significant changes in baseline airway resistance  
35 and airway responsiveness, but the combined exposure to both  $\text{O}_3$  + antigen produced statistically  
36 significant and greater than additive changes in both functional measurements. Additionally, cellular  
37 changes and significant structural changes in the respiratory tract have been observed in infant  
38 rhesus monkeys exposed to  $\text{O}_3$  (Fanucchi et al., 2006, [096491](#)). A more detailed description of these  
39 studies can be found in Section 7.2.3 (Pulmonary Structure and Function).

## 7.4.8. Developmental Central Nervous System Effects

### 7.4.8.1. Laterality

1 Two reports of laterality changes in mice developmentally exposed to O<sub>3</sub> have been reported in  
2 the literature. Mice developmentally exposed to 0.6 ppm O<sub>3</sub> (6 days before breeding to weaning at  
3 PND21) showed a turning preference (left turns) distinct from air exposed controls (clockwise turns)  
4 (Dell'Omo et al., 1995, [080787](#)); in previous studies this behavior in mice has been found to  
5 correlate with specific structural asymmetries of the hippocampal mossy fiber projections (Schöpke  
6 et al., 1991, [684254](#)). The 2006 AQCD evidence for the effect of O<sub>3</sub> on laterality or handedness  
7 demonstrated that rats exposed to O<sub>3</sub> during fetal and neonatal life showed limited, gender-specific  
8 changes in handedness after exposure to the intermediate dose of O<sub>3</sub> (only seen in female mice  
9 exposed to 0.6 ppm O<sub>3</sub>, and not in males at 0.6 ppm or in either sex of 0.3 or 0.9 ppm O<sub>3</sub> with  
10 exposure from 6 days before breeding to PND26) (Petruzzi et al., 1999, [012066](#)).

### 7.4.8.2. Brain Morphology and Neurochemical Changes

11 The nucleus tractus solitarius (NTS), a medullary area of respiratory control, of adult animals  
12 exposed prenatally to 0.5 ppm O<sub>3</sub> (12h/day, ED5-ED20) had significantly less tyrosine hydroxylase  
13 staining versus control (Boussouar et al., 2009, [596368](#)). Tyrosine hydroxylase is the rate-limiting  
14 enzyme for dopamine synthesis and serves as a precursor for catecholamine synthesis; thus,  
15 decreased staining is used as a marker of dopaminergic or catecholaminergic cell or activity loss in  
16 these regions and thus functions in neuronal plasticity. After physical restraint stress, control animals  
17 respond at the histological level with Fos activation, a marker of neuronal activity, and tyrosine  
18 hydroxylase activation in the NTS, a response which is absent or attenuated in adult animals exposed  
19 prenatally to 0.5 ppm O<sub>3</sub> (Boussouar et al., 2009, [596368](#)) when compared to control air exposed  
20 animals who also were restrained. The O<sub>3</sub>-exposed offspring in this study were cross-fostered to  
21 control air exposed dams to avoid O<sub>3</sub>-dependent dam related neonatal effects on offspring outcomes  
22 (i.e., dam behavioral or lactational contributions to pup outcomes) (Boussouar et al., 2009, [596368](#)).

23 Developmental exposure to 0.3 or 0.6 ppm O<sub>3</sub> prior to mating pair formation through GD17  
24 induced significant increased levels of BDNF in the striatum of adult (PND140) O<sub>3</sub> exposed  
25 offspring as compared to control air exposed animals; these O<sub>3</sub>-exposed animals also had  
26 significantly decreased level of NGF in the hippocampus versus control (Santucci et al., 2006,  
27 [596414](#)).

28 Changes in the pup cerebellum with prenatal 1 ppm O<sub>3</sub> exposure include altered morphology  
29 (Rivas-Manzano and Paz, 1999, [012072](#); Romero-Velazquez et al., 2002, [035575](#)), decreased total  
30 area (Romero-Velazquez et al., 2002, [035575](#)), decreased number of Purkinje cells (Romero-  
31 Velazquez et al., 2002, [035575](#)), and altered monoamine neurotransmitter content with the  
32 catecholamine system affected and the indoleamine system unaffected by O<sub>3</sub> (Gonzalez-Pina et al.,  
33 2008, [475317](#)).

### 7.4.8.3. Neurobehavioral Outcomes

1  
2 O<sub>3</sub> administration to dams during pregnancy with or without early neonatal exposure has been  
3 shown to contribute to multiple neurobehavioral outcomes in offspring that are described in further  
4 detail below.

5 O<sub>3</sub> administration (0.4, 0.8 or 1.2 ppm O<sub>3</sub>) during the majority of pregnancy (PD7-17) of CD-1  
6 mice did not affect pup behavioral outcomes including early behavioral ultrasonic vocalizations and  
7 more permanent later measurements (PND60 or 61) including pup activity, habituation and  
8 exploration and d-amphetamine-induced hyperactivity (Bignami et al., 1994, [076063](#)); these pups  
9 were all cross-fostered or reared on non- O<sub>3</sub> exposed dams.

10 Testing for aggressive behavior in mice continuously exposed to O<sub>3</sub> (0.3 or 0.6 ppm from  
11 30 days prior to mating to GD17) revealed that mice had significantly increased defensive/  
12 submissive behavior (increased freezing posturing on the first day only of a multiple-day exam)  
13 versus air exposed controls (Santucci et al., 2006, [596414](#)). Similar to this and as reported in  
14 previous AQCDs, continuous exposure of adult animals to O<sub>3</sub> induced significant increases in fear  
15 behavior and decreased aggression as measured by significantly decreased freezing behavior  
16 (Petruzzi et al., 1995, [077448](#)).

17 Developmentally exposed animals also had significantly decreased amount of time spent nose  
18 sniffing other mice (Santucci et al., 2006, [596414](#)); this social behavior deficit, decreased sniffing  
19 time, was not found in an earlier study with similar exposures (Petruzzi et al., 1995, [077448](#)), but  
20 sniffing of specific body areas was measured in Santucci et al. (2006, [596414](#)) and total number of  
21 sniffs of the entire body was measured in Petruzzi et al. (1995, [077448](#)). The two toxicology studies  
22 exploring social behavior (sniffing) employ different study designs and find opposite effects in  
23 animals exposed to O<sub>3</sub>.

### 7.4.8.4. Sleep Aberrations after Developmental Ozone Exposure

24 The effect of gestational O<sub>3</sub> exposure (1 ppm O<sub>3</sub>, 12h/day, during dark period) on sleep  
25 patterns in rat offspring was followed using 24 h polysomnographic recordings at 30, 60 and 90 days  
26 of age (Haro and Paz, 1993, [044194](#)). Ozone-exposed pups manifested with inverted sleep-wake  
27 patterns or circadian rhythm phase-shift. Rat vigilance was characterized in wakefulness, slow wave  
28 sleep (SWS), and paradoxical sleep (PS) using previously characterized criteria. The O<sub>3</sub> exposed  
29 offspring spent longer time in the wakefulness state during the light period, more time in SWS  
30 during the period of darkness, and showed significant decrements in PS. Chronic O<sub>3</sub> inhalation  
31 significantly decreased the duration of PS during both the light and dark periods (Haro and Paz,  
32 1993, [044194](#)). These effects were consistent at all time periods measured (30, 60 and 90 days of  
33 age). These sleep effects reported after developmental exposures expand upon the existing literature  
34 on sleep aberrations in adult animals exposed to O<sub>3</sub> [rodents: (Arito et al., 1992, [042759](#); Paz and  
35 Huitron-Resendiz, 1996, [082684](#)); and cats: (Paz and Bazan-Perkins, 1992, [036436](#))]. A role for  
36 inhibition of cyclooxygenase-2 and the interleukins and prostaglandins in the O<sub>3</sub>-dependent sleep

1 changes potentially exists with evidence from a publication on indomethacin pretreatment  
2 attenuating O<sub>3</sub>-induced sleep aberrations in adult male animals (Rubio and Paz, 2003, [053541](#)).

### 7.4.9. Early Life Mortality

3 Infants may be particularly susceptible to the adverse effects of air pollution. The lung is not  
4 well developed at birth, with 80% of alveoli being formed postnatally. An important question  
5 regarding the association between PM and infant mortality is the critical window of exposure during  
6 development for which infants are susceptible. Several age intervals have been explored: neonatal  
7 (<1 month); postneonatal (1 month to 1 year); and an overall interval for infants that includes both  
8 the neonatal and postneonatal periods (<1 year). Within these various age categories, multiple causes  
9 of deaths have been investigated, particularly total deaths and respiratory-related deaths. The studies  
10 reflect a variety of study designs, exposure periods, regions, and adjustment for confounders. Within  
11 the first year of life, infants develop rapidly; therefore their susceptibility may change within weeks  
12 or months. During the neonatal and post-neonatal periods, the developing lung is highly susceptible  
13 to environmental toxicants. As discussed below, a handful of studies have examined the effect of  
14 ambient air pollution on neonatal and postneonatal mortality, with the former the least studied. These  
15 studies varied somewhat with regard to the outcomes and exposure periods examined and study  
16 designs employed.

17 The results of these infant mortality studies are presented here, and in Table 7-6, with the other  
18 reproductive and developmental outcomes because it is likely that in utero exposures contribute to  
19 this outcome. Both long-term and short-term exposure studies of infant mortality are included in this  
20 section. A major issue in studying environmental exposures and infant mortality is selecting the  
21 relevant exposure period, since the biological mechanisms leading to death and the critical periods of  
22 vulnerability are poorly understood. Exposures proximate to the death may be most relevant if  
23 exposure causes an acute effect. However, exposure occurring in early life might affect critical  
24 growth and development, with results observable later in the first year of life, or cumulative  
25 exposure during the first year of life may be the most important determinant. The studies reviewed  
26 below have dealt with this issue in different ways. Many have considered several exposure metrics  
27 based on different periods of exposure.

#### 7.4.9.1. Stillbirth

28 Pereira et al. (1998, [007264](#)) investigated the association among daily counts of intrauterine  
29 mortality (over 28 weeks of gestation) and air pollutant concentrations in Sao Paulo, Brazil from  
30 1991 through 1992. The association was strong for NO<sub>2</sub>, but lesser for SO<sub>2</sub> and CO. These  
31 associations exhibited a short lag time, less than 5 days. No significant association was detected  
32 between O<sub>3</sub> and intrauterine mortality.

### 7.4.9.2. Infant Mortality, Less than 1 Year

1 Ritz et al. (2006, [089819](#)) linked birth and death certificates for infants who died between  
2 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South Coast  
3 Air Basin of California. The authors examined exposure periods 2 weeks, 1 month, 2 months, and  
4 6 months before each case subject's death and reported no association between ambient levels of O<sub>3</sub>  
5 and infant mortality. Similarly, Diaz et al. (2004, [089894](#)) analyzed the effects of extreme  
6 temperatures and air pollutants on daily mortality in children less than 1 year of age in Madrid,  
7 Spain, from 1986 to 1997 and observed no statistically significant association between mortality and  
8 O<sub>3</sub> concentrations. Hajat et al. (2007, [093276](#)) analyzed time-series data of daily infant mortality  
9 counts in 10 major cities in the UK to quantify any associations with short-term changes in air  
10 pollution. When the results from the 10 cities were combined there was no relationship between O<sub>3</sub>  
11 and infant mortality, even after restricting the analysis to just the summer months.

12 Conversely, a time-series study of infant mortality conducted in the southwestern part of  
13 Mexico City in the years 1993-1995 found that infant mortality was associated with the levels of  
14 NO<sub>2</sub> and O<sub>3</sub> 3-5 days before death, but not as consistently as with PM. A 10-ppb increase in 24-h avg  
15 O<sub>3</sub> was associated with a 2.78% increase (95% CI: 0.29, 5.26%) in infant mortality (lag 3) (Loomis  
16 et al., 1999, [087288](#)). This increase was attenuated, though still positive when evaluated in a two-  
17 pollutant model with PM<sub>2.5</sub>. One-hour max concentrations of O<sub>3</sub> exceeded prevailing Mexican and  
18 international standards nearly every day.

### 7.4.9.3. Neonatal Mortality, Less than 1 Month

19 Three studies have evaluated ambient O<sub>3</sub> concentrations and neonatal mortality and observed  
20 no association. Ritz et al. (2006, [089819](#)) linked birth and death certificates for infants who died  
21 between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South  
22 Coast Air Basin of California. The authors examined exposure periods 2 weeks, 1 month, 2 months,  
23 and 6 months before each case subject's death and reported no association between ambient levels of  
24 O<sub>3</sub> and neonatal mortality. Hajat et al. (2007, [093276](#)) analyzed time-series data of daily infant  
25 mortality counts in 10 major cities in the UK to quantify any associations with short-term changes in  
26 air pollution. When the results from the 10 cities were combined there was no relationship between  
27 O<sub>3</sub> and neonatal mortality, even after restricting the analysis to just the summer months. Lin et al.  
28 (2004, [095787](#)) assessed the impact of daily changes in air pollutants on the number of daily  
29 neonatal deaths in Sao Paulo, Brazil. The authors observed no association between ambient levels of  
30 O<sub>3</sub> and neonatal mortality.

### 7.4.9.4. Postneonatal Mortality, 1 Month to 1 Year

31 A number of studies focused on the postneonatal period when examining the effects of O<sub>3</sub> on  
32 infant mortality. Ritz et al. (2006, [089819](#)) linked birth and death certificates for infants who died  
33 between 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South

1 Coast Air Basin of California. The authors examined exposure periods 2 weeks, 1 month, 2 months,  
2 and 6 months before each case subject's death and reported no association between ambient levels of  
3 O<sub>3</sub> and postneonatal mortality. Woodruff et al. (2008, [098386](#)) evaluated the county-level  
4 relationship between cause-specific postneonatal infant mortality and chronic early-life (first  
5 2 months of life) exposure to air pollutants across the U.S. Similarly, they found no association  
6 between O<sub>3</sub> exposure and deaths from respiratory causes. In the U.K., Hajat et al. (2007, [093276](#))  
7 analyzed time-series data of daily infant mortality counts in 10 major cities to quantify any  
8 associations with short-term changes in air pollution. When the results from the 10 cities were  
9 combined there was no relationship between O<sub>3</sub> and postneonatal mortality, even after restricting the  
10 analysis to just the summer months. In Ciudad Juarez, Mexico, Romieu et al. (2004, [093074](#))  
11 examined the daily number of deaths between 1997 and 2001, estimating the modifying effect of  
12 SES on the risk of postneonatal mortality. Ambient O<sub>3</sub> concentrations were not related to infant  
13 mortality overall, or in any of the SES groups. In a follow-up study, Carbajal-Arroyo (In Press,  
14 [667773](#)) evaluated the relationship of 1-h daily max O<sub>3</sub> levels with postneonatal infant mortality in  
15 the Mexico City Metropolitan Area between 1997 and 2005. Generally, O<sub>3</sub> was not significantly  
16 related to infant mortality. However, upon estimating the modifying effect of SES on the risk of  
17 postneonatal mortality, the authors found that O<sub>3</sub> was significantly related to respiratory mortality  
18 among those with low SES. In a separate analysis, the effect of PM<sub>10</sub> was evaluated with O<sub>3</sub> level  
19 quartiles. PM<sub>10</sub> alone was related to a significant increase in all-cause mortality. The magnitude of  
20 this effect remained the same when only the days when O<sub>3</sub> was in the lowest quartile were included  
21 in the analyses. However, when only the days when O<sub>3</sub> was in the highest quartile were included in  
22 the analyses, the magnitude of the PM<sub>10</sub> effect increased dramatically (OR=1.06 [0.909, 1.241] for  
23 PM<sub>10</sub> on days with O<sub>3</sub> in lowest quartile; OR=1.26 [1.08, 1.47] for PM<sub>10</sub> on days with O<sub>3</sub> in the  
24 highest quartile. These results suggest that while O<sub>3</sub> alone may not have an effect on infant mortality,  
25 it may serve to potentiate the observed effect of PM<sub>10</sub> on infant mortality.

26 Tsai et al. (2006, [090709](#)) used a case-crossover analysis to examine the relationship between  
27 air pollution and postneonatal mortality in Kaohsiung, Taiwan during the period 1994-2000. The risk  
28 of postneonatal deaths was 1.023 (95% CI: 0.564, 1.858) per 10-ppb increase in 24-h avg O<sub>3</sub>. The  
29 confidence interval for this effect estimate is very wide, likely due to the small number of infants that  
30 died each day, making it difficult to interpret this result. Several other studies conducted in Asia did  
31 not find any association between O<sub>3</sub> concentrations and infant mortality in the postneonatal period.  
32 Ha et al. (2003, [042552](#)) conducted a daily time-series study in Seoul, Korea to evaluate the effect of  
33 short-term changes in ambient 8-h O<sub>3</sub> concentrations on postneonatal mortality. Son et al. (2008,  
34 [190323](#)) examined the relationship between air pollution and postneonatal mortality from all causes  
35 among firstborn infants in Seoul, Korea during 1999-2003. Yang et al. (2006, [090760](#)) used a case-  
36 crossover analysis to examine the relationship between air pollution exposure and postneonatal  
37 mortality in Taipei, Taiwan for the period 1994-2000. The authors observed no associations between  
38 ambient levels of O<sub>3</sub> and postneonatal mortality.

#### 7.4.9.5. Sudden Infant Death Syndrome

1           The strongest evidence for an association between ambient O<sub>3</sub> concentrations and SIDS comes  
2 from a study that evaluated the county-level relationship between SIDS and chronic early-life (first  
3 2 months of life) exposure to air pollutants across the U.S.(Woodruff et al., 2008, [098386](#)). The  
4 authors observed a 1.20 (95% CI: 1.09, 1.32) odds ratio for a 10-ppb increase in O<sub>3</sub> and deaths from  
5 SIDS. There was a monotonic increase in odds of SIDS for each quartile of O<sub>3</sub> exposure compared  
6 with the lowest quartile (highest quartile OR = 1.51; [95% CI: 1.17, 1.96]). In a multi-pollutant  
7 model including PM<sub>10</sub> or PM<sub>2.5</sub>, CO and SO<sub>2</sub>, the OR for SIDS and O<sub>3</sub> was not substantially lower  
8 than that found in the single-pollutant model. When examined by season, the relationship between  
9 SIDS deaths and O<sub>3</sub> was generally consistent across seasons with a slight increase for those babies  
10 born in the summer. When stratified by birth weight, the OR for LBW babies was 1.27 (95% CI:  
11 0.95, 1.69) per 10-ppb increase in O<sub>3</sub> and the OR for normal weight babies was 1.16 (95% CI: 1.01,  
12 1.32) per 10-ppb increase in O<sub>3</sub>.

13           Conversely, two additional studies reported no association between ambient levels of O<sub>3</sub> and  
14 SIDS. Ritz et al. (2006, [089819](#)) linked birth and death certificates for infants who died between  
15 1989 and 2000 to evaluate the influence of outdoor air pollution on infant death in the South Coast  
16 Air Basin of California. The authors examined exposure periods 2 weeks, 1 month, 2 months, and  
17 6 months before each case subject's death and reported no association between ambient levels of O<sub>3</sub>  
18 and SIDS. Dales et al. (2004, [087342](#)) used time-series analyses to compare the daily mortality rates  
19 for SIDS and the daily air pollution concentrations in 12 Canadian cities during the period of  
20 1984-1999. Increased daily rates of SIDS were associated with previous day increases in the levels  
21 of SO<sub>2</sub>, NO<sub>2</sub>, and CO, but not O<sub>3</sub> or PM<sub>2.5</sub>.

**Table 7-6. Brief summary of infant mortality studies**

Study	Location	Mean O <sub>3</sub> (ppb)	Exposure Assessment	Effect Estimate (95% CI):
Pereira et al. (1998, <a href="#">007264</a> )	Sao Paulo, Brazil	1-h max: 33.8	Citywide avg	L0-2: 1.00 (0.99, 1.01)
Diaz et al. (2004, <a href="#">089894</a> )	Madrid, Spain	24-h avg: 11.4	Citywide avg	NR
Loomis et al. (1999, <a href="#">087288</a> )	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, <a href="#">089819</a> )	southern California	24-h avg: 21.9-22.1	Nearest Monitor	2 wk 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, <a href="#">093276</a> )	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. (2004, <a href="#">095787</a> )	Sao Paulo, Brazil	24-h avg: 38.06	Citywide avg	L0: 1.00 (0.99, 1.01)
Ha et al. (2003, <a href="#">042552</a> )	Seoul, South Korea	8-h avg: 21.2	Citywide avg	L0: 0.93 (0.90, 0.96)
Romieu et al. (2004, <a href="#">093074</a> )	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)
Carbajal-Arroyo et al. (In Press, <a href="#">667773</a> )	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, <a href="#">190323</a> )	Seoul, South Korea	8-ha avg: 25.61	Citywide avg	L(NR): 0.984 (0.976, 0.992)*
Tsai et al. (2006, <a href="#">090709</a> )	Kaohsiung, Taiwan	24-h avg: 23.60	Citywide avg	L0-2 cum: 1.02 (0.56, 1.86)
Woodruff et al. (2008, <a href="#">098386</a> )	Nationwide, US	24-h avg: 26.6	County wide avg	First 2 mo of life: 1.04 (0.98, 1.10)
Yang et al. (2006, <a href="#">090760</a> )	Taipei, Taiwan	24-h avg: 18.14	Citywide avg	L0-2 cum: 1.00 (0.62, 1.61)
Dales et al. (2004, <a href="#">087342</a> )	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

#Relative risk of infant mortality per 10 ppb change in O<sub>3</sub>

\* No 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

#### 7.4.10. Summary and Causal Determination

1           The 2006 O<sub>3</sub> AQCD concluded that the limited number of studies that investigated O<sub>3</sub>  
2 demonstrated no associations between O<sub>3</sub> and birth outcomes, with the possible exception of birth  
3 defects. The current review included an expanded body of evidence on the associations between O<sub>3</sub>  
4 and reproductive and developmental effects. Recent epidemiologic and toxicological studies provide  
5 evidence for an effect of prenatal exposure to O<sub>3</sub> on pulmonary structure and function, including  
6 lung function changes in the newborn, incident asthma, ultrastructural changes in bronchiole  
7 development, alterations in placental and pup cytokines, and increased pup airway hyper-reactivity.  
8 Also, there is limited toxicological evidence for an effect of prenatal and early life exposure on  
9 central nervous system effects, including laterality, brain morphology, neurobehavioral  
10 abnormalities, and sleep aberration. Recent epidemiologic studies have begun to explore the effects  
11 of O<sub>3</sub> on sperm quality, and provide limited evidence for decrements in sperm concentration, while  
12 there is limited toxicological evidence for testicular degeneration associated with O<sub>3</sub>.

13           While the collective evidence for many of the birth outcomes examined is generally  
14 inconsistent (including birth defects), there are several well-designed, well-conducted studies that  
15 indicate an association between O<sub>3</sub> and adverse outcomes. For example, as part of the southern  
16 California Children's Health Study, Salam et al. (2005, [087885](#)) observed a concentration-response  
17 relationship of decreasing birth weight with increasing O<sub>3</sub> concentrations averaged over the entire  
18 pregnancy that was clearest above the 30-ppb level (see Figure 7-4). Similarly, Hansen et al. (2008,  
19 [190273](#)) utilized fetal ultrasonic measurements and found a change in ultrasound measurements  
20 associated with O<sub>3</sub> during days 31-60 of gestation indicated that increasing O<sub>3</sub> concentration  
21 decreased an ultrasound measurement for women living within 2 km of the monitoring site.

22           There is no evidence that prenatal or early life O<sub>3</sub> concentrations are associated with infant  
23 mortality. Collectively, there is limited though positive toxicological evidence for O<sub>3</sub>-induced  
24 developmental effects, including effects on pulmonary structure and function and central nervous  
25 system effects. Limited epidemiologic evidence for an effect on prenatal O<sub>3</sub> exposure on respiratory  
26 development provides coherence with the effects observed in toxicological studies. There is also  
27 limited epidemiologic evidence for an association with O<sub>3</sub> concentration and decreased sperm  
28 concentration. A recent toxicological study provides limited evidence for a possible biological  
29 mechanism (histopathology showing impaired spermatogenesis) for such an association.  
30 Additionally, though the evidence for an association between O<sub>3</sub> concentrations and adverse birth  
31 outcomes is generally inconsistent, there are several influential studies that indicate an association  
32 with reduced birth weight and restricted fetal growth. Taking into consideration the positive evidence  
33 for developmental and reproductive outcomes from toxicological and epidemiological studies, and  
34 the few influential birth outcome studies, the evidence **is suggestive of a causal relationship between**  
35 **long-term exposures to O<sub>3</sub> and reproductive and developmental effects.**

## 7.5. Central Nervous System Effects

### 7.5.1. Effects on the Brain and Behavior

1 An epidemiologic study has recently been published examining the association between O<sub>3</sub>  
2 exposure and neurobehavioral effects. Chen et al. (2009, [179945](#)) utilized data from the NHANES  
3 III cohort to study the relationship between O<sub>3</sub> levels (mean annual O<sub>3</sub> concentration 26.5 ppb) and  
4 neurobehavioral effects among adults aged 20-59 years. The authors observed an association  
5 between annual exposure to O<sub>3</sub> and tests measuring coding ability (symbol-digit substitution test)  
6 and attention/short-term memory (serial-digit learning test). Each 10-ppb increase in annual O<sub>3</sub>  
7 levels corresponded to an aging-related cognitive performance decline of 3.5 yr for coding ability  
8 and 5.3 years for attention/short-term memory. These associations persisted in both crude and  
9 adjusted models. There was no association between O<sub>3</sub> levels and reaction time tests. The authors  
10 conclude that overall, there is an association between long-term O<sub>3</sub> exposure and reduced  
11 performance on neurobehavioral tests.

12 In a subchronic study, rats were exposed to 0.25 ppm O<sub>3</sub> for 4 h/day for 15-90 days (Rivas-  
13 Arancibia et al., 2010, [201544](#)). The exposures caused a complex array of responses, including a  
14 time-dependent increase in lipid peroxidation products and immunohistochemical changes in the  
15 hippocampus, that were correlated with decrements in passive avoidance behavioral tests.

16 A protective effect of estradiol has been observed in ovariectomized female rats exposed to  
17 0.25 ppm O<sub>3</sub> (4 h/day) for 30 or 60 days (Guevara-Guzmán et al., 2009, [596385](#)). In the olfactory  
18 bulb, lipid peroxidation was significantly less in rats exposed to O<sub>3</sub> and treated daily with estradiol.  
19 This protective effect of estradiol was also demonstrated for O<sub>3</sub>-induced decrements in a selective  
20 olfactory recognition memory test and an olfactory-dependent reward test. Similarly, estradiol  
21 protected against O<sub>3</sub>-induced changes in nigral cell morphology and loss of dopamine neurons in rats  
22 exposed to O<sub>3</sub> for 30 days (Angoa-Pérez et al., 2006, [596366](#)). Thus, repeated exposure of rats to O<sub>3</sub>  
23 produces lipid peroxidation at multiple sites in the brain and this oxidative stress is accompanied by  
24 gene expression changes and decrements in behavioral tests. Olfactory changes and loss of  
25 substantia nigra neurons are associated with Parkinson's disease in humans. Inhibition of these  
26 effects with estradiol treatment is consistent with the higher incidence of Parkinson's disease in men  
27 and the amelioration of Parkinsonian symptoms by estrogen therapy.

28 Adverse CNS effects have also been demonstrated in newborn and adult rats whose only  
29 exposure to O<sub>3</sub> occurred in utero. Several neurotransmitters were assessed in male offspring of dams  
30 exposed to 1 ppm O<sub>3</sub> during the entire pregnancy (Gonzalez-Pina et al., 2008, [475317](#)). The data  
31 showed that catecholamine neurotransmitters were affected to a greater degree than indole-amine  
32 neurotransmitters in the cerebellum. Adverse CNS changes, including behavioral, cellular, and  
33 biochemical effects, have also been observed after in utero exposure to 0.5 ppm O<sub>3</sub> for 12 h/day from  
34 GD5 to GD20 (Boussouar et al., 2009, [596368](#)). Tyrosine hydroxylase labeling in the nucleus tractus  
35 solitarius was increased after in utero exposure to O<sub>3</sub> whereas Fos protein labeling did not change.

1 When these offspring were challenged by immobilization stress, neuroplasticity pathways, which  
2 were activated in air offspring, were inhibited in O<sub>3</sub> offspring. Although the effect of O<sub>3</sub> exposure  
3 concentration was not studied in these two in utero studies, it has been examined in one study.  
4 Santucci et al. (2006, [596414](#)) investigated behavioral effects and gene expression after in utero  
5 exposure of mice to as little as 0.3 ppm O<sub>3</sub>. Increased defensive/submissive behavior and reduced  
6 social investigation were observed in both the 0.3- and 0.6-ppm O<sub>3</sub> groups. Changes in gene  
7 expression of brain-derived neurotrophic factor (BDNF, increased in striatum) and nerve growth  
8 factor (NGF, decreased in hippocampus) accompanied these behavioral changes. Thus, these three  
9 studies demonstrate that CNS effects can occur as a result of in utero exposure to O<sub>3</sub>, and although  
10 the mode of action of these effects is not known, it has been suggested that circulating lipid  
11 peroxidation products may play a role (Boussouar et al., 2009, [596368](#)). Importantly, these adverse  
12 CNS effects occurred in rodent models after in utero only exposure to (semi-) relevant  
13 concentrations of O<sub>3</sub>.  
14

## 7.5.2. Summary and Causal Determination

15 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) included toxicological evidence that acute  
16 exposures to O<sub>3</sub> are associated with alterations in neurotransmitters, motor activity, short and long  
17 term memory, and sleep patterns. Additionally, histological signs of neurodegeneration have been  
18 observed. However, evidence regarding chronic exposure and neurobehavioral effects was not  
19 available. Recent research in the area of O<sub>3</sub>-induced neurotoxicity has included several long-term  
20 exposure studies. Notably, the first epidemiologic study to examine the relationship between O<sub>3</sub>  
21 exposure and neurobehavioral effects observed an association between annual O<sub>3</sub> levels and an  
22 aging-related cognitive performance decline in tests measuring coding ability and attention/short-  
23 term memory. This observation is supported by studies in rodents which demonstrate oxidative stress  
24 in the brain and associated decrements in behavioral tests, including those measuring memory, after  
25 subchronic exposure to 0.25 ppm O<sub>3</sub>. Additionally, neurobehavioral changes are evident in animals  
26 whose only exposure to O<sub>3</sub> occurred in utero. Collectively, the limited epidemiologic and  
27 toxicological evidence is coherent and **suggestive of a causal relationship between O<sub>3</sub> exposure**  
28 **and adverse CNS effects.**

## 7.6. Carcinogenic and Genotoxic Potential of Ozone

### 7.6.1. Introduction

29 The radiomimetic and clastogenic qualities of O<sub>3</sub>, combined with its ability to stimulate  
30 proliferation of cells in the respiratory tract, have suggested that O<sub>3</sub> could act as a carcinogen.  
31 However, toxicological studies of tumorigenesis in the rodent lung have yielded mixed and often  
32 confusing results, and the epidemiologic evidence is equally conflicted. The 2006 O<sub>3</sub> AQCD

1 concluded that, “the weight of evidence from recent animal toxicological studies and a very limited  
2 number of epidemiologic studies do not support ambient O<sub>3</sub> as a pulmonary carcinogen” (U.S. EPA,  
3 2006, [088089](#)).

4 Multiple epidemiologic studies reported in the 2006 O<sub>3</sub> AQCD examined the direct association  
5 between O<sub>3</sub> exposure and cancer. The largest of these studies, by Pope et al. (2002, [024689](#)),  
6 included 500,000 adults from the American Cancer Society’s (ACS) Cancer Prevention II study. In  
7 this study, no association was observed between O<sub>3</sub> and lung cancer mortality. The Adventist Health  
8 Study of Smog (AHSMOG) also examined the association between O<sub>3</sub> and lung cancer mortality  
9 (Abbey et al., 1999, [047559](#)). There was a positive association between O<sub>3</sub> levels and lung cancer  
10 mortality among men. No association was reported for women. Another study using the AHSMOG  
11 cohort assessed the risk of incident lung cancer (Beeson et al., 1998, [048890](#)). Among males, an  
12 association with incidence of lung cancer was observed with increasing O<sub>3</sub> concentrations. When  
13 stratified by smoking status, the association persisted among never smokers but was null for former  
14 smokers. No association was detected for females. The Six Cities Study examined various air  
15 pollutants and mortality but did not specifically explore the association between O<sub>3</sub> concentrations  
16 and lung cancer mortality due to low variability in O<sub>3</sub> levels across the cities (Dockery et al., 1993,  
17 [044457](#)). An ecologic study performed in Sao Paulo City, Brazil examined the correlations between  
18 O<sub>3</sub> levels in four of the city districts and incident cancer of the larynx and lung reported in 1997  
19 (Pereira et al., 2005, [073851](#)). A correlation between the average number of days O<sub>3</sub> levels exceeded  
20 air quality standards from 1981 to 1990 and cancer incidence was present for larynx cancer but not  
21 for lung cancer.

22 Early toxicological research demonstrated lung adenoma<sup>1</sup> acceleration in mice with daily  
23 exposure to 1 ppm over 15 months (Stokinger, 1962, [015101](#)). Later work demonstrated a significant  
24 increase in lung tumor numbers in one strain of mouse (A/J) but not another after exposure to  
25 0.3-0.8 ppm O<sub>3</sub> (Hassett et al., 1985, [040704](#); Last et al., 1987, [040830](#)). The A/J mouse strain is  
26 known to have a high incidence of spontaneous adenomas, and further studies using this strain found  
27 a statistically significant increase in lung tumor incidence after a 9-month exposure to 0.5 ppm and  
28 incidence and multiplicity after a 5 month exposure to 0.12 ppm with a 4-month recovery period  
29 (Witschi et al., 1999, [011602](#)). However, these findings were discounted by the study authors due to  
30 the lack of a clear dose response, and results from the Hassett et al. and Last et al. studies were  
31 retrospectively deemed spurious based on what appeared to be unusually low spontaneous tumor  
32 incidences in the control groups (Witschi, 1991, [042509](#)). A study of carcinogenicity of O<sub>3</sub> by the  
33 National Toxicology Program (NTP, 1994, [011143](#)) reported increased incidences of  
34 alveolar/bronchiolar adenoma or carcinoma (combined) in female B6C3F<sub>1</sub> mice exposed over  
35 2 years or a lifetime to 1.0 ppm and marginally increased incidences in male mice exposed to 0.5 and  
36 1.0 ppm. Thus there was equivocal evidence of carcinogenic activity in male mice and some

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<sup>1</sup> 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 O<sub>3</sub> AQCD: “No true lung cancers have been reported, however, from experimental exposures to either O<sub>3</sub> alone or any other combination or ingredient of photochemical oxidants.”

1 evidence of carcinogenic activity of O<sub>3</sub> in females. Some semblance of a dose-response relationship  
2 was also evident in this study.

3 In Fischer-344/N rats (50 of each sex per group), neither a 2-year nor lifetime exposure to O<sub>3</sub>  
4 ranging from 0.12 to 1.0 ppm was found to be carcinogenic (Boorman et al., 1994, [038195](#)).  
5 However, a marginally significant carcinogenic effect of 0.2 ppm O<sub>3</sub> was reported in a study of male  
6 Sprague-Dawley rats exposed for 6 months (n = 50) (Monchaux et al., 1996, [086197](#)). These two  
7 studies also examined co-carcinogenicity of O<sub>3</sub> with NNK<sup>1</sup> (Boorman et al., 1994, [038195](#)) or a  
8 relatively high dose of radon (Monchaux et al., 1996, [086197](#)), finding no enhancement of NNK  
9 related tumors and a slight non-significant increase in tumor incidence after combined exposure with  
10 radon, respectively. Another study exploring co-carcinogenicity was conducted in hamsters. Not only  
11 was there no enhancement of chemically induced tumors in the peripheral lung or nasal cavity, but  
12 results suggested that O<sub>3</sub> could potentially delay or inhibit tumor development (Witschi et al., 1993,  
13 [043206](#)). Thus there is no concrete evidence that O<sub>3</sub> can act as a co-carcinogen.

14 Immune surveillance is an important defense against cancer, and it should be noted that natural  
15 killer (NK) cells, which destroy tumor cells in the lung, appear to be inhibited by higher doses of O<sub>3</sub>  
16 and either unaffected or stimulated at lower doses (Section 6.2.5.4, Infection and Adaptive  
17 Immunity). This aspect of tumorigenesis adds yet another layer of complexity which may be  
18 reflected by conflicting results across studies.

19 The following sections will examine epidemiologic studies of cancer incidence and mortality  
20 that have been published since the 2006 O<sub>3</sub> AQCD. One study has been published with cancer as the  
21 outcome; most studies examine markers of exposure or susceptibility and will be reported on later in  
22 this section. Recent toxicological studies are also described.

## 7.6.2. Lung Cancer Incidence and Mortality

23 A recent re-analysis of the full ACS CPSII cohort by the Health Effects Institute is the only  
24 epidemiologic study that has explored the association between O<sub>3</sub> and cancer mortality since the last  
25 O<sub>3</sub> AQCD. Krewski et al. (2009, [191193](#)) conducted an extended follow-up of the cohort  
26 (1982-2000). Mean O<sub>3</sub> levels [obtained from the Aerometric Information Retrieval System (AIRS)  
27 for 1980] were 22.91 ppb for the full year and 30.15 ppb for the summer months (April-September).  
28 No association was reported between lung cancer mortality and O<sub>3</sub> (HR 1.00 [95% CI: 0.96-1.04]  
29 per 10 ppb O<sub>3</sub>). Additionally, no association was observed when O<sub>3</sub> was restricted to the summer  
30 months. There was also no association present in a sub-analysis of the cohort examining the  
31 relationship between O<sub>3</sub> and lung cancer mortality in the Los Angeles area.

32 Since the 2006 O<sub>3</sub> AQCD, two toxicological studies have examined potential carcinogenicity  
33 of O<sub>3</sub> (Kim and Cho, 2009, [200775](#); Kim and Cho, 2009, [200773](#)). Looking across both studies,  
34 which used the same mouse strain as the National Toxicology Program study described above,  
35 0.5 ppm O<sub>3</sub> alone or in conjunction with chemical tumor inducers did not enhance lung tumor

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<sup>1</sup> 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

1 incidence in males or females. However, a 10% incidence of oviductal carcinoma was observed in  
2 mice exposed to 0.5 ppm O<sub>3</sub> for 16 weeks. The implications of this observation are unclear,  
3 particularly in light of the lack of statistical information reported. Additionally, there is no mention  
4 of oviductal carcinoma after 32 weeks of exposure, and no oviductal carcinoma was observed after  
5 one year of exposure.

### 7.6.3. DNA Damage

6 The potential for genotoxic effects relating to O<sub>3</sub> exposure was predicted from the  
7 radiomimetic properties of O<sub>3</sub>. The decomposition of O<sub>3</sub> in water produces OH and HO<sub>2</sub> radicals, the  
8 same species that are generally considered to be the biologically active products of ionizing  
9 radiation. Ozone has been observed to cause degradation of DNA in a number of different models  
10 and bacterial strains. Until the reports of Zelac et al.(1971, [039743](#); 1971, [039752](#)), the toxic effects  
11 of O<sub>3</sub> were generally assumed to be confined to the tissues directly in contact with the gas, such as  
12 the respiratory epithelium. Due to the highly reactive nature of O<sub>3</sub>, little systemic absorption was  
13 predicted. Zelac et al., however, reported a significant increase in chromosome aberrations in  
14 peripheral blood lymphocytes from Chinese hamsters exposed to 0.2 ppm for 5 hours. Other in vivo  
15 exposure studies found increased DNA strand breaks in respiratory cells from guinea pigs (Feng et  
16 al., 1997, [083578](#)) and mice (Bornholdt et al., 2002, [036677](#)) but only with exposure to higher doses  
17 of O<sub>3</sub> (1 ppm for 72 hours and 1 or 2 ppm for 90 minutes, respectively). In other studies there were  
18 no observations of chromosomal aberrations in germ cells, but mutagenic effects have been seen in  
19 offspring of mice exposed to 0.2 ppm during gestation (blepharophimosis or dysplasia of the  
20 eyelids). The overall evidence for mutagenic activity from in vitro studies is positive, and in the  
21 National Toxicology Program report described above, O<sub>3</sub> was found to be mutagenic in Salmonella,  
22 with and without S9 metabolic activation. No new toxicological studies of DNA damage have  
23 become available since the 2006 O<sub>3</sub> AQCD.

24 A number of epidemiologic studies looked at the association between O<sub>3</sub> and DNA and cellular  
25 level damages. These changes may be relevant to mechanisms leading to cancers development and  
26 serve as early indicators of elevated risk of mutagenicity.

27 Two studies performed in California examined cytogenetic damage in relation to O<sub>3</sub>  
28 exposures. Huen et al. (2006, [089035](#)) examined cytogenetic damage among African American  
29 children and their mothers in Oakland, CA. Increased O<sub>3</sub> (mean monthly 8-h O<sub>3</sub> concentrations  
30 ranged from about 30 ppb in April to 14 ppb in November) was associated with increased  
31 cytogenetic damage (micronuclei frequency among lymphocytes and buccal cells) even after  
32 adjustment for household/personal smoking status and distance-weighted traffic density. Chen et al.  
33 (2006, [196504](#)) recruited college students at the University of California, Berkeley who reported  
34 never smoking and compared their levels of cytogenetic damage (micronuclei frequency from buccal  
35 cells) in the spring and fall. Cytogenetic damage was greater in the fall, which the authors attributed  
36 to the increase in O<sub>3</sub> over the summer. However, O<sub>3</sub> levels over 2, 7, 10, 14, or 30 days  
37 (concentrations not given) before collection of buccal cells did not correlate with cytogenetic

1 damage. Estimated lifetime O<sub>3</sub> exposure was also not correlated with cytogenetic damage.  
2 Additionally, the authors exposed a subset of the students (n=15) to 200 ppb O<sub>3</sub> for 4 hours while the  
3 students exercised intermittently. Ozone was found to be associated with an increase in cytogenetic  
4 damage in degenerated cells but not in normal cells 9-10 days after exposure. Increased cytogenetic  
5 damage was also noted in peripheral blood lymphocytes collected 18 hours after exposure.

6 A study performed in Mexico recruited 55 male workers working indoors (n=27) or outdoors  
7 (n=28) in Mexico City or Puebla, Mexico in order to study the relationship between O<sub>3</sub> and DNA  
8 damage (detected from peripheral blood samples using the Comet assay) (Tovalin et al., 2006,  
9 [091322](#)). The median estimated daily O<sub>3</sub> concentrations were estimated to be 28.5 ppb for outdoor  
10 workers and 5.1 ppb for indoor workers in Mexico City and 36.1 ppb for outdoor workers and  
11 19.5 ppb for indoor workers in Puebla. Overall, a positive correlation between O<sub>3</sub> levels and DNA  
12 damage was observed. However, when examining the relationship by city and workplace, only DNA  
13 damage in outdoor workers in Mexico City remained correlated with O<sub>3</sub> levels.

14 Three studies examining the relationship between O<sub>3</sub> and DNA-level damage have been  
15 performed in Europe. The largest of these was the GenAir case-control study, which was nested  
16 within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, and included  
17 individuals recruited between 1993 and 1998 from ten European countries. Only non-smokers (must  
18 not have smoked for at least 10 years prior to enrollment) were enrolled in the study. The researchers  
19 examined DNA adduct levels (DNA bonded to cancer-causing chemicals) and their relationship with  
20 O<sub>3</sub> concentrations (concentrations not given) (Peluso M Hainaut et al., 2005, [089057](#)). A positive  
21 association was seen between DNA adduct levels and O<sub>3</sub> concentrations from 1990-1994 but not O<sub>3</sub>  
22 levels from 1995-1999. In adjusted analyses with DNA adduct levels dichotomized as high and low  
23 (detectable versus non-detectable), the OR was 1.97 (95% CI: 1.08, 3.58) when comparing the upper  
24 tertile of O<sub>3</sub> concentration to the lower two tertiles. Two other European studies were conducted in  
25 Florence, Italy. The most recent of these enrolled individuals from the EPIC study into a separate  
26 study between March and September of 1999 (Palli et al., 2009, [196688](#)). The purpose of the study  
27 was to examine oxidative DNA damage (determined by Comet assay using blood lymphocytes) in  
28 association with varying periods of O<sub>3</sub> exposure. The researchers observed that longer periods of  
29 high O<sub>3</sub> exposure (concentrations not given) were more strongly correlated with oxidative DNA  
30 damage than shorter exposures (i.e., the rho [p-value] was 0.26 [0.03] for 0-10 days and 0.35 [0.002]  
31 for 0-90 days). This correlation was stronger among men compared to women. The correlations for  
32 all time periods had p-values <0.05 for ex- and never-smokers. For current smokers, the correlation  
33 was only observed among time periods  $\geq$  25 days. When adjusted for age, gender, smoking history,  
34 traffic pollution exposure, period of blood draw, and area of residence, the association between O<sub>3</sub>  
35 levels and oxidative DNA damage was positive for O<sub>3</sub> levels 0-60 days, 0-75 days, and 0-90 days  
36 prior to blood draw. Positive, statistically significant associations were not observed among shorter  
37 time periods. The other study performed in Florence recruited healthy volunteers who reported being  
38 non-smokers or light smokers (Giovannelli et al., 2006, [199894](#)). The estimated O<sub>3</sub> levels during the  
39 study ranged from approximately 4-40 ppb for 3-day averages, 5-35 ppb for 7-day averages, and

1 7.5-32.5 ppb for 30-day averages. Ozone concentrations were correlated with DNA strand breaks  
2 (measured from blood lymphocytes) over longer exposure periods (p-value: 0.002 at 30 days,  
3 p-value: 0.04 at 7 days; p-value: 0.17 at 3 days). This association was robust to control for  
4 temperature, solar radiation, gender, and age. No association was seen between O<sub>3</sub> concentrations  
5 and measures of oxidative DNA damage at 3, 7, or 30 days.

#### 7.6.4. Summary and Causal Determination

6 The 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) reported that evidence did not support ambient  
7 O<sub>3</sub> as a pulmonary carcinogen. Since the 2006 O<sub>3</sub> AQCD, very few epidemiologic and toxicological  
8 studies have been published that examine O<sub>3</sub> as a carcinogen, but collectively, study results indicate  
9 that O<sub>3</sub> may contribute to DNA damage. Overall, the evidence is **inadequate to determine if a**  
10 **causal relationship exists between ambient O<sub>3</sub> exposures and cancer.**

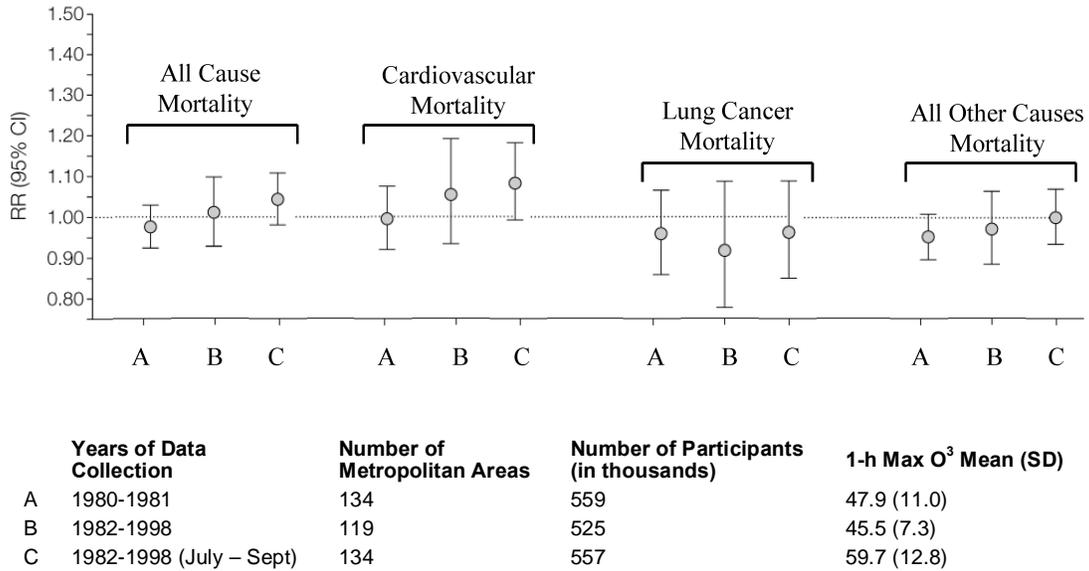
### 7.7. Mortality

11 A limited number of epidemiologic studies have assessed the relationship between long-term  
12 exposure to O<sub>3</sub> and mortality in adults. The 2006 O<sub>3</sub> AQCD concluded that an insufficient amount of  
13 evidence existed “to suggest a causal relationship between chronic O<sub>3</sub> exposure and increased risk  
14 for mortality in humans” (U.S. EPA, 2006, [088089](#)). In addition to the infant mortality studies  
15 discussed in Section 7.4.9, two additional studies have been conducted among adults since the last  
16 review; an ecologic study that finds no association between mortality and O<sub>3</sub>, and a reanalysis of the  
17 ACS cohort that specifically points to a relationship between long-term O<sub>3</sub> exposure and an  
18 increased risk of respiratory mortality. These studies supplement the evidence from long-term cohort  
19 studies characterized in previous reviews of O<sub>3</sub>, (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#))  
20 and are summarized here briefly.

21 In the Harvard Six Cities Study (Dockery et al., 1993, [044457](#)), adjusted mortality rate ratios  
22 were examined in relation to long-term mean O<sub>3</sub> concentrations in six cities: Topeka, KS; St. Louis,  
23 MO; Portage, WI; Harriman, TN; Steubenville, OH; and Watertown, MA. Mean O<sub>3</sub> concentrations  
24 from 1977 to 1985 ranged from 19.7 ppb in Watertown to 28.0 ppb in Portage. Long-term mean O<sub>3</sub>  
25 concentrations were not found to be associated with mortality in the six cities. However, the authors  
26 noted that “The small differences in O<sub>3</sub> levels among the (six) cities limited the power of the study to  
27 detect associations between mortality and O<sub>3</sub> levels.” In addition, while total and cardio-pulmonary  
28 mortality were considered in this study, respiratory mortality was not specifically considered.

29 In a subsequent large prospective cohort study of approximately 500,000 U.S. adults, Pope et  
30 al. (2002, [024689](#)) examined the effects of long-term exposure to air pollutants on mortality  
31 (American Cancer Society, Cancer Prevention Study II). All-cause, cardiopulmonary, lung cancer  
32 and other mortality risk estimates for long-term O<sub>3</sub> exposure are shown in Figure 7-5. While no  
33 consistently significant positive associations were observed between O<sub>3</sub> and mortality, the mortality  
34 risk estimates were larger when analyses considered more accurate exposure metrics, rising when the

1 entire period was considered (versus just at the start of the study) and becoming marginally  
 2 significant when the exposure estimate was restricted to the summer months (July to September),  
 3 especially when considering cardio-pulmonary deaths. In contrast, consistent positive and significant  
 4 effects of PM<sub>2.5</sub> were observed for both lung cancer and cardio-pulmonary mortality.



Source: Derived with permission from American Medical Association, Pope et al. (2002, [024689](#)).

**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.**

5 A study by Abbey et al. (1999, [047559](#)) examined the effects of long-term air pollution  
 6 exposure, including O<sub>3</sub>, on all-cause (n = 1,575), cardiopulmonary (n = 1,029), nonmalignant  
 7 respiratory (n = 410), and lung cancer (n = 30) mortality in the long-term prospective Adventist  
 8 Health Study of Smog (AHSMOG) of 6,338 nonsmoking, non-Hispanic white individuals living in  
 9 California. A particular strength of this study was the extensive effort devoted to assessing long-term  
 10 air pollution exposures, including interpolation to residential and work locations from monitoring  
 11 sites over time and space. No associations with long-term O<sub>3</sub> exposure were observed for all cause,  
 12 cardiopulmonary, and nonmalignant respiratory mortality. In a follow-up, Chen et al. (2005, [087942](#))  
 13 utilized data from the AHSMOG study and reported no significant associations between long-term  
 14 O<sub>3</sub> exposure (mean O<sub>3</sub> concentration 26.2 ppb) and fatal coronary heart disease. Thus, no association  
 15 of chronic O<sub>3</sub> exposure with mortality outcomes has been detected in this study.

16 Lipfert et al. (2000, [004087](#); 2003, [052250](#)) reported positive effects on all-cause mortality for  
 17 peak O<sub>3</sub> exposures (95th percentile levels) in the U.S. Veterans Cohort study of approximately  
 18 50,000 middle-aged men recruited with a diagnosis of hypertension. The actual analysis involved  
 19 smaller subcohorts based on exposure and mortality follow-up periods. Four separate exposure

1 periods were associated with three mortality follow-up periods. For concurrent exposure periods,  
2 peak O<sub>3</sub> was positively associated with all-cause mortality, with a 9.4% (95% CI: 0.4, 18.4) excess  
3 risk per mean 95th percentile O<sub>3</sub> less estimated background level (not stated). “Peak” refers, in this  
4 case, to the 95th percentile of the hourly measurements, averaged by year and county. In a further  
5 analysis, Lipfert et al. (2003, [052250](#)) reported the strongest positive association for concurrent  
6 exposure to peak O<sub>3</sub> for the subset of subjects with low diastolic blood pressure during the 1982 to  
7 1988 period. Two more recent studies of this cohort focused specifically on traffic density (Lipfert et  
8 al., 2006, [088756](#); 2006, [088218](#)). Lipfert (2006, [088218](#)) concluded that: “Traffic density is seen to  
9 be a significant and robust predictor of survival in this cohort, more so than ambient air quality, with  
10 the possible exception of O<sub>3</sub>,” reporting a significant O<sub>3</sub> effect even with traffic density included in  
11 the model: RR=1.080 per 40 ppb peak O<sub>3</sub> (95% CI: 1.019, 1.146). In Lipfert (2006, [088756](#)), which  
12 considers only the EPA Speciation Trends Network (STN) sites, O<sub>3</sub> drops to non-significant predictor  
13 of total mortality for this cohort. However, the authors acknowledge that: “Peak O<sub>3</sub> has been  
14 important in analyses of this cohort for previous periods, but in the STN data set, this variable has  
15 limited range and somewhat lower values and its small coefficient of variation results in a relatively  
16 large standard error.” The restriction to subjects near STN sites likely reduced the power of this  
17 analysis, though the size of the remaining subjects considered was not reported in this paper. In  
18 addition, these various Veteran's Cohort studies considered only total mortality, and did not consider  
19 mortality on a by-cause basis.

20 An ecological study in Brisbane, Australia used a geospatial approach to analyze the  
21 association of long-term exposure to gaseous air pollution with cardio-respiratory mortality, in the  
22 period 1996-2004 (Wang et al., 2009, [199990](#)). A generalized estimating equations model was  
23 employed to investigate the impact of NO<sub>2</sub>, O<sub>3</sub> and SO<sub>2</sub>, but PM was not addressed. The results  
24 indicated that long-term exposure to SO<sub>2</sub> was associated with cardio-respiratory mortality, but the  
25 fact that this study considered only one city, and that the range of O<sub>3</sub> exposure across that city  
26 (23.7-35.6 ppb) was low and slight in variation in comparison to the range of other pollutants across  
27 the city, limited study power. In addition, confounding factors (e.g., smoking) could not be addressed  
28 at the individual level in this ecological study. Respiratory mortality was not evaluated separately.

29 In the most recent follow-up analysis of the ACS cohort (Jerrett et al., 2009, [194160](#)),  
30 cardiopulmonary deaths were subdivided into respiratory and cardiovascular, separately, as opposed  
31 to combined in the Pope et al. (2002, [024689](#)) work. This analysis utilized the ACS cohort with data  
32 from 1977 through 2000 (mean O<sub>3</sub> concentration ranged from 33.3 to 104.0 ppb). A 10-ppb  
33 increment in exposure to O<sub>3</sub> elevated the risk of death from the cardiopulmonary, cardiovascular,  
34 ischemic heart disease, and respiratory causes. Inclusion of the concentration of PM<sub>2.5</sub> measured in  
35 1999-2000 as a co-pollutant attenuated the association with exposure to O<sub>3</sub> for all end points except  
36 death from respiratory causes, for which a significant association persisted (Table 7.7). The  
37 association between increased O<sub>3</sub> concentrations and increased risk of death from respiratory causes  
38 was insensitive to the use of a random-effects survival model allowing for spatial clustering within  
39 the metropolitan area and state of residence, and to adjustment for several ecologic variables

1 considered individually. Subgroup analyses showed that temperature and region of country, but not  
 2 sex, age at enrollment, body-mass index, education, or PM<sub>2.5</sub> concentration, modified the effects of  
 3 O<sub>3</sub> on the risk of death from respiratory causes (i.e., risks were higher at higher temperature, and in  
 4 the Southeast, Southwest, and Upper Midwest). Ozone threshold analyses indicated that the  
 5 threshold model was not a better fit to the data (p > 0.05) than a linear representation of the overall  
 6 O<sub>3</sub>-mortality association. Overall, this new analysis indicates that long-term exposure to PM<sub>2.5</sub>  
 7 increases risk of cardiac death, while long-term exposure to O<sub>3</sub> is specifically associated with an  
 8 increased risk of respiratory death.

**Table 7-7. Relative risk (and 95% CI) of death attributable to a 10-ppb change in the ambient ozone concentration**

Cause of Death	O <sub>3</sub> (96 MSAs)	O <sub>3</sub> (86 MSAs)	O <sub>3</sub> +PM <sub>2.5</sub> (86 MSAs)
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)

Source: Used with permission from Massachusetts Medical Society, Jerrett et al. (2009, [194160](#))

### 7.7.1. Summary and Causal Determination

9 The 2006 O<sub>3</sub> AQCD concluded that an insufficient amount of evidence existed “to suggest a  
 10 causal relationship between chronic O<sub>3</sub> exposure and increased risk for mortality in humans”  
 11 (U.S. EPA, 2006, [088089](#)). Two additional studies have been conducted since the last review, an  
 12 ecologic study that finds no association between mortality and O<sub>3</sub> (Wang et al., 2009, [199990](#)), and a  
 13 re-analysis of the ACS cohort that specifically points to a relationship between long-term O<sub>3</sub>  
 14 exposure and an increased risk of respiratory mortality (Jerrett et al., 2009, [194160](#)). The findings  
 15 from the Jerrett et al. (2009, [194160](#)) study are consistent and coherent with the evidence from  
 16 epidemiologic, controlled human exposure, and animal toxicological studies for the effects of short-  
 17 and long-term exposure to O<sub>3</sub> on respiratory effects. Additionally, the evidence for short- and long-  
 18 term respiratory morbidity provides biological plausibility for mortality due to respiratory disease.  
 19 Collectively, the evidence **is suggestive of a causal relationship between long-term O<sub>3</sub> exposures**  
 20 **and all-cause mortality.**

# References

A list of all epidemiologic references considered for inclusion in this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=403](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=403)

A list of all toxicological references considered for inclusion in this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=401](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=401)

A list of all controlled human exposure references considered for inclusion in this chapter can be found at

[http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group\\_id=477](http://hero.epa.gov/index.cfm?action=search.do&submit=Search&group_id=477)

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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[039752](#)

# Chapter 8. Populations Susceptible to Ozone-related Health Effects

1 Interindividual variation in human responses to air pollution exposure suggests that some  
2 populations are at increased risk for detrimental effects of ambient exposure to an air pollutant. The  
3 NAAQS are intended to provide an adequate margin of safety for both the population as a whole and  
4 those individuals potentially at increased risk for health effects in response to ambient air pollution  
5 (Section 1.1). To facilitate the identification of populations at greater risk for O<sub>3</sub>-related health  
6 effects, studies have evaluated factors that contribute to the susceptibility and/or vulnerability of an  
7 individual to O<sub>3</sub>. The definition for both of these terms has been found to vary across studies, but in  
8 most instances susceptibility refers to biological or intrinsic factors (e.g., lifestage, sex) while  
9 vulnerability refers to non-biological or extrinsic factors (e.g., SES) (U.S. EPA, 2009, [179916](#);  
10 U.S. EPA, 2010, [626035](#)). Additionally, in some cases, the terms “at-risk” and sensitive populations  
11 have been used to encompass these concepts more generally. However, in many cases, a factor  
12 identified that increases an individual's risk for morbidity or mortality effects from exposure to an air  
13 pollutant cannot be easily categorized as either a susceptibility or vulnerability factor.

14 As developed in previous ISAs and reviews (Sacks et al., In Press, [664486](#); U.S. EPA, 2009,  
15 [179916](#); U.S. EPA, 2010, [626035](#)), an all encompassing definition for “susceptible population” is  
16 used to circumvent the need to distinguish between susceptible and vulnerable, and to identify the  
17 populations at greater risk for O<sub>3</sub>-induced health effects. This definition identifies susceptible  
18 populations as the following:

Individual- and population-level characteristics that increase the risk of O<sub>3</sub>-related health effects in a population including, but not limited to: genetic background, birth outcomes (e.g., low birth weight, birth defects), race, sex, lifestage, lifestyle (e.g., smoking status, nutrition), preexisting disease, SES (e.g., educational attainment, reduced access to health care), and characteristics that may modify exposure to O<sub>3</sub> (e.g., time spent outdoors).

19 To examine whether O<sub>3</sub> differentially affects certain populations, epidemiologic studies  
20 conduct stratified analyses to identify the presence or absence of effect measure modification. A  
21 thorough evaluation of potential effect measure modifiers may help identify populations that are  
22 more susceptible to O<sub>3</sub>. Although the design of toxicological and controlled human exposure studies  
23 do not allow for the examination of effect measure modifiers, both can provide support and  
24 biological plausibility for factors that may lead to increased susceptibility for O<sub>3</sub>-related health  
25 effects through the study of animal models of disease or individuals with underlying disease or

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

1 genetic polymorphisms that allow for comparisons between subgroups. Therefore, the results from  
2 these studies, combined with those results obtained through stratified analyses in epidemiologic  
3 studies, comprise the overall weight of evidence for the increased susceptibility of specific  
4 populations to O<sub>3</sub>-related health effects.

5 This chapter discusses the epidemiologic, controlled human exposure, and toxicological  
6 studies evaluated in Chapters 5, 6, and 7 that provide information on potentially susceptible  
7 populations. The studies in this chapter include only those epidemiologic studies that presented  
8 stratified results (e.g., males versus females or <65 years of age versus ≥ 65 years of age). This  
9 approach allowed for a comparison between populations exposed to similar O<sub>3</sub> concentrations and  
10 within the same study design. Thus, numerous studies that focus on only one potentially susceptible  
11 population are described in previous chapters, but these studies are not discussed in detail in this  
12 chapter because of the lack of an adequate comparison group within the study. Included controlled  
13 human exposure studies are those that consisted of individuals with an underlying disease or genetic  
14 polymorphism, or studies that categorized the study population by age, race, etc. Included  
15 toxicological studies were those with animal models of disease.

16 Factors examined for possible susceptibility to O<sub>3</sub>-related health effects based on the overall  
17 evidence integrated across disciplines are described in greater detail in the following sections.

## 8.1. Pre-existing Disease/Conditions

18 Individuals with pre-existing disease are likely to constitute a susceptible population. Recent  
19 studies that examined whether pre-existing diseases and conditions lead to increased susceptibility to  
20 O<sub>3</sub> were identified and are summarized below. Table 8-1 displays the prevalence rates of these  
21 conditions by age and region among adults in the U.S. population. Substantial proportions of the  
22 U.S. population are affected by these conditions and therefore may represent a potentially large  
23 susceptible population.

**Table 8-1. Prevalence of respiratory diseases, cardiovascular diseases, and diabetes by age and region among individuals 18 years and older in the U.S.**

Chronic Disease/Condition	N (in thousands)	Age				Region			
		18-44	45-64	65-74	75+	Northeast	Midwest	South	West
<b>Respiratory Diseases</b>									
Asthma	28,260	13.5	12.0	12.0	10.0	12.8	13.4	11.2	13.9
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
<b>Cardiovascular Diseases</b>									
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
<b>Diabetes</b>	18,651	2.3	12.1	20.4	17.3	4.5	7.6	9.0	7.7

Source: Pleis et al. (2009, [629608](#)).

### 8.1.1. Influenza/Infections

1 Recent studies have indicated that underlying infections may increase susceptibility of  
2 individuals to O<sub>3</sub>-related health effects, although there are only a limited number of studies. A study  
3 of hospitalizations in Hong Kong reported that increased levels of influenza intensity resulted in  
4 increased excess risk of respiratory disease hospitalizations related to O<sub>3</sub> exposure (Wong et al.,  
5 2009, [196722](#)). In addition, a study of lung function in asthmatic children reported decreases in lung  
6 function with increased short-term O<sub>3</sub> exposure for those with upper respiratory infections but not  
7 those without infections (Lewis et al., 2005, [081079](#)).

### 8.1.2. Asthma/Corticosteroid Use

8 Previous O<sub>3</sub> AQCDs (U.S. EPA, 1996, [080828](#); U.S. EPA, 2006, [088089](#)) identified asthmatic  
9 individuals as a population susceptible to O<sub>3</sub>-related health effects, and approximately 12% of adults  
10 have reported ever having asthma (Pleis et al., 2009, [629608](#)).

11 Multiple epidemiologic studies included in this ISA have evaluated the potential for the  
12 susceptibility of asthmatics to O<sub>3</sub>-related health effects. No evidence for increased susceptibility was  
13 found in a study that examined the effect of short-term O<sub>3</sub> exposure on respiratory health (Barraza-  
14 Villarreal et al., 2008, [156254](#)). A positive association was reported for airway inflammation among  
15 asthmatic children, but the observed association was similar in magnitude to that of non-asthmatics.  
16 However, several studies have indicated some evidence for increased susceptibility of asthmatics  
17 related to O<sub>3</sub> exposure. A study of lifeguards in Texas reported lung function decreases with short-  
18 term O<sub>3</sub> exposure among both asthmatics and non-asthmatics, however, the decrease was greater  
19 among asthmatics (Thaller et al., 2008, [195869](#)). A Mexican study of children ages 6-14 detected an

1 association between short-term O<sub>3</sub> and wheeze, cough, and bronchodilator use among asthmatics but  
2 not non-asthmatics although this may have been the result of a small non-asthmatic population  
3 (Escamilla-Nuñez et al., 2008, [594284](#)). A study of the modification of the effect of greater O<sub>3</sub>  
4 associated decreases in short-term O<sub>3</sub> exposure on lung function by airway hyperresponsiveness  
5 (AHR) (a condition common among asthmatics) reported greater O<sub>3</sub>-associated decreases in lung  
6 function in elderly individuals with airway hyperresponsiveness, especially among those who were  
7 obese (Alexeeff et al., 2007, [195862](#)). Finally, a study of O<sub>3</sub> exposure and airway inflammation  
8 (FE<sub>NO</sub>) among elderly individuals stratified the study population by asthmatics and non-asthmatics  
9 (Delfino et al., 2010, [647222](#)). The regression coefficient was higher among asthmatics but the 95%  
10 CIs were wide due to the small number of asthmatics in the study (n=4), resulting in the inability to  
11 clearly identify a difference between the populations. Finally, some studies have reported null results  
12 for both asthmatics and nonasthmatics. Khatri et al. (2009, [594282](#)) found no association between  
13 short-term O<sub>3</sub> exposure and lung function for either asthmatic or non-asthmatic adults, but did note a  
14 decrease in lung function among individuals with allergies5)[594282](#)Khatri et al., 2009,  
15 (5)[594282](#)Khatri et al., 2009, (. One study compared individuals with asthma to individuals with  
16 other diseases/conditions (chronic obstructive pulmonary disease [COPD] or ischemic heart disease  
17 [IHD]) (Lagorio et al., 2006, [089800](#)). No association was observed between O<sub>3</sub> exposure and  
18 decrease in lung function among the asthmatic group or the other groups.

19 Additional evidence for difference in effects among asthmatics has been observed in studies  
20 that examined the association between O<sub>3</sub> exposure and lung function by asthma medication use. A  
21 study of asthmatic children living in Detroit reported a greater association between short-term O<sub>3</sub> and  
22 lung function for corticosteroid users compared with non-corticosteroid users (Lewis et al., 2005,  
23 [081079](#)). Conversely, another study found decreased lung function among non-corticosteroid users  
24 compared to users, although in this study, a large proportion of non-users were considered to be  
25 persistent asthmatics (Hernández-Cadena et al., 2009, [594283](#)). Lung function was not related to  
26 short-term O<sub>3</sub> exposure for corticosteroid users and non-users in a study taking place during the  
27 winter months in Canada (Liu et al., 2009, [192003](#)). Additionally, a study of airway inflammation  
28 reported a counterintuitive inverse association with O<sub>3</sub> of similar magnitude for all groups of  
29 corticosteroid users and non-users (Qian et al., 2009, [548793](#)).

30 Controlled human exposures studies that have examined the effects of O<sub>3</sub> on both asthmatic  
31 and healthy controls are limited. Based on studies reviewed in the 1996 and 2006 O<sub>3</sub> AQCD  
32 (U.S. EPA, 1996, [017831](#); U.S. EPA, 2006, [088089](#)), asthmatic subjects appear to be more sensitive  
33 to acute effects of O<sub>3</sub> in terms of FEV<sub>1</sub> and inflammatory responses than healthy nonasthmatic  
34 subjects. For instance, Horstman et al. (1995, [075834](#)) observed mild-to-moderate asthmatics to, on  
35 average, experiences double the O<sub>3</sub>-induced FEV<sub>1</sub> decrement of healthy subjects (19% versus 10%,  
36 respectively, p = 0.04). Moreover, a statistically significant positive correlation between FEV<sub>1</sub>  
37 responses to O<sub>3</sub> and baseline lung function was observed in the asthmatic individuals, i.e., responses  
38 increased with severity of disease. Only study reported a tendency for asthmatics to have smaller O<sub>3</sub>-  
39 induced FEV<sub>1</sub> decrements than healthy subjects (3% versus 8%, respectively) (Mudway et al., 2001,

1 [025327](#)). However, the asthmatics in that study also tended to be older than the healthy subjects,  
2 which could partially explain their lesser response since FEV<sub>1</sub> responses to O<sub>3</sub> diminish with age.  
3 Asthmatics also show significantly more neutrophils in the BALF (18 hours postexposure) than  
4 similarly exposed healthy individuals (Basha et al., 1994, [075950](#); Peden et al., 1997, [085842](#);  
5 Scannell et al., 1996, [080755](#)).

6 Toxicological studies provide support for greater effects of O<sub>3</sub> among those with asthma or  
7 airway hyperresponsiveness. In animal toxicological studies, an asthmatic phenotype is modeled by  
8 allergic sensitization of the respiratory tract. Many of the studies that provide evidence that O<sub>3</sub> is an  
9 inducer of airway hyperresponsiveness and remodeling utilize these types of animal models. For  
10 example, a series of experiments in infant rhesus monkeys show these effects, but only in monkeys  
11 sensitized to house dust mite allergen (Fanucchi et al., 2006, [096491](#); Joad et al., 2006, [596390](#);  
12 Schelegle et al., 2003, [053778](#)). Similarly, Funabashi et al. (2004, [596384](#)) demonstrated adverse  
13 changes in pulmonary function in mice exposed to O<sub>3</sub>, and Wagner et al. (2007, [596420](#))  
14 demonstrated enhanced inflammatory responses in rats exposed to O<sub>3</sub>, but only in animals sensitized  
15 to allergen. In general, it is the combined effects of O<sub>3</sub> and allergic sensitization which result in  
16 measurable effects on pulmonary function. In a bleomycin induced pulmonary fibrosis model,  
17 exposure to 250 ppb O<sub>3</sub> for 5 days increased pulmonary inflammation and fibrosis, along with the  
18 frequency of bronchopneumonia in rats. Thus short-term exposure to O<sub>3</sub> may enhance damage in a  
19 previously injured lung (Oyarzún et al., 2005, [596407](#)).

20 In the 2006 O<sub>3</sub> AQCD, the potential for asthmatics to have greater susceptibility to O<sub>3</sub>-related  
21 effects was supported by a number of controlled human exposure studies, evidence from  
22 toxicological studies, and a limited number of epidemiologic studies. Overall, in the recent  
23 epidemiologic literature some, but not all, studies report greater effects among individuals with  
24 asthma. Studies examining effect measure modification of the relationship between short-term O<sub>3</sub>  
25 and lung function by corticosteroid use had mixed results. Inconsistent findings of epidemiologic  
26 studies may be due to the differences in O<sub>3</sub> concentration across the studies. In addition, recent  
27 studies of behavioral responses have found studies that do not take into account individuals  
28 behavioral adaptation to forecasted air pollution levels (such as avoidance and reduced time  
29 outdoors) may be biased towards the null (Neidell and Kinney, 2010, [384492](#)). Evidence from  
30 controlled human exposure studies support greater FEV<sub>1</sub> and inflammatory responses to O<sub>3</sub> in  
31 asthmatics than in healthy individuals without a history of asthma. Information from recent  
32 toxicological studies adds to the evidence for heightened susceptibility of asthmatics to effects of O<sub>3</sub>  
33 exposure.

### 8.1.3. Chronic obstructive pulmonary disease (COPD)

34 Although not extensively examined in the literature, initial evidence suggests that pre-existing  
35 COPD may modify of the association between short-term O<sub>3</sub> exposure and cardiovascular-related  
36 health effects. In the U.S. over 4% of adults report having chronic bronchitis and almost 2% report  
37 having emphysema, both of which are classified as COPD.

1 In a recent study, Peel et al. (2007, [090442](#)) found that individuals with COPD were more  
2 susceptible to effects of short-term O<sub>3</sub> exposure on cardiovascular ED visits compared to healthy  
3 individuals in Atlanta, GA. They reported that short-term O<sub>3</sub> exposure was associated with higher  
4 odds of an ED visit for peripheral and cerebrovascular disease among individuals with COPD  
5 compared to individuals without COPD. However, pre-existing COPD did not increase the odds of  
6 hospitalization for all CVD outcomes (i.e. IHD, dysrhythmia, or congestive heart failure). In an  
7 additional study performed in Taiwan, both individuals with and without COPD had higher odds of  
8 congestive heart failure associated with O<sub>3</sub> exposure on warm days (Lee et al., 2008, [192076](#)).

9 In a study of elderly individuals, although O<sub>3</sub> was associated with greater increases in airway  
10 inflammation (FE<sub>NO</sub>) among elderly individuals with than without COPD, the number of individuals  
11 with COPD was small (n=5) and the 95% CI for the association in COPD subjects was wide  
12 (Delfino et al., 2010, [647222](#)). An additional study also found no association between O<sub>3</sub> exposure  
13 and lung function regardless of whether the study participant had COPD or other health issues  
14 (asthma or IHD) (Lagorio et al., 2006, [089800](#)).

15 Recent epidemiologic evidence does not indicate that COPD modifies the association between  
16 O<sub>3</sub> exposure and respiratory effects, but COPD may affect O<sub>3</sub>-related cardiovascular effects.

#### 8.1.4. Cardiovascular Disease

17 Cardiovascular disease (CVD) has become increasingly prevalent in the U.S., with about 12%  
18 of adults reporting being diagnosed with heart disease. Additionally, a high prevalence of other  
19 cardiovascular-related conditions has also been observed, such as hypertension, which is prevalent  
20 among approximately 24% of adults. In the 2006 AQCD, little evidence was available regarding pre-  
21 existing CVD as a susceptibility factor. Recent epidemiologic studies have examined cardiovascular-  
22 related diseases as modifiers of the O<sub>3</sub>-outcome associations; however, no recent evidence is  
23 available from controlled human studies or toxicological studies.

24 Peel et al. (2007, [090442](#)) compared the associations between short-term O<sub>3</sub> exposure and  
25 cardiovascular ED visits in Atlanta, GA among multiple comorbid conditions. The authors found no  
26 evidence of increased risk of cardiovascular ED visits in individuals previously diagnosed with  
27 dysrhythmia, congestive heart failure, or hypertension compared to healthy individuals. In Taiwan, a  
28 positive association was observed for O<sub>3</sub> on warm days and congestive heart failure hospital  
29 admissions (HAs), but the association did not differ between individuals with/without hypertension  
30 or with/without dysrhythmia (Lee et al., 2008, [192076](#)). Another study in Taiwan reported that the  
31 association between O<sub>3</sub> levels and ED visits for arrhythmias were greater on warm days among those  
32 with congestive heart failure compared to those without congestive heart failure; however, the  
33 estimate and 95% CI for those without congestive heart failure is completely contained within the  
34 95% CI of those with congestive heart failure (Chiu and Yang, 2009, [603236](#)).

35 Among individuals with a history of CVD there was a greater association between O<sub>3</sub>  
36 exposure and certain, but not all, blood inflammatory markers. Liao et al. (2005, [088677](#)) found that  
37 fibrinogen was positively associated with short-term O<sub>3</sub> exposure but this association was present

1 only among individuals with a history of CVD. Those without CVD showed a null association.  
2 However, for another biomarker (vWF), CVD status did not modify the positive association with  
3 short-term O<sub>3</sub> exposure)088677Liao et al., 2005, (0)088677Liao et al., 2005, (.  
4

5 Some modification by pre-existing atrial fibrillation and atherosclerosis were noted in  
6 mortality studies. A study of 48 U.S. cities reported increased risk of mortality with short-term O<sub>3</sub>  
7 exposure among only individuals with secondary atrial fibrillation (Medina-Ramón and Schwartz,  
8 2008, [193829](#)). No association was observed for short-term O<sub>3</sub> exposure and mortality in a study of  
9 diabetics with or without CVD prior to death; however, there was some evidence of increased effects  
10 during the warm season if individuals had diabetes and atherosclerosis compared to having only  
11 diabetes (Goldberg et al., 2006, [088641](#)).

12 Finally, a study of O<sub>3</sub> exposure and lung function was performed among participants with  
13 IHD, asthma, or COPD (Lagorio et al., 2006, [089800](#)). No association was observed regardless of  
14 whether the participant had IHD.

15 Overall, most studies do not report increased O<sub>3</sub>-related health effects for individuals with  
16 CVD with the possible exception of O<sub>3</sub> exposure and mortality. Future research among those with  
17 CVD compared to those without will increase the understanding of potential susceptibility of  
18 O<sub>3</sub>-related health effects among this group.

### 8.1.5. Diabetes

19 Recent literature has not extensively examined whether individuals with diabetes (about 8% of  
20 U.S. adults) are potentially susceptible to O<sub>3</sub>-related health effects. In a study of short-term O<sub>3</sub>  
21 exposure and cardiovascular ED visits in Atlanta, GA, no association was seen for individuals with  
22 or without diabetes (Peel et al., 2007, [090442](#)). A similar study conducted in Taiwan reported a  
23 positive association between O<sub>3</sub> exposure on warm days and HAs for congestive heart failure but  
24 again no modification by diabetes was observed (Lee et al., 2008, [192076](#)). Finally, in a study of ED  
25 visits for arrhythmia in Taiwan, there was no effect measure modification by diabetes on warm or  
26 cool days (Chiu and Yang, 2009, [603236](#)).

## 8.2. Life stage

27 The 2006 AQCD (U.S. EPA, 2006, [088089](#)) identifies children, especially those with asthma,  
28 and older adults as susceptible populations. New evidence, summarized below, further supports these  
29 findings.

### 8.2.1. Children

30 The 2000 Census reports that 28.6% of the U.S. population is under 20 years of age, with  
31 14.1% under the age of 10 (Social Science Data Analysis Network; CensusScope and CensusScope,  
32 2010, [647298](#)). Children are considered to be more susceptible to O<sub>3</sub>-related health effects compared  
33 to adults because they spend more time outside and are more highly active, especially during the

1 summer when O<sub>3</sub> concentrations are the highest (U.S. EPA, 2006, [088089](#)). Moreover, children's  
2 respiratory systems are undergoing development until about age 18-20 and are therefore thought to  
3 be more sensitive to O<sub>3</sub>-induced damage (U.S. EPA, 2006, [088089](#)).

4 Multiple studies have been performed examining different age groups and their susceptibility  
5 to O<sub>3</sub>-related respiratory HAs and emergency department (ED) visits. A study in Cyprus of short-  
6 term O<sub>3</sub> concentrations and respiratory HA detected possible effect measure modification by age  
7 with a larger association among individuals less than 15 years of age compared with those over  
8 15 years of age. However, this difference was only apparent with a 2-day lag (Middleton et al., 2008,  
9 [156760](#)). Similarly, a Canadian study of asthma-ED visits reported a positive association among 5-  
10 to 14-year olds but no association in any of the other age groups (ages examined 0-75+) (Villeneuve  
11 et al., 2007, [195859](#)). A study in Finland reported a greater O<sub>3</sub>-associated change in asthma-related  
12 ED visits among children (<15 year) as compared to adults (15-64 years) (Halonen et al., 2009,  
13 [625764](#)). A study of New York City HAs demonstrated an increase in the association between O<sub>3</sub>  
14 exposure and asthma-related hospitalizations for 6- to 18-year olds compared to those less than 6 and  
15 those older than 18 year of age (Silverman and Ito, 2010, [386252](#)). A study of long-term O<sub>3</sub> exposure  
16 and asthma HA among children reported larger associations among children 1- to 2-year old  
17 compared to children 2- to 6-year old (Lin et al., 2008, [196680](#)). A few studies reported positive  
18 associations among both children and adults and no modification of the effect by age. A study  
19 performed in Hong Kong examined O<sub>3</sub> and asthma-related HAs for ages 0-14, 15-65, and >65 (Ko et  
20 al., 2007, [092844](#)). The researchers reported that the association was greater among the 0-14 and  
21 14-65 age groups compared to the >65 age group. Another study looking at asthma-related ED visits  
22 in Maine reported positive associations for all age groups (ages 2-65) (Paulu and Smith, 2008,  
23 [180168](#)). A study performed in Washington found effects of O<sub>3</sub> on asthma hospitalizations among  
24 both children and adults (<18 and 18 years old) but reported that only children had statistically  
25 significant results at lag day 0, which the authors write, "suggests that children are more immediately  
26 responsive to adverse effects of O<sub>3</sub> exposure." (Mar and Koenig, 2009, [594410](#)). Additionally, a  
27 study examining asthma physician visits reported consistently negative effects in all age groups  
28 (1-17 and 18-64) (Burra et al., 2009, [195868](#)).

29 The 1996 O<sub>3</sub> AQCD, reported clinical evidence that children, adolescents, and young adults  
30 (<18 years of age) appear, on average, to have nearly equivalent spirometric responses to O<sub>3</sub>, but  
31 have greater responses than middle-aged and older adults when exposed to comparable O<sub>3</sub> doses  
32 (U.S. EPA, 1996, [017831](#)). Symptomatic responses (e.g., cough, shortness of breath, pain on deep  
33 inspiration) to O<sub>3</sub> exposure, however, appear to increase with age until early adulthood and then  
34 gradually decrease with increasing age (U.S. EPA, 1996, [017831](#)). For subjects aged 18-36 years,  
35 McDonnell et al. (1999, [010939](#)) reported that symptom responses from O<sub>3</sub> exposure also decrease  
36 with increasing age. Lung growth and development is not achieved until 18-20 years of age in  
37 females and the early 20s for males; pulmonary function is at its maximum during this time as well.  
38 Additionally, PBPK modeling reported regional extraction of O<sub>3</sub> to be higher in infants compared to  
39 adults. This is thought to be due to the smaller nasal and pulmonary regions surface area in children

1 under the age of 5 compared to the total airway surface area observed in adults (Sarangapani et al.,  
2 2003, [054581](#)).

3 Recent toxicological studies support previous findings of greater susceptibility in immature  
4 animals. Early life exposures of multiple species of laboratory animals, including infant monkeys,  
5 resulted in changes in conducting airways at the cellular, functional, ultra-structural, and  
6 morphological levels as is detailed below. Carey et al. (2007, [195752](#)) conducted a study of O<sub>3</sub>  
7 exposure in infant rhesus macaques, whose nasal airways closely resemble that of humans. Monkeys  
8 were exposed either acutely for 5 days to 0.5 ppm O<sub>3</sub>, or episodically for 5 biweekly cycles  
9 alternating 5 days of 0.5 ppm O<sub>3</sub> with 9 days of filtered air, designed to mimic human exposure  
10 (70 days total). All monkeys acutely exposed to O<sub>3</sub> had moderate to marked necrotizing rhinitis, with  
11 focal regions of epithelial exfoliation, numerous infiltrating neutrophils, and some eosinophils. The  
12 distribution, character, and severity of lesions in episodically exposed monkeys were similar to that  
13 of acutely exposed animals. Neither group exhibited mucous cell metaplasia proximal to the lesions,  
14 a protective adaptation observed in adult monkeys exposed continuously to 0.3 ppm O<sub>3</sub> in another  
15 study (Harkema et al., 1987, [040816](#)). Functional (increased airway resistance and responsiveness  
16 with antigen + O<sub>3</sub> co-exposure) and cellular changes in conducting airways (increased numbers of  
17 inflammatory eosinophils) also manifested among the infant monkeys (Plopper et al., 2007, [596412](#)).  
18 In addition, the lung structure of the conducting airways was significantly stunted or altered versus  
19 control animals and this aberrant development was persistent 6 months postexposure (Fanucchi et  
20 al., 2006, [096491](#)).

21 Similarly, rat fetuses exposed to O<sub>3</sub> in utero had significant ultra-structural changes in  
22 bronchiolar epithelium when examined near the end of gestation ((López et al., 2008, [197786](#)). In  
23 addition, exposure of mice to mixtures of air pollutants early in development affected pup lung  
24 cytokine levels (TNF, IL-1, KC, IL-6, and MCP-1). In utero exposure of animals to PM augmented  
25 O<sub>3</sub>-induced airway hyper-reactivity in these pups as juveniles (Auten et al., 2009, [200760](#)).

26 Age may affect the immune response to O<sub>3</sub> exposure. In comparing neonatal mice to adults,  
27 increased bronchoalveolar lavage (BAL) neutrophils were observed in four strains of neonates 24 h  
28 after exposure to 0.8 ppm O<sub>3</sub> for 5 hours (Vancza et al., 2009, [596419](#)). Three of these strains also  
29 exhibited increased BAL protein, although the two endpoints were not necessarily consistently  
30 correlated in a given strain. In some strains, however, adults were more sensitive, indicating a strain-  
31 age interaction. In young mice, healing of skin wounds is not significantly affected by O<sub>3</sub> exposure  
32 (Lim et al., 2006, [670834](#)). However, exposure to 0.5 ppm O<sub>3</sub> for 6 h/day significantly delays wound  
33 closure in aged mice.

34 Increased susceptibility found in the younger lifestage may be due to age-related changes in  
35 endogenous antioxidants and sensitivity to oxidative stress. A recent study demonstrated that  
36 0.25 ppm O<sub>3</sub> differentially alters expression of metalloproteinases in the skin of young (8 weeks) and  
37 aged (18 months) mice, indicating age-related susceptibility to oxidative stress (Fortino et al., 2007,  
38 [596382](#)). Valacchi et al. (2007, [596418](#)) found that aged mice had more vitamin E in their plasma but  
39 less in their lungs compared to young mice, which may affect their pulmonary antioxidant defenses.

1 Servais et al. (2005, [195667](#)) found higher levels of oxidative damage indicators in three week-old  
2 (immature) and 20 month-old (aged) rats compared to adult rats, which were relatively resistant to an  
3 intermittent 7-day exposure to 0.5 ppm O<sub>3</sub>. Immature rats exhibited a higher ventilation rate, which  
4 may have increased exposure. Senescent rats had similar ventilatory rates as adults, but their  
5 antioxidant enzyme responses had a different profile from those of adult rats.

6 Additionally, a series of toxicological studies reported an association between O<sub>3</sub> exposure and  
7 bradycardia that was present among young mice but not among older mice (Hamade and Tankersley,  
8 2009, [596386](#); Hamade et al., 2008, [156515](#); Hamade et al., 2010, [666324](#); Tankersley et al., 2010,  
9 [628062](#)). Regression analysis revealed a significant interaction between age and strain on heart rate,  
10 which implies that aging may affect heart rate differently between mouse strains (Tankersley et al.,  
11 2010, [628062](#)). The authors propose that the genetic differences between the mice strains could be  
12 altering the formation of ROS, which tends to increase with age, thus modulating the changes in  
13 cardiopulmonary physiology after O<sub>3</sub> exposure.

14 The human clinical and toxicological studies reported evidence of increased susceptibility for  
15 younger ages. Studies of respiratory HA and ED visits observed mixed findings for associations  
16 among children and young adults, although generally studies reported positive associations among  
17 both children and adults or just among children. For other outcomes, inconsistent findings regarding  
18 susceptibility to O<sub>3</sub>-related health effects. The interpretation of these studies is limited by the lack of  
19 consistency in comparison age groups and outcomes examined.

## 8.2.2. Older Adults

20 The gradual decline in physiological processes that occur with aging may lead to increased  
21 susceptibility to O<sub>3</sub>-related health effects (U.S. EPA, 2006, [192082](#)). Diminished symptomatic  
22 responses may also put the elderly at increased risk for continued O<sub>3</sub> exposure. In addition, older  
23 adults have a higher prevalence of pre-existing diseases compared to younger age groups and this  
24 may also lead to increased susceptibility to O<sub>3</sub>-related health effects (see Table 8-1 that gives pre-  
25 existing rates by age). Moreover, with the number of older Americans increasing in upcoming years  
26 (estimated to increase from 12.4% of the U.S. population to 19.7% between 2000 to 2030, which is  
27 approximately 35 million and 71.5 million individuals, respectively) this group represents a large  
28 population potentially susceptible to O<sub>3</sub>-related health effects (Social Science Data Analysis  
29 Network; CensusScope and CensusScope, 2010, [647298](#); U.S. Census Bureau, 2010, [647312](#)).

30 A positive association was reported between O<sub>3</sub> levels and respiratory HAs for adults 65 and  
31 older but not for those adults aged 15-64 (Halonon et al., 2009, [625764](#)). In the same study, no  
32 association was observed between O<sub>3</sub> levels and respiratory mortality among those 65 years and  
33 older or those 15-64 years; however, an inverse association between O<sub>3</sub> levels and cardiovascular  
34 mortality was present among those 65 years and older but not among those under 65 years of age.  
35 This inverse association among those 65 and older persisted when examining hospitalizations for  
36 coronary heart disease. A study of CVD-related hospital visits in Bangkok reported an increase in  
37 percent change for hospital visits with previous day and cumulative 2-day O<sub>3</sub> levels among those

1 65 years and older, whereas no association was present for individuals less than 65 years of age. No  
2 association was observed for current day or cumulative three-day averages in any age group  
3 (Buadong et al., 2009, [602060](#)). A study examining O<sub>3</sub> and HAs for CVD-related health effects  
4 reported no association for individuals aged 15-64 or individuals aged 65 and older, although one  
5 lag-time did show an inverse effect for coronary heart disease among elderly that was not present  
6 among 15- to 64-year olds (Halonen et al., 2009, [625764](#)). No modification by age (40-64 versus  
7 >64) was observed in a study from Brazil examining O<sub>3</sub> levels and COPD ED visits (Arbex et al.,  
8 2009, [184334](#)).

9 The majority of studies reported greater effects of short-term O<sub>3</sub> exposure and mortality  
10 among older adults, which is consistent with the findings of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006,  
11 [088089](#)). A study conducted in 48 cities across the U.S. reported larger effects among adults 65 and  
12 older compared to those younger than 65 years (Medina-Ramón and Schwartz, 2008, [193829](#)).  
13 Further investigation of this study population revealed no association between O<sub>3</sub> and mortality until  
14 age 50 and a reduced effect after age 80 (Zanobetti and Schwartz, 2008, [195755](#)). A study of 7 urban  
15 centers in Chile reported similar results, with greater effects in adults 65 and older, however the  
16 effects were smaller among those 85 year of age and older compared to those in the 75-84 years old  
17 age range (Cakmak et al., 2007, [091170](#)). A study performed in China reported greater effects in  
18 populations 45 years and older (compared to 5-44 year olds), with statistically significant effects  
19 present only among those 65 years and older (Kan et al., 2008, [156621](#)). An Italian study reported  
20 higher risk of all-cause mortality associated with increased O<sub>3</sub> concentrations among individuals  
21 85 year and older as compared to those 35-84 years old. Those 65-74 and 75-84 years did not show a  
22 greater increase in risk compared to those age 35-64 years (Stafoggia et al., 2010, [625034](#)). The Air  
23 Pollution and Health: A European and North American Approach (APHENA) project examined the  
24 association between O<sub>3</sub> exposure and mortality for those <75 and ≥ 75 years of age. In Canada, the  
25 associations for all-cause and cardiovascular mortality were greater among those 75 years and older  
26 in the summer-only and all-year analyses. Age groups were not compared in the analysis for  
27 respiratory mortality in Canada. In the U.S., the association for all-cause mortality was slightly  
28 greater for those younger than 75 years of age compared to those 75 and older in summer-only  
29 analyses. No consistent pattern was observed for CVD mortality. In Europe, slightly larger  
30 associations for all-cause mortality were observed in those younger than 75 in all-year and summer-  
31 only analyses. Larger associations were reported among those <75 for CVD mortality in all-year  
32 analyses, but the reverse was true for summer-only analyses (Katsouyanni et al., 2009, [199899](#)).

33 Biological plausibility for increased susceptibility among older adults is provided by clinical  
34 and toxicological studies. Respiratory symptom responses to O<sub>3</sub> exposure appears to increase with  
35 age until early adulthood and then gradually decrease with increasing age (U.S. EPA, 1996, [017831](#)).  
36 The decrease in symptomatic responses with age was observed by McDonnell et al. (1999, [010939](#))  
37 in subjects aged 18 to 36 years. In contrast to young adults, the diminished symptomatic responses in  
38 older adults may put them at increased risk for continued O<sub>3</sub> exposure. Regarding cardiac outcomes,  
39 O<sub>3</sub> exposure resulted in an increase in left ventricular chamber dimensions at end diastole (LVEDD)

1 in young and old mice, whereas decreases in left ventricular posterior wall thickness at end systole  
2 (PWTES) were only observed among older mice (Tankersley et al., 2010, [628062](#)).

### 8.3. Sex

3 The distribution of males and females in the U.S. is similar. In 2000, 49.1% of the U.S.  
4 population was male and 50.9% were female. The distribution did vary by age with a greater  
5 prevalence of females  $\geq$  65 years old compared to males (Social Science Data Analysis Network;  
6 CensusScope and CensusScope, 2010, [647298](#)). Recent epidemiologic studies have evaluated the  
7 effects of short-term and long-term exposure to O<sub>3</sub> on multiple health endpoints stratified by sex.

8 A study in Maine on short-term O<sub>3</sub> concentrations and asthma ED visits detected greater  
9 effects among males ages 2-14 and among females ages 15-34 compared to males and females in the  
10 same age groups (no difference was detected for males and females aged 35-64) (Paulu and Smith,  
11 2008, [180168](#)). A New York study found no effect measure modification of the association between  
12 long-term O<sub>3</sub> exposure and asthma HA among males and females between 1 and 6 years old (Lin et  
13 al., 2008, [196680](#)). Additionally, a Canadian study reported no associations between short-term O<sub>3</sub>  
14 and respiratory infection HAs for either boys or girls under the age of 15 (Lin et al., 2005, [087828](#)),  
15 whereas another Canadian study reported a slightly higher but non-statistically significant increase in  
16 respiratory HA for males (mean ages 47.6-69.0 years) (Cakmak et al., 2006, [093272](#)). A recent study  
17 from Hong Kong examining individuals of all ages reported no effect measure modification by sex  
18 for overall respiratory disease HAs, but did detect a greater excess risk of HAs for COPD among  
19 females compared to males (Wong et al., 2009, [196722](#)). Similarly a study in Brazil found higher  
20 effect estimates for COPD ED visits among females compared to males (Arbex et al., 2009, [184334](#)).  
21 Higher levels of respiratory HA with greater O<sub>3</sub> concentrations was also observed for females in a  
22 study of individuals living in Cyprus (Middleton et al., 2008, [156760](#)). A study of lung function  
23 unrelated to HA and ED visits was conducted among lifeguards in Texas and reported decreased lung  
24 function with increased O<sub>3</sub> exposure among females but not males (Thaller et al., 2008, [195869](#)).  
25 This study included individuals aged 16-27, and the majority of participants were male.

26 In addition to examining the potential modification of O<sub>3</sub> associations with respiratory  
27 outcomes by sex, studies also examined cardiovascular-related outcomes specifically HAs and ED  
28 visits. All of these studies reported no effect modification by sex with some studies reporting null  
29 associations for both males and females (Middleton et al., 2008, [156760](#); Villeneuve et al., 2006,  
30 [090191](#); Wong et al., 2009, [196722](#)) and one study reporting a positive associations for both sexes  
31 (Cakmak et al., 2006, [099068](#)). A French study examining the associations between O<sub>3</sub>  
32 concentrations and risk of ischemic strokes (not limited to ED visits or HAs) reported no association  
33 for either males or females with lags of 0, 2, or 3 days (Henrotin et al., 2007, [093270](#)). A positive  
34 association was reported for males with a lag of 1 day, but this association was null for females. The  
35 authors note that men in the study had much higher rates of current and former smoking than women  
36 (67.4% versus 9.3%).

1 A biomarker study investigating the effects of O<sub>3</sub> concentrations on high-sensitivity C-reactive  
2 protein (hs-CRP), fibrinogen, and white blood cell count (WBC), reported observations for various  
3 lag times ranging from 0 to 7 days (Steinvil et al., 2008, [188893](#)). Most of the associations were null  
4 for males and females although one association between O<sub>3</sub> and fibrinogen was positive for males  
5 and null for females (lag day 4); however, this positive association was null or negative when other  
6 pollutants were included in the model. Only one study examining correlations between O<sub>3</sub> levels and  
7 oxidative DNA damage examined results stratified by sex. In this study Palli et al. (2009, [196688](#))  
8 reported stronger correlations for males than females, both during short-term exposure (less than  
9 30 days) and long-term exposure (0-90 days). However, the authors comment that this difference  
10 could be partially explained by different distributions of exposure to traffic pollution at work.

11 A few studies have examined the association between short-term O<sub>3</sub> concentrations and  
12 mortality stratified by sex and in contrast with studies of other endpoints, were more consistent in  
13 reporting elevated risks among females. These studies, conducted in the U.S. (Medina-Ramón and  
14 Schwartz, 2008, [193829](#)), Italy (Stafoggia et al., 2010, [625034](#)), and Asia (Kan et al., 2008, [156621](#)),  
15 reported higher effects in females. In the U.S. study, the elevated risk of mortality among females  
16 was greater specifically among those 60 years of age and older (Medina-Ramón and Schwartz, 2008,  
17 [193829](#)). One long-term O<sub>3</sub> exposure study of respiratory mortality stratified their results by sex and  
18 reported relative risks of 1.01 (95 % CI: 0.99, 1.04) for males and 1.04 (95% CIs 1.03, 1.07) for  
19 females (Jerrett et al., 2009, [194160](#)).

20 Experimental research provides a further understanding of the possible differential  
21 susceptibility of males and females to O<sub>3</sub> exposure. Several studies have suggested that physiological  
22 differences between sexes may predispose females to a greater susceptibility to O<sub>3</sub>. Lower plasma  
23 and nasal lavage fluid (NLF) levels of uric acid (most prevalent antioxidant) in females, the initial  
24 defense mechanism of O<sub>3</sub> neutralization, may be a contributing factor (Housley et al., 1996, [080811](#)).  
25 Consequently, reduced absorption of O<sub>3</sub> in the upper airways of females may promote its deeper  
26 penetration. Dosimetric measurements have shown that the absorption distribution of O<sub>3</sub> is  
27 independent of gender when absorption is normalized to anatomical dead space (Bush et al., 1996,  
28 [080763](#)). Thus, a differential removal of O<sub>3</sub> by uric acid seems to be minimal. In general, the  
29 physiologic response of young healthy females to O<sub>3</sub> exposure appears comparable to the response  
30 of young males (Hazucha et al., 2003, [048168](#)). During the follicular phase of the menstrual cycle,  
31 lung function response to O<sub>3</sub> is enhanced (Fox et al., 1993, [043906](#)). Seal et al. (1996, [044251](#)) later  
32 reported no effect of menstrual cycle phase in their analysis of responses of 150 women, but  
33 conceded that the methods used by Fox et al. (1993, [043906](#)) more precisely defined the menstrual  
34 cycle phase. In a toxicological study, small sex differences were seen in adult mice with respect to  
35 pulmonary inflammation and injury after a 5-h exposure to 0.8 ppm O<sub>3</sub>, and although adult females  
36 were generally more susceptible, these differences were strain-dependent, with some strains  
37 exhibiting greater susceptibility in males (Vancza et al., 2009, [596419](#)). The most obvious sex  
38 difference was apparent in lactating females, which incurred the greatest lung injury or inflammation  
39 among several of the strains.

1 Overall, results have varied, with evidence for increased susceptibility for O<sub>3</sub>-related health  
2 effects present for females in some studies and males in other studies. Most studies examining O<sub>3</sub>  
3 and mortality report females to be more susceptible than males. Little evidence is available regarding  
4 a difference between the sexes for other outcomes. Mixed findings are reported on whether effect  
5 measure modification exists by sex for respiratory and cardiovascular HA and ED visits, although  
6 this inconsistency, at least in part, could be attributable to additional comparisons of different age  
7 groups and different respiratory health endpoints by the various studies.

## 8.4. Genetics

8 Multiple studies that examined the effect of short- and long-term O<sub>3</sub> exposure on respiratory  
9 function have focused on whether various genes modify the effect of O<sub>3</sub> on health. A study  
10 examining the relationship between a mother's asthma and her infant's respiratory health illustrated  
11 the potential for genetics to play a role in O<sub>3</sub>-related susceptibility to health effects. A study of  
12 wheeze in infants reported larger associations between short-term O<sub>3</sub> exposure and wheeze and  
13 difficulty breathing in infants whose mothers have asthma compared to infants of mothers without  
14 asthma (Triche et al., 2006, [093274](#)).

15 Multiple genes, including glutathione S-transferase Mu 1 (GSTM1) and tumor necrosis  
16 factor- $\alpha$  (TNF- $\alpha$ ) were evaluated in the 2006 AQCD (U.S. EPA, 2006, [088089](#)) and found to have a  
17 “potential role... in the innate susceptibility to O<sub>3</sub>.” Studies performed since the last AQCD have  
18 continued to examine the roles of GSTM1 and TNF $\alpha$  on O<sub>3</sub>-related health effects and have also  
19 examined other gene variants that may increase susceptibility to O<sub>3</sub>-related health effects.

20 Epidemiologic studies that examined the effects of short-term exposure to O<sub>3</sub> on lung function  
21 included analyses of potential gene-environment interactions. Romieu et al. (2006, [090969](#)) reported  
22 an association between O<sub>3</sub> and respiratory symptoms that were larger among children with GSTM1  
23 null or glutathione S-transferase P 1 (GSTP1) Val/Val genotypes. However, results suggested that O<sub>3</sub>-  
24 associated decreases in lung function may be greater among children with GSTP1 Ile/Ile or Ile/Val  
25 compared to GSTP1 Val/Val. Alexeef et al. (2008, [195864](#)) reported greater decreases in lung  
26 function among GSTP1 Val/Val adults than those with other genotypes. In addition, they detected  
27 greater decreases for adults with long GT dinucleotide repeats in heme-oxygenase-1 (HMOX1)  
28 promoters.

29 Several controlled human exposure studies have reported that genetic polymorphism of  
30 antioxidant enzymes may modulate pulmonary function and inflammatory response to O<sub>3</sub> challenge.  
31 It appears that healthy carriers of NAD(P)H quinone oxidoreductase 1 (NQO1) wild type (wt) in  
32 combination with GSTM1 null genotype had greater decreases in lung function parameters with  
33 exposure to O<sub>3</sub> (Bergamaschi et al., 2001, [052670](#)). Adults with GSTM1 null only genotype did not  
34 show the same response to O<sub>3</sub>. In contrast, asthmatic children with GSTM1 null genotype (Romieu  
35 et al., 2004, [056796](#)) were reported to have greater decreases in lung function in relation to O<sub>3</sub>  
36 exposure. In a similar study, Vagaggini et al. (2010, [387127](#)) exposed mild-to-moderate asthmatics to

1 O<sub>3</sub> with moderate exercise. In subjects with NQO1 wt and GSTM1 null, there was no evidence of  
2 changes in lung function or inflammatory responses to O<sub>3</sub>.

3 In a study of healthy volunteers with GSTM1 sufficient (n=19; 24±3) and GSTM1 null (n=16;  
4 25 ± 5) exposed to 400 ppb O<sub>3</sub> for 2 hours with exercise, Alexis et al. (2009, [628542](#)) found  
5 genotype effects on inflammatory responses but not lung function responses to O<sub>3</sub>. At 4 h post O<sub>3</sub>  
6 exposure, individuals with both GSTM1 genotypes had significant increases in sputum neutrophils  
7 with a tendency for a greater increase in GSTM1 sufficient than nulls. At 24 hours postexposure,  
8 neutrophils had returned to baseline levels in the GSTM1 sufficient individuals. In the GSTM1 null  
9 subjects, neutrophil levels increased from 4 to 24 hours and were significantly greater than both  
10 baseline levels and levels at 24 hours in the GSTM1 sufficient individuals. Since there was no FA  
11 control in the Alexis et al. (2009, [628542](#)) study, effects of the exposure other than O<sub>3</sub> can not be  
12 ruled out. In general, the findings between studies are inconsistent and additional, better-controlled  
13 studies are needed to clarify the influence of genetic polymorphisms on O<sub>3</sub> responsiveness in  
14 humans.

15 Several epidemiologic studies of long-term O<sub>3</sub> exposure examined interactions with different  
16 gene variants, including GSTP1, HMOX1, and TNF- $\alpha$ . A study among children reported a three-way  
17 interaction effect between Ile105 homozygotes of GSTP1, O<sub>3</sub>, and playing more than two team  
18 sports, and new onset of asthma (Islam et al., 2009, [196715](#)). Additionally, Islam et al. found that  
19 non-Hispanic white children with less than 23 repeats in the HMOX-1 gene had decreased risk of  
20 new-onset asthma (Islam et al., 2008, [097348](#)). ARG1 and ARG2 (encoded by arginases)  
21 modification were examined for the association between genotypes and new-onset asthma (Salam et  
22 al., 2009, [596644](#)). Reduced asthma risk was observed among atopic children living in high O<sub>3</sub> areas  
23 and having the ARG1 haplotypes. There was no difference in risk for children with ARG2  
24 haplotypes. A decreased risk of bronchitic symptoms was observed among asthmatic children in low  
25 O<sub>3</sub> areas with TNF- $\alpha$  variant G-308A (TNF-308GG genotype), a variant that may alter gene  
26 expression. There was no decrease in risk for children with this TNF- $\alpha$  variant but living in areas  
27 with high O<sub>3</sub> concentrations. Additionally, this modification for high and low levels of O<sub>3</sub> was not  
28 present among non-asthmatic children (Lee et al., 2009, [199915](#)). Wenten et al. (2009, [597084](#))  
29 observed increased risk of respiratory-related school absences among children with variants of  
30 catalase (CAT) and myeloperoxidase (MPO) genes, especially when the children were living in high  
31 O<sub>3</sub> areas.

32 Toxicological studies have reported differences in cardiac and respiratory effects after O<sub>3</sub>  
33 exposure among different mouse strains, which alludes to susceptibility among individuals due to  
34 genetic variability (Chuang et al., 2009, [197202](#); Hamade and Tankersley, 2009, [596386](#); Hamade et  
35 al., 2008, [156515](#); Tankersley et al., 2010, [628062](#)). Altered O<sub>3</sub> responses between two strains could  
36 be due to genetic variability in nuclear factor erythroid 2-related factor 2 (Nrf-2), suggesting a role  
37 for genetic differences in altering the formation of ROS. Another difference among strains is  
38 attributed to differences in O<sub>3</sub>-induced lung hyperpermeability (Kleeberger et al., 2000, [014895](#);  
39 Kleeberger et al., 2001, [016163](#)). Additionally, some studies have reported O<sub>3</sub>-related effects to vary

1 by Inf-1 and Inf-2 genes (Tankersley and Kleeberger, 1994, [021420](#)) and a gene coding for Clara cell  
2 secretory protein (CCSP) (Broeckeaert et al., 2003, [055490](#); Wattiez et al., 2003, [043783](#)).

3 Voynow et al. (2009, [194311](#)) have shown that NQO1 deficient mice, like their human  
4 counterparts, are resistant to O<sub>3</sub>-induced airway hyperresponsiveness and inflammation. Reduced  
5 production of inflammatory mediators and cells and blunted airway hyperresponsiveness were  
6 observed in NQO1-null mice after exposure to 1 ppm O<sub>3</sub> for 3 hours. These results correlated with  
7 those from in vitro experiments in which human bronchial epithelial cells treated with an NQO1  
8 inhibitor exhibited reduced inflammatory responses to exposure to 0.4 ppm O<sub>3</sub> for 5 hours.

9 The role of TNF- $\alpha$  signaling in O<sub>3</sub>-induced responses has been previously established through  
10 depletion experiments, but a more recent toxicological study investigated the effects of combined O<sub>3</sub>  
11 and PM exposure in transgenic TNF overexpressing mice. Kumarathasan et al. (2005, [596398](#)) found  
12 that subtle effects of these pollutants were difficult to identify in the midst of the severe pathological  
13 changes caused by constitutive TNF- $\alpha$  overexpression. However, there was evidence that TNF  
14 transgenic mice were more susceptible to O<sub>3</sub>/PM-induced oxidative stress, and they exhibited  
15 elevation of a serum creatine kinase after pollutant exposure, which may suggest potential systemic  
16 or cardiac related effects. Differential susceptibility to O<sub>3</sub> among inbred strains of animals does not  
17 seem to be dose dependent since absorption of <sup>18</sup>O in various strains of mice did not correlate with  
18 resistance or sensitivity (Vancza et al., 2009, [596419](#)).

19 Defects in DNA repair mechanisms may also confer susceptibility to O<sub>3</sub>-related health effects.  
20 Cockayne syndrome, a rare autosomal recessive disorder in humans, is characterized by UV  
21 sensitivity abnormalities, neurological abnormalities, and premature aging. The same genetic defect  
22 in mice (Csb<sup>-/-</sup>) makes them sensitive to oxidative stressors, including O<sub>3</sub>. Kooter et al. (2007,  
23 [596397](#)) demonstrated that Csb<sup>-/-</sup> mice produced significantly more TNF- $\alpha$  after exposure to 0.8 ppm  
24 O<sub>3</sub> than their wild-type counterparts. However, there were no significant differences in other markers  
25 of inflammation or lung injury between the two strains of mice.

## 8.5. Diet

26 Diet was not examined as a susceptibility factor in previous AQCDs, but recent studies have  
27 examined modification of the association between O<sub>3</sub> and health effects by dietary factors. Because  
28 O<sub>3</sub> mediates its toxic effects through oxidative stress, the antioxidant status of an individual is an  
29 important factor that may contribute to increased susceptibility to O<sub>3</sub>-related health effects.  
30 Supplementation with vitamin E has been investigated in a number of studies as a means of  
31 inhibiting O<sub>3</sub>-mediated damage.

32 Epidemiologic studies have examined effect measure modification by diet and found evidence  
33 that certain dietary components are related to the effect of O<sub>3</sub> has on respiratory outcomes. The most  
34 recent study examined fruit/vegetable intake and Mediterranean diet (Romieu et al., 2009, [548788](#)).  
35 Increases in these food patterns, which have been noted for their high vitamins C and E and omega-3  
36 fatty acid content, protected against O<sub>3</sub>-related decreases in lung function among children living in

1 Mexico City. Another study examined supplementation of the diets of asthmatic children in Mexico  
2 with Vitamins C and E (Sienra-Monge et al., 2004, [196422](#)). Associations were detected between  
3 short-term O<sub>3</sub> and nasal airway inflammation among children in the placebo group but not in those  
4 receiving the supplementation. The authors concluded that “vitamin C and E supplementation above  
5 the minimum dietary requirement in asthmatic children with a low intake of vitamin E might provide  
6 some protection against the nasal acute inflammatory response to ozone.”

7 The epidemiologic evidence is supported by the controlled human exposure studies, which  
8 have shown that the first line of defense against oxidative stress is antioxidants-rich extracellular  
9 lining fluid (ELF) which scavenge free radicals and limit lipid peroxidation. Exposure to O<sub>3</sub> depletes  
10 the antioxidant level in nasal ELF probably due to scrubbing of O<sub>3</sub> (Mudway et al., 1999, [001270](#));  
11 however, the concentration and the activity of antioxidant enzymes either in ELF or plasma do not  
12 appear to be related to O<sub>3</sub> responsiveness (Avisar et al., 2000, [012528](#); Blomberg et al., 1999,  
13 [001267](#); Samet et al., 2001, [019034](#)). Carefully controlled studies of dietary antioxidant  
14 supplementation have demonstrated some protective effects of alpha-tocopherol (a form of vitamin  
15 E) and ascorbate (vitamin C) on spirometric lung function from O<sub>3</sub> but not on the intensity of  
16 subjective symptoms and inflammatory response including cell recruitment, activation and a release  
17 of mediators (Samet et al., 2001, [019034](#); Trenga et al., 2001, [019845](#)). Dietary antioxidants have  
18 also afforded partial protection to asthmatics by attenuating postexposure bronchial  
19 hyperresponsiveness (Trenga et al., 2001, [019845](#)).

20 Toxicological studies provide evidence of biological plausibility to the epidemiologic and  
21 controlled human exposure studies. Wagner et al. (2007, [596420](#); 2009, [201574](#)) have shown  
22 reductions in O<sub>3</sub>-exacerbated nasal allergy responses in rats with gamma-tocopherol treatment (a  
23 form of vitamin E). Ozone-induced inflammation and mucus production were also inhibited by  
24 gamma-tocopherol. Inconsistent results are observed in toxicological studies of ascorbate deficiency  
25 and O<sub>3</sub> responses. Guinea pigs deficient in ascorbate displayed only minimal injury and  
26 inflammation after exposure to O<sub>3</sub> (Kodavanti et al., 1995, [077440](#)). A recent study in mice  
27 demonstrated a protective effect of beta-carotene in the skin, where it limited the production of  
28 proinflammatory markers and indicators of oxidative stress induced by O<sub>3</sub> exposure (Valacchi et al.,  
29 2009, [201554](#)). In addition to the studies of antioxidants, one toxicological study examined protein  
30 deficiency. Protein deficiency alters the levels of enzymes and chemicals in the brain involved with  
31 redox status; exposure to 0.75 ppm O<sub>3</sub> has been shown to differentially affect Na<sup>+</sup>/K<sup>+</sup> ATPase,  
32 glutathione, and lipid peroxidation, depending on the nutritional status of the animal, but the  
33 significance of these changes is unclear (Calderon Guzman et al., 2006, [596371](#)).

## 8.6. Body Mass Index

34 Obesity, defined as a BMI of 30 kg/m<sup>2</sup> or greater, is an issue of increasing importance in the  
35 U.S., with self-reported rates of 26.7% in 2009, up from 19.8% in 2000 (Sherry et al., 2010,  
36 [667866](#)). A few studies have been performed examining the association between BMI and lung

1 function. An epidemiologic study reported decreased lung function with increased short-term O<sub>3</sub>  
2 exposure for both obese and non-obese subjects; however, the magnitude of the reduction in lung  
3 function was greater for those subjects who were obese (Alexeeff et al., 2007, [195862](#)). Further  
4 decrements in lung function were noted for obese individuals with airway hyperresponsiveness.  
5 Controlled human exposure studies have also detected differential effects of O<sub>3</sub> on lung function for  
6 individuals with varying BMIs. In a retrospective analysis of data from 541 healthy, nonsmoking,  
7 white males between the ages of 18-35 years from 15 studies conducted at the U.S. EPA Human  
8 Studies Facility in Chapel Hill, North Carolina, McDonnell et al. (2010, [383972](#)) found that  
9 increased body mass index (BMI) was found to be associated with enhanced FEV<sub>1</sub> responses. The  
10 BMI effect was of the same order of magnitude but in the opposite direction of the age effect  
11 whereby FEV<sub>1</sub> responses diminish with increasing age. In a similar analysis, Bennett et al. (2007,  
12 [418827](#)) found enhanced FEV<sub>1</sub> decrements following O<sub>3</sub> exposure with increasing BMI in a group of  
13 healthy, nonsmoking, women (BMI range 15.7 to 33.4), but not among healthy, nonsmoking men  
14 (BMI range 19.1 to 32.9). In the women, greater O<sub>3</sub>-induced FEV<sub>1</sub> decrements were seen in  
15 overweight/obese (BMI >25) than in normal weight (BMI from 18.5 to 25), and in normal weight  
16 than in underweight (BMI <18.5). Even disregarding the five underweight women, a greater O<sub>3</sub>  
17 response in the overweight/obese category (BMI >25), compared with the normal weight group  
18 (BMI from 18.5 to 24.9).

19 Studies in genetically and dietarily obese mice have shown enhanced pulmonary inflammation  
20 and injury with acute O<sub>3</sub> exposure, but responses to longer exposures at more relevant doses appear  
21 to differ. A recent study found that obese mice are actually resistant to O<sub>3</sub>-induced pulmonary injury  
22 and inflammation and reduced lung compliance following exposure to 0.3 ppm O<sub>3</sub> for 72 hours,  
23 regardless of whether obesity was genetic or diet-induced (Shore et al., 2009, [201551](#)).

24 Multiple epidemiologic and human clinical studies have reported increased O<sub>3</sub>-related  
25 respiratory health effects among obese individuals. Future research of the effect modification of the  
26 relationship between O<sub>3</sub> and other health-related outcomes besides respiratory health effects by BMI  
27 will advance understanding of obesity as a potential susceptibility factor.

## 8.7. Socioeconomic Status

28 SES is often represented by personal or neighborhood SES, educational attainment, health  
29 insurance status, and other such factors. Based on the 2000 Census data, 12.4% of Americans live in  
30 poverty (poverty threshold for family of four was \$17,463) (Social Science Data Analysis Network;  
31 CensusScope and CensusScope, 2010, [647297](#)).

32 Multiple epidemiologic studies have reported individuals of low SES to be more susceptible to  
33 the effects of short-term O<sub>3</sub> exposure on respiratory HAs and ED visits. A study performed in Korea  
34 examined the association between O<sub>3</sub> concentrations and asthma HA and reported larger effect  
35 estimates in areas of moderate and low SES compared with areas of high SES (SES was based on  
36 average regional insurance rates) (Lee et al., 2006, [098248](#)). Another Canadian study reported

1 inverse effects of O<sub>3</sub> on respiratory HA and ED visits regardless of SES, measured by average census  
2 tract household income (Burra et al., 2009, [195868](#)). In addition, a study conducted across 10 cities  
3 in Canada found the largest association between O<sub>3</sub> and respiratory HA was among those with an  
4 educational level less than grade 9, but no consistent trend in the effect was seen across quartiles of  
5 income (Cakmak et al., 2006, [093272](#)). One study performed among children in New York State  
6 reported greater associations between long-term O<sub>3</sub> exposure and asthma HA among children of  
7 mothers who did not graduate from high school, whose births were covered by Medicaid/self-paid,  
8 and who were living in poor neighborhoods compared to children whose mothers graduated from  
9 high school, whose births were covered by other insurance, and who were not living in poor  
10 neighborhoods, respectively (Lin et al., 2008, [196680](#)).

11 One study reported the association between short-term O<sub>3</sub> and ED visits for cardiac disease by  
12 quartiles of neighborhood-level education and income. No effect measure modification was apparent  
13 for either measure of SES (Cakmak et al., 2006, [099068](#)).

14 Several studies were conducted examining the modification by SES of the relationship  
15 between short-term O<sub>3</sub> concentrations and mortality. A U.S. multicity study reported that  
16 communities with a higher proportion of the population unemployed had higher mortality effect  
17 estimates (Bell and Dominici, 2008, [193828](#)). A study examining effect measure modification of the  
18 association between O<sub>3</sub> and mortality by percentage unemployed reported a higher percent change in  
19 mortality with increased percent unemployed but this varied across the regions included in the study  
20 (U.S., Canada, Europe) (Katsouyanni et al., 2009, [199899](#)). A Chinese study reported that the  
21 greatest effects between O<sub>3</sub> concentrations and mortality at lag day 0 were among those living in  
22 areas of high social deprivation (i.e. low SES), but this association was not consistent across lag days  
23 (at other lag times, the middle social deprivation index category had the greatest association) (Wong  
24 et al., 2008, [157151](#)). However, another study in Asia comparing low to high educational attainment  
25 populations reported no evidence of greater mortality effects (total, CVD, or respiratory) (Kan et al.,  
26 2008, [156621](#)). Additionally, a study in Italy reported no difference in risk of mortality among  
27 census-block level derived income levels (Stafoggia et al., 2010, [625034](#)). A study of infant mortality  
28 in Mexico reported no association between O<sub>3</sub> concentrations and infant mortality among any of the  
29 three levels of SES determined using a socioeconomic index based on residential areas (Romieu et  
30 al., 2004, [093074](#)). Another study in Mexico reported a positive association between O<sub>3</sub> levels at lag  
31 0 and respiratory-related infant mortality in only the low SES group (determined based on education,  
32 income, and household conditions across residential areas), but no association was observed in any  
33 of the SES groups with other lags (Carbajal-Arroyo et al., In Press, [667773](#)).

34 Evidence from a controlled human exposure study that examined O<sub>3</sub> effects on lung function  
35 does not provide support for greater O<sub>3</sub>-related health effects in individuals of lower SES. In a  
36 follow-up study (Seal et al., 1993, [039357](#)) on modification by race, Seal et al. (1996, [044251](#))  
37 reported that, of three SES categories, individuals in the middle SES category showed greater  
38 concentration-dependent decline in percent-predicted FEV<sub>1</sub> (4-5% at 400 ppb O<sub>3</sub>) than in low and  
39 high SES groups. The authors did not have an “immediately clear” explanation for this finding.

1 Overall, most studies of individuals and those living in neighborhoods with low SES have  
2 reported that individuals with low SES are more susceptible to O<sub>3</sub>-related health effects, resulting in  
3 higher odds of respiratory HAs and ED visits. This was not supported by a single controlled human  
4 exposure study conducted to examine O<sub>3</sub>-related effects on lung function for individuals from  
5 varying SES groups. Inconsistent results have been observed in the few studies examining effect  
6 modification of associations with mortality.

## 8.8. Air Conditioning Use

7 Air conditioning use is an important component of exposure, as use of central air conditioning  
8 will limit exposure to O<sub>3</sub> by blocking the penetration of O<sub>3</sub> into the indoor environment (further  
9 information can be found in Section 4.4). Air conditioning use is a difficult effect measure modifier  
10 to examine, as it represents multiple components. More generally, air conditioning prevalence is  
11 associated with temperature of a region; those areas with higher temperatures have a greater  
12 prevalence of households with air conditioning. Second, it is a marker of SES, with individuals of  
13 low SES less likely to have an air conditioner. Finally, air conditioning use is often measured based  
14 on area prevalence and may not reflect individual-level use. Despite these limitations, a few studies  
15 have examined effect measure modification by prevalence of air conditioning use in an area.

16 Studies examining multiple cities across the U.S. have assessed whether associations between  
17 O<sub>3</sub> concentrations and HA and mortality varied among areas with high and low prevalence of air  
18 conditioning. Medina-Ramon et al. (2006, [087721](#)) conducted a study during the warm season and  
19 observed a greater association between O<sub>3</sub> levels and pneumonia HAs among areas with a lower  
20 proportion of households having central air conditioning compared to areas with a larger proportion  
21 of households without air conditioning. The same trend of increased association for areas with a  
22 lower prevalence of central air conditioning was noted in a study of O<sub>3</sub> concentrations and mortality  
23 (Bell and Dominici, 2008, [193828](#)). Conversely, Medina-Ramón and Schwartz (2008, [193829](#)) found  
24 that among individuals with atrial fibrillation, a lower risk of mortality was observed for areas with a  
25 lower prevalence of central air conditioning.

## 8.9. Involvement in Outdoor Activities

26 Studies included in the 2006 O<sub>3</sub> AQCD reported individuals who participate in outdoor  
27 activities or work to be a susceptible population based on consistently reported associations between  
28 O<sub>3</sub> exposure and respiratory health outcomes in these groups (U.S. EPA, 2006, [088089](#)). Outdoor  
29 workers are exposed to ambient O<sub>3</sub> concentrations outside for a greater period of time than  
30 individuals who spend their days indoors. Additionally, an increase in dose to the lower airways is  
31 possible with exercise due to both increases in amount of air breathed (i.e., minute ventilation) and a  
32 shift from nasal to oronasal breathing (Hu et al., 1994, [041323](#); Nodelman and Ultman, 1999,  
33 [015112](#); Sawyer et al., 2007, [195142](#)). For further discussion of the association between FEV<sub>1</sub>

1 responses to O<sub>3</sub> and minute ventilation, refer to Section 6.2.3.1 of the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
2 2006, [088089](#)).

3 A recent study has explored the potential effect measure modification of O<sub>3</sub> exposure and  
4 DNA damage by indoor/outdoor workplace (Tovalin et al., 2006, [091322](#)). In a study of indoor and  
5 outdoor workers in Mexico, individuals who worked outdoors in Mexico City had a slight  
6 association between O<sub>3</sub> exposure and DNA damage (measured by comet tail length assay), whereas  
7 no association was observed for indoor workers in Mexico City. Workers in another Mexican city,  
8 Puebla, demonstrated no association between O<sub>3</sub> levels and DNA damage, regardless of whether they  
9 worked indoors or outdoors.

10 Although there is no evidence of modification by outdoor activity in this recent study, previous  
11 work has shown that increased dose of O<sub>3</sub> concentrations from outdoor work leads to increased  
12 susceptibility to O<sub>3</sub>-related health effects among individuals who participate in outdoor activities or  
13 work.

## 8.10. Race/Ethnicity

14 Based on the 2000 Census, 69.1% of the U.S. population comprises Non-Hispanic Whites.  
15 Approximately 12.1% of people reported their race/ethnicity as Non-Hispanic Black and 12.6%  
16 reported being Hispanic (Social Science Data Analysis Network; CensusScope and CensusScope,  
17 2010, [647301](#)).

18 A couple of studies examined the associations between short-term O<sub>3</sub> concentrations and  
19 mortality and reported higher effect estimates among Blacks (Medina-Ramón and Schwartz, 2008,  
20 [193829](#)) and among communities with larger proportions of Blacks (Bell and Dominici, 2008,  
21 [193828](#)). Another study examined short-term exposure to O<sub>3</sub> concentrations and asthma HAs among  
22 children in New York State. These authors reported no statistically significant difference in the odds  
23 of asthma HA for Blacks compared to other races but did detect higher odds for Hispanics compared  
24 to non-Hispanics (Lin et al., 2008, [196680](#)).

25 Support for the epidemiologic studies is provided by a controlled human exposure study (Seal  
26 et al., 1993, [039357](#)), which has compared lung function responses of Whites and Blacks exposed to  
27 a range of O<sub>3</sub> concentrations. The independent effects of gender-race group and O<sub>3</sub> concentration on  
28 lung function were positive, but the interaction between gender-race group and O<sub>3</sub> concentration was  
29 not statistically significant. The findings indicate some overall difference between the gender-race  
30 groups that is independent of O<sub>3</sub> concentration (the concentration-response curves for the four  
31 gender-race groups are parallel). In a multiple comparison procedure on data collapsed across all O<sub>3</sub>  
32 concentrations for each sex-race group, both Black men and Black women had larger decrements in  
33 FEV<sub>1</sub> than did White men. The authors noted that the O<sub>3</sub> dose per unit of lung tissue would be  
34 greater in blacks and females than whites and males, respectively. That this difference in tissue dose  
35 might have affected responses to O<sub>3</sub> cannot be ruled out. The college students recruited for the Seal

1 et al. (1993, [039357](#)) study are probably from better educated and more SES advantaged families,  
2 thus reducing potential for these variables to be confounding factors.

3 Overall, the results of recent studies suggest that there may be race-related susceptibility for  
4 some outcomes, although the overall understanding of potential effect measure modification by race  
5 is limited by the small number of studies. Additionally, these results may be confounded by other  
6 factors, such as socioeconomic status.

## 8.11. Physical Conditioning

7 The 2008 *Summary of Health Statistics for U.S. Adults* from the CDC reported the prevalence  
8 of regular leisure-time physical activity as slightly above 30% for adults 18 years of age and older in  
9 the U.S. Forty-nine percent of individuals 65 and older reported no leisure-time physical activity  
10 (Pleis et al., 2009, [629608](#)). Physical activity is of interest as a susceptibility factor because studies  
11 have demonstrated that exercise affects both the amount of air breathed (flow rate and breathing  
12 frequency increase) and type of breathing (switch from nasal to oronasal) (Hu et al., 1994, [041323](#);  
13 Nodelman and Ultman, 1999, [015112](#); Sawyer et al., 2007, [195142](#)). A study of effect measure  
14 modification by exercise habits ten years prior to death observed excess risk of mortality with  
15 increasing O<sub>3</sub> concentrations among individuals that never exercised compared to individuals that  
16 exercised at least once a month for both adults 30 years of age and older and adults 65 years of age  
17 and older (Wong et al., 2007, [093278](#)). No recent studies examining modification of O<sub>3</sub>-related  
18 health effects by current physical activity were identified.

## 8.12. Smoking

19 Previous O<sub>3</sub> AQCDs have concluded that smoking does not increase susceptibility to  
20 O<sub>3</sub>-related health effects; in fact, in controlled human exposure studies, smokers have been found to  
21 be less susceptible to O<sub>3</sub>-related health effects than non-smokers. Data from recent interviews  
22 conducted as part of the 2008 National Health Interview Survey (NHIS) (Pleis et al., 2009, [629608](#))  
23 have shown the rate of smoking among adults 18 year and older to be approximately 20% in the U.S.  
24 Approximately 21% of individuals surveyed were identified as former smokers.

25 Baccarelli et al. (2007, [091310](#)) performed a study of O<sub>3</sub> concentrations and plasma  
26 homocysteine levels (a risk factor for vascular disease). They found no interaction of smoking  
27 (smokers versus non-smokers) for the associations between O<sub>3</sub> concentrations and plasma  
28 homocysteine levels. Another study examined the association between O<sub>3</sub> and resting heart rate and  
29 also reported no interaction with smoking status (current smokers versus current non-smokers)  
30 (Ruidavets et al., 2005, [089443](#)).

31 A study examining correlations between O<sub>3</sub> levels and oxidative DNA damage examined  
32 results stratified by current versus never and former smokers (Palli et al., 2009, [196688](#)). Ozone was  
33 positively associated with DNA damage for short-term and long-term exposures among never/former

1 smokers. For current smokers, short-term O<sub>3</sub> concentrations were inversely associated with DNA  
2 damage; however, the number of current smokers was small (n=12).

3 The findings of Palli et al. (2009, [196688](#)) are consistent with those from controlled human  
4 exposure studies that have confirmed that smokers are less responsive to O<sub>3</sub> than non-smokers.  
5 Spirometric and plethysmographic pulmonary function decline, nonspecific airway hyperreactivity,  
6 and inflammatory response of smokers to O<sub>3</sub> were all weaker than the ones reported for non-  
7 smokers. Similarly, the time course of development and recovery of these effects as well their  
8 reproducibility was not different from non-smokers. Chronic airway inflammation with  
9 desensitization of bronchial nerve endings and an increased production of mucus may plausibly  
10 explain the pseudo-protective effect of smoking (Frampton et al., 1997, [082692](#); Torres et al., 1997,  
11 [084265](#)).

12 These findings for smoking are consistent with previous AQCD conclusions. An  
13 epidemiologic study of O<sub>3</sub>-associated DNA damage reported smokers to be less susceptible to O<sub>3</sub>-  
14 related health effects. However, both epidemiologic studies of short-term exposure and CVD  
15 outcomes found no effect measure modification by smoking.

### 8.13. Hyperthyroidism

16 A potential susceptibility factor has been identified in toxicological studies but has not yet  
17 been explored in epidemiologic or controlled human exposure studies. Lung damage and  
18 inflammation due to oxidative stress may be modulated by thyroid hormones. Compared to controls,  
19 hyperthyroid rats exhibited elevated levels of BAL neutrophils and albumin after a 4-h exposure to  
20 O<sub>3</sub>, indicating inflammation and damage. Hyperthyroidism did not affect production of reactive  
21 oxygen or nitrogen species, but BAL phospholipids were increased, indicating greater activation of  
22 Type II cells and surfactant protein production compared to normal rats (Huffman et al., 2006,  
23 [596388](#)). Thus, this study provides some underlying evidence which suggests that individuals with  
24 hyperthyroidism may represent a susceptible population. Future studies in humans have the potential  
25 to identify this as additional susceptibility factors.

### 8.14. Summary

26 In this section, epidemiologic, controlled human exposure, and toxicological studies have been  
27 evaluated that contribute information on potential susceptibility factors. Overall, this review provides  
28 evidence that various factors may lead to increased susceptibility to O<sub>3</sub>-related health effects.

29 The populations identified in this section that are most susceptible to O<sub>3</sub>-related health effects  
30 are individuals with influenza/infection, individuals with asthma, and older age groups. There were a  
31 small number of studies on influenza/infection but both reported influenza/infection to modify the  
32 association between O<sub>3</sub> exposure and respiratory effects, with individuals having influenza or an  
33 infection being at increased susceptibility. Asthma as a susceptibility factor was supported by  
34 controlled human exposure and toxicological studies, as well as some evidence from epidemiologic

1 studies. Most studies comparing age groups reported greater effects of short-term O<sub>3</sub> exposure on  
2 mortality among older adults. Diet and obesity are also both likely susceptibility factors. Multiple  
3 epidemiologic, controlled human exposure, and toxicological studies reported that diets deficient in  
4 Vitamins E and C are associated with susceptibility to O<sub>3</sub>-related health effects. Similarly, studies of  
5 effect measure modification by BMI observed greater O<sub>3</sub>-related respiratory decrements for  
6 individuals who were obese.

7 Other potential factors [pre-existing conditions (such as COPD and CVD) young age, sex, and  
8 multiple genes (such as GSTM1, GSTP1, HMOX-1, NQO1, and TNF- $\alpha$ )] provided some evidence  
9 of susceptibility, but further evidence is needed. In addition, examination of modification of the  
10 associations between O<sub>3</sub> exposure and health effects by SES and race were available in a limited  
11 number of studies, and demonstrated possible increased odds of health effects related to O<sub>3</sub> exposure  
12 among those with low SES and Blacks.

13 Individuals involved in outdoor activities were examined in a recent study but no effect  
14 modification was observed. However, previous evidence along with biological plausibility from  
15 toxicological and controlled human studies has shown this population to be susceptible to O<sub>3</sub>-related  
16 health effects. The only studies examining effect measure modification by diabetes examined O<sub>3</sub>  
17 exposure and cardiovascular outcomes, but none of the studies reported any change in the  
18 association by diabetes.

19 Studies of air conditioning use, physical conditioning, and smoking were conducted but not  
20 much evidence was available to determine whether susceptibility to O<sub>3</sub>-related health effects is  
21 present for these factors. Toxicological studies also identified hyperthyroidism and the lifestage of  
22 gestation to be factors warranting further examination. Future research on these will provide  
23 additional insight into whether these factors affect susceptibility to O<sub>3</sub>-related health effects.

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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# Chapter 9. Environmental Effects: Ozone Effects on Vegetation and Ecosystems

## 9.1. Introduction

1 This chapter synthesizes and evaluates the most policy-relevant science to help form the  
2 scientific foundation for the review of a vegetation- and ecologically-based secondary NAAQS for  
3 O<sub>3</sub>. The secondary NAAQS are based on welfare effects. The Clean Air Act (CAA) definition of  
4 welfare effects includes, but is not limited to, effects on soils, water, wildlife, vegetation, visibility,  
5 weather, and climate, as well as effects on materials, economic values, and personal comfort and  
6 well-being. The effects of O<sub>3</sub> as a greenhouse gas and its direct effects on climate are discussed in  
7 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” (42U.S.C.7408 (1990,  
10 [080701](#)) 42U.S.C.7409 (1990, [037658](#))). This chapter of the ISA includes scientific research from  
11 biogeochemistry, soil science, plant physiology, and ecology conducted at multiple scales (e.g.,  
12 organ, individual, population, community, ecosystem). Key information and judgments formerly  
13 found in the AQCDs regarding O<sub>3</sub> effects on vegetation and ecosystems are found in this chapter.  
14 This chapter of the O<sub>3</sub> ISA serves to update and revise Chapter 9 and AX9 of the 2006 O<sub>3</sub> AQCD  
15 (U.S. EPA, 2006, [088089](#)).

16 Numerous studies of the effects of O<sub>3</sub> on vegetation and ecosystems were reviewed in the  
17 2006 O<sub>3</sub> AQCD. That document concluded that the effects of ambient O<sub>3</sub> on vegetation and  
18 ecosystems appear to be widespread across the U.S., and experimental studies demonstrated  
19 plausible mechanisms for these effects. Ozone effect studies published from 2005 to September 2010  
20 are reviewed in this document in the context of the previous O<sub>3</sub> AQCDs (U.S. EPA, 2006,  
21 [088089](#))(U.S. EPA, 1996, [080827](#))(U.S. EPA, 1984, [029711](#))(U.S. EPA, 1978, [040586](#)). From 2005  
22 to 2010, some areas have had very little new research published and the reader is referred back to  
23 sections of the 2006 O<sub>3</sub> AQCD for a more comprehensive treatment of those subjects. This chapter is  
24 focused on studies of vegetation and ecosystems that occur in the U.S. and that report endpoints or  
25 processes 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 Europe and Asia.  
27 This document includes discussion of studies of vegetation and ecosystems outside of North America  
28 only if those studies contribute to the general understanding of O<sub>3</sub> effects across species and  
29 ecosystems. For example, studies outside North America are discussed that consider physiological

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

1 and biochemical processes that contribute to the understanding of effects of O<sub>3</sub> across species. Also,  
2 ecosystem studies outside of North America that contribute to the understanding of O<sub>3</sub> effects on  
3 general ecosystem processes are discussed in the chapter.

4 This chapter is organized in sections that discuss exposure methods, followed by effects on  
5 vegetation and ecosystems at various scales and ends with policy-relevant discussions of exposure  
6 indices and exposure-response. First, Section 9.2 presents summary information and conclusions  
7 based on the literature assessed in this chapter and the assessments and conclusions of the previous  
8 O<sub>3</sub> AQCDs. A brief overview of various methodologies that have been, and continue to be, central to  
9 quantifying O<sub>3</sub> effects on vegetation is provided in Section 9.3 (AX9.1 of the 2006 O<sub>3</sub> AQCD for  
10 more detailed discussion) (U.S. EPA, 2006, [088089](#)). Sections 9.4 through 9.6 begin with a  
11 discussion of effects at the cellular and subcellular level followed by consideration of the whole  
12 plant and finally, O<sub>3</sub> impacts on ecosystem-level processes (Figure 9-1). In Section 9.4, research is  
13 reviewed from the molecular to the biochemical and physiological levels in impacted plants, offering  
14 insight into the mode of action of O<sub>3</sub>. Section 9.5 provides a review of the effects of O<sub>3</sub> exposure on  
15 major endpoints at the whole plant scale including growth, reproduction, visible foliar injury and leaf  
16 gas exchange in woody and herbaceous plants in the U.S., as well as a brief discussion of O<sub>3</sub> effects  
17 on agricultural crop yield and quality. The response of plants to O<sub>3</sub> as influenced by numerous  
18 environmental biotic and abiotic factors is also discussed Section 9.5. In Section 9.6, available  
19 research for assessing the effect of O<sub>3</sub> on ecosystems is reviewed, along with data potentially  
20 available for estimating the loss of various ecosystem services. The development of indices of O<sub>3</sub>  
21 exposure and dose modeling is discussed in Section 9.7. Finally, exposure-response relationships for  
22 a number of tree species, native vegetation, and crop species and cultivars are reviewed, tabulated,  
23 and compared in Section 9.8 to form the basis for an assessment of the potential risk to vegetation  
24 from current ambient levels of O<sub>3</sub>.

## 9.2. Summary and Integration

### 9.2.1. Introduction

25 The subsequent sections of this chapter will present the most policy-relevant information  
26 related to this review of the NAAQS for the effects of O<sub>3</sub> on vegetation and ecosystems. This section  
27 integrates the key findings from the disciplines evaluated in this current assessment of the O<sub>3</sub>  
28 scientific literature, which includes plant physiology, biochemistry, whole plant biology, ecosystems  
29 and exposure-response.

30 Ozone effects at small scales, such as the leaf of an individual plant, can result in effects at a  
31 continuum of larger scales. Figure 9-1 is a simplified diagram of the major pathway through which  
32 O<sub>3</sub> enters plants and the major endpoints O<sub>3</sub> may affect from small to large scales. The subsequent  
33 sections in this chapter are organized around this paradigm of effects at the cellular and subcellular  
34 level followed by consideration of the whole plant and finally, O<sub>3</sub> impacts on ecosystem-level

1 processes. Ozone enters leaves through stomata, and can alter stomatal conductance and disrupt CO<sub>2</sub>  
2 fixation (Section 9.4). These effects can change rates of leaf gas exchange, growth and reproduction  
3 at the individual plant level (Section 9.5). Those O<sub>3</sub>-induced effects can translate from the individual  
4 plant level to the ecosystem level, and cause changes in ecosystem services, such as C storage, water  
5 production, nutrient cycling, and community composition (Section 9.6). The EPA framework for  
6 causal determinations described in Chapter 1 has been applied to the body of scientific evidence to  
7 collectively examine effects attributed to O<sub>3</sub> exposure (See Table 9-1).

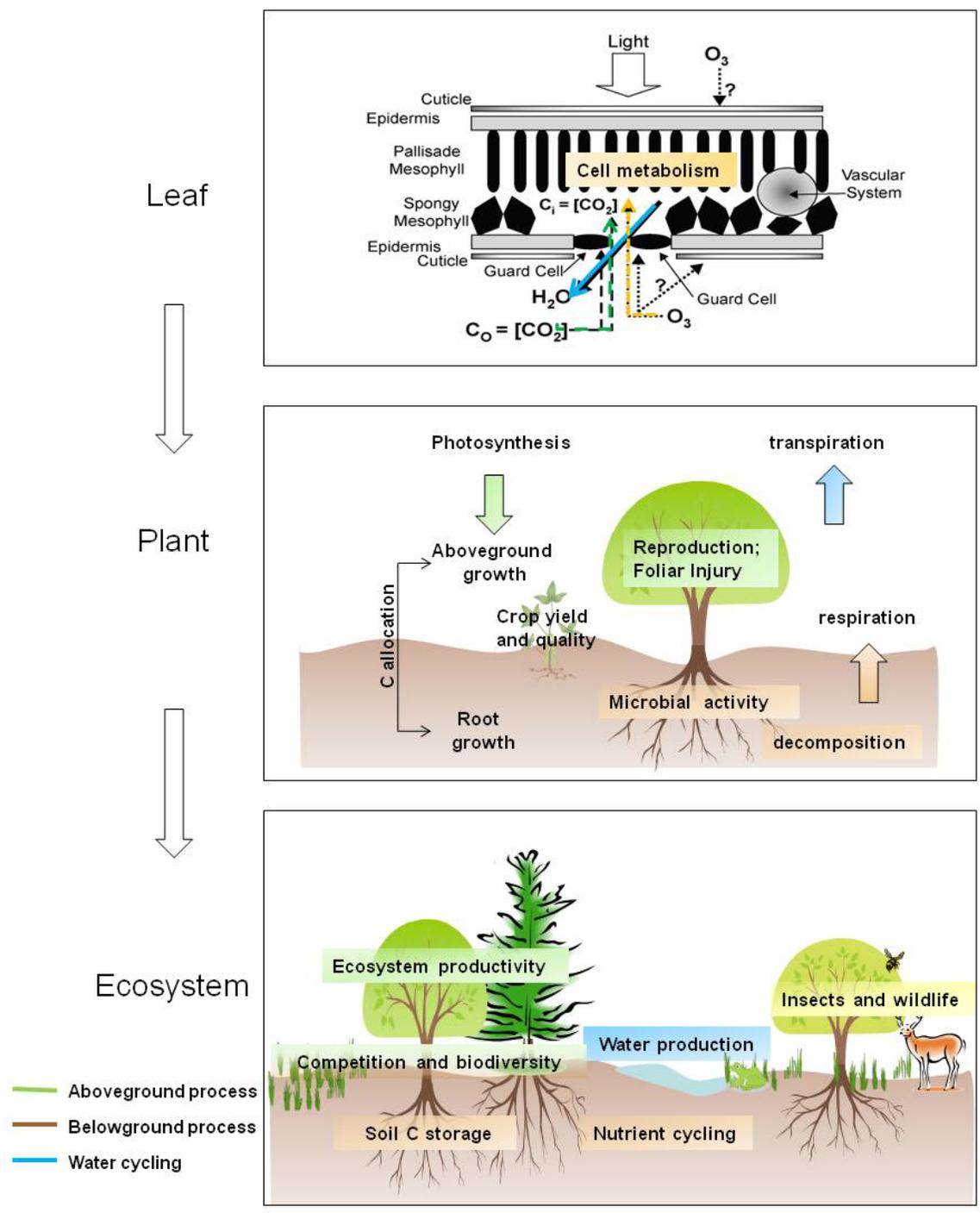


Figure 9-1. The effects of ozone at leaf, plant and ecosystem scales.

**Table 9-1 Summary of ozone causal determinations for vegetation and ecosystem effects**

<b>Vegetation and Ecosystem Effects</b>	<b>Causality Determination</b>
Reduced Vegetation Growth	Causal
Alteration of Vegetation Reproduction	Causal
Visible Foliar Injury Effects on Vegetation	Causal
Alteration of Leaf Gas Exchange in Vegetation	Causal
Reduced Yield and Quality of Agricultural Crops	Causal
Reduced Productivity in Terrestrial Ecosystems	Causal
Reduced Carbon (C) Sequestration in Terrestrial Ecosystems	Likely Causal
Alteration of Terrestrial Ecosystem Water Cycling	Likely Causal
Alteration of Below-ground Biogeochemical Cycles	Causal
Alteration of Terrestrial Community Composition	Likely Causal

## 9.2.2. Mechanisms Governing Response

1 Section 9.4 focuses on the effects of O<sub>3</sub> stress on plants and their responses to that stress on the  
2 molecular, biochemical and physiological levels. Many of the studies focus on the molecular  
3 mechanisms that underlie the observed biochemical and physiological changes observed in many  
4 plant species in response to O<sub>3</sub> exposure. The results support and strengthen those reported in the  
5 2006 O<sub>3</sub> AQCD. The most significant change in this section from the 2006 O<sub>3</sub> AQCD is the emphasis  
6 on molecular mechanisms as new techniques, such as those used in evaluating transcriptomes (total  
7 set of RNA transcripts in a particular cell at a particular time) and proteomes (total set of proteins  
8 expressed in a particular cell at a particular time), have been utilized to perform very comprehensive  
9 analyses of changes in gene transcription and protein expression in plants exposed to O<sub>3</sub>. These  
10 newer molecular studies not only provide very important and wide-ranging information regarding  
11 the many mechanisms of plant responses to O<sub>3</sub>, they also allow for the analysis of interactions  
12 between various biochemical pathways which are induced in response to O<sub>3</sub>. However, many of  
13 these studies are conducted in artificial conditions with model plants which are typically exposed to  
14 very high, short doses of O<sub>3</sub>. Therefore, additional work remains to elucidate whether these plant  
15 responses are transferable to other plant species exposed to more realistic ambient conditions.

16 Ozone is taken up into leaves through open stomata. Once inside the substomatal cavity, O<sub>3</sub> is  
17 thought to rapidly react with the aqueous layer surrounding the cell (apoplast) to form breakdown  
18 products such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), superoxide (O<sub>2</sub><sup>-</sup>), hydroxyl radicals (HO<sup>•</sup>) and peroxy  
19 radicals (HO<sub>2</sub><sup>•</sup>). These radicals may play a role in signaling processes and may also interact with  
20 sensitive molecules both outside and inside the cell to cause damage. This process was very

1 comprehensively described in the 2006 O<sub>3</sub> AQCD and is only summarized in this document in  
2 Section 9.4.2.

3 As plants have been shown to respond to O<sub>3</sub> exposure very rapidly, this response must result  
4 from a plant's ability to sense the presence of O<sub>3</sub> and/or its breakdown products and then  
5 communicate that information to the nucleus to initiate changes in gene expression. While it remains  
6 unclear what the exact mechanism is by which the plant senses the presence of O<sub>3</sub>, whether there are  
7 multiple simultaneous mechanisms by which O<sub>3</sub> can be sensed, and how much variation exists in O<sub>3</sub>  
8 sensing between species and exposure conditions, some progress has been made in the understanding  
9 of this process since the 2006 O<sub>3</sub> AQCD. Experimental evidence described in Section 9.4.3.1  
10 suggests that O<sub>3</sub> and/or its breakdown products may be directly sensed by apoplastic receptor  
11 proteins (although they have not yet been identified). Additionally, a change in cellular redox state  
12 due to plant exposure to O<sub>3</sub> could be the manner in which plants sense the presence of the pollutant.  
13 Once the plant has sensed the presence of the pollutant, there is much evidence to suggest that  
14 mitogen-activated protein kinases (MAPK) play an important role in communicating signals to the  
15 nucleus that result in gene expression changes in response to O<sub>3</sub>. Calcium has also been implicated to  
16 play a role in the signal transduction processes. To summarize, the evidence to date suggests there  
17 may be several mechanisms by which plants sense the presence of O<sub>3</sub> and then communicate this  
18 signal to the nucleus to induce changes in gene expression.

19 New technologies have allowed for the evaluation of changes in the entire transcriptome and  
20 proteome, rather than analyzing the modification of the expression of individual genes and proteins;  
21 the results of these studies are presented in Section 9.4.3.2. While transcriptome and proteome  
22 analyses per se were not previously addressed, the 2006 O<sub>3</sub> AQCD did provide much information  
23 regarding changes in gene expression and protein quantity of individual genes and proteins in  
24 O<sub>3</sub>-treated plants. In the transcriptome and proteome studies described here, O<sub>3</sub> exposure conditions  
25 (concentration, duration of exposure), plant species and sampling times vary significantly; however,  
26 functional classification of the genes and proteins that are either up- or down-regulated by plant  
27 exposure to O<sub>3</sub> exhibit common trends. In summary, genes involved in plant defense, signaling, and  
28 those associated with the synthesis of plant hormones and secondary metabolism are generally up-  
29 regulated in plants exposed to O<sub>3</sub>, while those related to photosynthesis and general metabolism are  
30 typically down-regulated. Proteome studies support these results by demonstrating concomitant  
31 increases or decreases in the proteins encoded by these genes. The transcriptome and proteome  
32 results support and enhance the findings of the 2006 O<sub>3</sub> AQCD.

33 The 2006 O<sub>3</sub> AQCD included a discussion on the role of phytohormones, including salicylic  
34 acid, ethylene and jasmonic acid, in plant response to O<sub>3</sub>. Many additional studies using microarray  
35 technology (used to determine changes in the transcriptome) and a variety of Arabidopsis mutants  
36 are described in Section 9.4.3.3 and support the conclusions from the 2006 O<sub>3</sub> AQCD. Transcriptome  
37 analysis has also illuminated the complex interactions that exist between these hormones to better  
38 define plant response to O<sub>3</sub>. To summarize, the results indicate that while ethylene and salicylic acid  
39 are needed to develop O<sub>3</sub>-induced leaf lesions, jasmonic acid acts antagonistically to ethylene and

1 salicylic acid to limit the spread of the lesions. Abscisic acid, in addition to its role in regulating  
2 stomatal aperture, may also act antagonistically to the jasmonic acid signaling pathway. Nitric oxide  
3 has also been proposed to play a role in regulating O<sub>3</sub>-induced changes in gene expression; however,  
4 its role is not yet well defined. Changes in phytohormones and the interactions between them reveal  
5 some of the complexity of plant responses to an oxidative stressor such as O<sub>3</sub>.

6 Antioxidant metabolites, such as ascorbate and glutathione, and the enzymes that regenerate  
7 them are a critical part of plant defense responses to oxidative stress. The role of ascorbate, which is  
8 located in several cellular compartments and also in the apoplast, was comprehensively evaluated in  
9 the 2006 O<sub>3</sub> AQCD as a first line of defense (due to its location in the apoplast) against oxidative  
10 stress. Ascorbate has also been the focus of studies investigating differences in O<sub>3</sub> tolerance between  
11 plant species or cultivars/genotypes within one species. While the studies evaluated for the current  
12 document support the important role of ascorbate, several studies suggest that ascorbate quantity,  
13 especially in the apoplast, is not the primary factor in determining plant tolerance to O<sub>3</sub>. In summary,  
14 antioxidant metabolites and enzymes increase in quantity in plants exposed to O<sub>3</sub>. In most cases,  
15 there is a correlation between the degree to which these defensive systems are induced and the  
16 ability of the plant to tolerate exposure to O<sub>3</sub>. This up-regulation of antioxidant defenses and the  
17 need to keep antioxidant metabolites in a reduced state requires a significant shift in C metabolism  
18 away from growth and reproduction to sustain the energy needs of the plant for defense.

19 While declines in C fixation as a result of plant exposure to O<sub>3</sub> were extensively described in  
20 the 2006 O<sub>3</sub> AQCD, some recent studies (described in Section 9.4.5.1) of O<sub>3</sub>-induced declines in  
21 photosynthesis have focused also on O<sub>3</sub> effects on the light reactions. Declines in the Fv/Fm ratio (a  
22 measure of the maximum efficiency of the light reactions of photosynthesis) were observed in  
23 several studies using a variety of plant species and exposure conditions. Additionally, O<sub>3</sub> increased  
24 the coefficient of non-photochemical quenching in several species, an indication that defense and  
25 repair mechanisms of a non-photochemical nature are activated in these plants while less absorbed  
26 light is being used to drive photosynthesis. This indicates a shift away from photosynthesis to  
27 defense, resulting in negative impacts on growth and reproduction.

28 Section 9.4.5.2 evaluates the effects of O<sub>3</sub> on respiration. While C assimilation declines in O<sub>3</sub>  
29 exposed plants, respiration is generally up-regulated. These increases in respiration are thought to  
30 result from a plant's greater energy needs for defense (maintaining its antioxidant metabolites in a  
31 reduced state) and repair. The increased energy needs will negatively impact plant growth and  
32 reproduction.

33 Secondary metabolism is most often up-regulated in a variety of species exposed to either  
34 acute or chronic O<sub>3</sub> exposures as a part of a generalized plant defense mechanism. Changes in gene  
35 expression, quantity and activity of enzymes associated with secondary metabolism and alterations  
36 in secondary metabolite quantity have been documented in plants exposed to O<sub>3</sub>. Some secondary  
37 metabolites, such as flavonoids and polyamines, are of particular interest as they are known to have  
38 antioxidant properties. Investigations on the importance of isoprenes in plant response to O<sub>3</sub> have  
39 revealed conflicting results; however, there is some evidence to suggest that they may play a

1 protective role. In summary, secondary metabolites increase in quantity in O<sub>3</sub>-treated plants as part of  
2 a generalized plant defense response. Some secondary metabolites are of particular importance in  
3 O<sub>3</sub>-treated plants as they may have antioxidant functions. Increased synthesis of secondary  
4 metabolites represents a large energy investment of the plant into defense responses and away from  
5 growth and reproduction.

6 Section 9.4.6 focuses on O<sub>3</sub>-induced changes in stomatal function. Stomata play a critical role  
7 in limiting O<sub>3</sub> uptake into the plant by reducing stomatal aperture. Declines in stomatal conductance  
8 in response to O<sub>3</sub> have been documented for many plant species, and much evidence suggests that  
9 this results from increases in intercellular CO<sub>2</sub> concentration due to reductions in C fixation.  
10 Additionally, sensitivity of some plants to O<sub>3</sub> has been related to a sluggish stomatal response, in  
11 which plants are unable to close their stomata rapidly in response to O<sub>3</sub>. To summarize, stomatal  
12 response to O<sub>3</sub> can help to determine plant sensitivity to the pollutant, and the decreases in stomatal  
13 conductance are thought to be related to declines in C fixation rates. Reduced stomatal conductance  
14 will decrease rates of C assimilation and lead to diminished growth and reproduction in plants.

### 9.2.3. Nature of Effects on Vegetation

15 Ambient O<sub>3</sub> concentrations have long been known to cause visible foliar injury, decreases in  
16 photosynthetic rate, decreases in growth, and decreases in the quality and yield of some plant species  
17 (U.S. EPA, 2006, [088089](#))(U.S. EPA, 1996, [080827](#))(U.S. EPA, 1984, [029711](#))(U.S. EPA, 1978,  
18 [040586](#)). Numerous studies have related O<sub>3</sub> exposure to plant responses, with most research effort  
19 focused on the growth of tree seedlings and the yield of crops as endpoints. The response of a plant  
20 species to O<sub>3</sub> exposure depends upon many factors, including genetic characteristics, biochemical  
21 and physiological status, and previous and current exposure to other stressors. The associated  
22 sections in Section 9.5 focus mainly on studies published since the release of the 2006 O<sub>3</sub> AQCD  
23 (U.S. EPA, 2006, [088089](#)). However, because much O<sub>3</sub> research was conducted prior to the 2006 O<sub>3</sub>  
24 AQCD, the conclusions presented below are collectively based on this ISA as well as the 1978,  
25 1986, 1996, and 2006 AQCDs (U.S. EPA, 2006, [088089](#))(U.S. EPA, 1996, [080827](#))(U.S. EPA, 1984,  
26 [029711](#))(U.S. EPA, 1978, [040586](#)).

#### 9.2.3.1. Effects on Woody and Herbaceous Vegetation

##### **Growth and Biomass Allocation**

27 The previous O<sub>3</sub> AQCDs concluded that there is strong and consistent evidence that ambient  
28 concentrations of O<sub>3</sub> decrease growth in numerous plant species across the U.S. Studies published  
29 since the last review continue to support that conclusion (Section 9.5.2.1).

30 In a recently published meta-analysis of 263 studies, Wittig et al. (2009, [191631](#)) reported that  
31 current ambient O<sub>3</sub> concentrations (~40 ppb) significantly decreased annual total biomass growth of  
32 forest species by an average of 7%, with potentially greater decreases (11-17%) in areas that have

1 higher O<sub>3</sub> concentrations and as background O<sub>3</sub> increases in the future. This meta-analysis  
2 demonstrates the coherence of O<sub>3</sub> effects across numerous studies and species using a variety of  
3 experimental techniques. In a study conducted on mature forest trees, McLaughlin et al. (2007,  
4 [090348](#)) reported that the cumulative effects of ambient levels of O<sub>3</sub> decreased seasonal stem growth  
5 by 30-50% for most of the species in a high O<sub>3</sub> year in comparison to a low O<sub>3</sub> year.

6 Since the 2006 O<sub>3</sub> AQCD, several studies were published based on the Aspen free-air carbon-  
7 dioxide/ozone enrichment (FACE) experiment using “free air”, O<sub>3</sub>, and CO<sub>2</sub> exposures in a forest in  
8 Wisconsin. It was found that O<sub>3</sub> caused reductions in total biomass relative to the control in aspen,  
9 paper birch, and sugar maple communities during the first seven years of stand development.

10 Overall, the studies at the Aspen FACE experiment were consistent with many of the open-top  
11 chamber (OTC) studies that were the foundation of previous O<sub>3</sub> NAAQS reviews. These results  
12 strengthen our understanding of O<sub>3</sub> effects on forests and demonstrate the relevance of the  
13 knowledge gained from trees grown in open-top chamber studies.

14 In recent studies, O<sub>3</sub> was shown to have either negative, non-significant, or positive effects on  
15 root biomass and root:shoot ratio. While the findings of individual studies were mixed, recent meta-  
16 analyses have generally indicated that O<sub>3</sub> reduced C allocated to roots (Grantz et al., 2006,  
17 [191545](#))(Wittig et al., 2009, [191631](#)).

18 For some annual species, particularly crops, the endpoint for an assessment of the risk of O<sub>3</sub>  
19 exposure can be defined as yield or growth, e.g., production of grain. For plants grown in mixtures  
20 such as hayfields, and natural or semi-natural grasslands (including native nonagricultural species),  
21 endpoints other than production of biomass may be important. Such endpoints include biodiversity  
22 or species composition, and measures of plant quality. Effects may also result from competitive  
23 interactions among plants in mixed-species communities. Most of the available data on non-crop  
24 herbaceous species are for grasslands with many of the recent studies conducted in Europe.

25 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
26 **and reduced growth of woody and herbaceous vegetation.**

## Reproduction

27 Studies during recent decades have demonstrated O<sub>3</sub> effects on different stages of plant  
28 reproduction (Section 9.5.2.2). Several recent studies published since the 2006 O<sub>3</sub> AQCD further  
29 demonstrate the effects of O<sub>3</sub> on reproductive processes in herbaceous and woody plant species.

30 The impacts of O<sub>3</sub> on reproductive development can occur by influencing (1) age at time of  
31 initial flowering, particularly in long-lived trees that often have long juvenile periods of early growth  
32 without flower and seed production; (2) flower bud initiation and development; (3) pollen  
33 germination and pollen tube growth; and (4) seed, fruit, or cone yields and seed quality.

34 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
35 **and changes in reproduction of vegetation.**

## Visible Foliar Injury

1 Visible foliar injury resulting from exposure to O<sub>3</sub> has been well characterized and  
2 documented over several decades of research on many tree, shrub, herbaceous, and crop species  
3 (U.S. EPA, 2006, [088089](#))(U.S. EPA, 1996, [080827](#))(U.S. EPA, 1984, [029711](#))(U.S. EPA, 1978,  
4 [040586](#))(Section 9.5.2.3). Ozone-induced visible foliar injury symptoms on certain bioindicator plant  
5 species are considered diagnostic as they have been verified experimentally in exposure-response  
6 studies, using exposure methodologies such as continuous stirred tank reactors (CSTRs), OTCs, and  
7 free-air fumigation. Experimental evidence has clearly established a consistent association of visible  
8 injury with O<sub>3</sub> exposure, with greater exposure often resulting in greater and more prevalent injury.  
9 Since the 2006 O<sub>3</sub> AQCD, several multiple-year field surveys of O<sub>3</sub>-induced visible foliar injury  
10 have been conducted at National Wildlife Refuges in Maine, Michigan, New Jersey, and South  
11 Carolina. New sensitive species showing visible foliar injury continue to be identified from field  
12 surveys and verified in controlled exposure studies.

13 The use of biological indicators in field surveys to detect phytotoxic levels of O<sub>3</sub> is a  
14 longstanding and effective methodology. The USDA Forest Service through the Forest Health  
15 Monitoring (FHM) Program (1990-2001) and currently the Forest Inventory and Analysis (FIA)  
16 Program has been collecting data regarding the incidence and severity of visible foliar injury on a  
17 variety of O<sub>3</sub> sensitive plant species throughout the U.S. The network has provided evidence that O<sub>3</sub>  
18 concentrations were high enough to induce visible symptoms on sensitive vegetation. From repeated  
19 observations and measurements made over a number of years, specific patterns of areas experiencing  
20 visible O<sub>3</sub> injury symptoms can be identified.

21 In addition, a study by Kohut (2007, [093289](#)) assessed the risk of O<sub>3</sub>-induced visible foliar  
22 injury on bioindicator plants (NPS, 2006, [677536](#)) in 244 national parks in support of the National  
23 Park Service's Vital Signs Monitoring Network (NPS, 2007, [677537](#)). Kohut (2007, [093289](#))  
24 concluded that the risk of visible foliar injury was high in 65 parks (27%), moderate in 46 parks  
25 (19%), and low in 131 parks (54%). Some of the well-known parks with a high risk of O<sub>3</sub>-induced  
26 visible foliar injury include Gettysburg, Valley Forge, Delaware Water Gap, Cape Cod, Fire Island,  
27 Antietam, Harpers Ferry, Manassas, Wolf Trap Farm Park, Mammoth Cave, Shiloh, Sleeping Bear  
28 Dunes, Great Smoky Mountains, Joshua Tree, Sequoia and Kings Canyon, and Yosemite.

29 Evidence is sufficient to conclude that **there is a causal relationship between ambient O<sub>3</sub>**  
30 **exposure and the occurrence of O<sub>3</sub>-induced visible foliar injury on sensitive vegetation across**  
31 **the U.S.**

## Gas Exchange

32 There is strong experimental evidence over several decades of research that exposure to O<sub>3</sub>  
33 reduces photosynthesis and alters stomatal conductance in a wide variety of plant species. The mode  
34 of action, as characterized in Section 9.4 and in previous reviews, provides biological plausibility for  
35 O<sub>3</sub> effects on leaf gas exchange.

1 In compiling more than 55 studies, Wittig et al. (2007, [191695](#)) reported that current O<sub>3</sub>  
2 concentrations in the northern hemisphere are decreasing photosynthesis (11%) and stomatal  
3 conductance (13%) across tree species. It was also found that younger trees (<4 year) were affected  
4 less by O<sub>3</sub> than older trees. Further, the authors also found that decreases in photosynthesis are  
5 consistent with the cumulative uptake of O<sub>3</sub> into the leaf. In contrast, several studies reported that O<sub>3</sub>  
6 exposure may result in loss of stomatal control, incomplete stomatal closure at night and a  
7 decoupling of photosynthesis and stomatal conductance, which may have implications for whole-  
8 plant water use (Section 9.6.3).

9 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
10 **and the alteration of leaf gas exchange in vegetation.**

### 9.2.3.2. Agricultural Crops

#### Yield and Crop Quality

11 The detrimental effect of O<sub>3</sub> on crop production has been recognized since the 1960's and a  
12 large body of research has subsequently stemmed from those initial findings. Previous O<sub>3</sub> AQCDs  
13 have extensively reviewed this body of literature (U.S. EPA, 2006, [088089](#)). Recent experimental  
14 studies of O<sub>3</sub> effects on crops are discussed in Section 9.5.3 and summarized in Table 9-3 and 9-16

15 Current O<sub>3</sub> concentrations across the U.S. are high enough to cause yield loss for a variety of  
16 agricultural crops including, but not limited to, soybean, wheat, cotton, potato, watermelon, beans,  
17 turnip, onion, lettuce, and tomato. Continued increases in O<sub>3</sub> concentration may further decrease  
18 yield in these sensitive crops while also initiating yield losses in less sensitive crops. Despite the  
19 well-documented yield losses due to increasing O<sub>3</sub> concentration, there is still a knowledge gap  
20 pertaining to the exact mechanism of O<sub>3</sub>-induced yield loss. Research has linked increasing O<sub>3</sub>  
21 concentration to decreased photosynthetic rates and accelerated senescence, which are related to  
22 yield.

23 Recent modeling research has correlated satellite air-column observations with direct air-  
24 sampling O<sub>3</sub> data and modeled the yield-loss due to O<sub>3</sub> over the continuous tri-state area of Illinois,  
25 Iowa and Wisconsin. This modeling data correlates well with the previous results from FACE-type  
26 experiments and OTC experiments.

27 New research is beginning to consider the mechanism of damage caused by long, lower O<sub>3</sub>  
28 concentration (so-called chronic exposure) compared to short, very high O<sub>3</sub> concentration (so-called  
29 acute exposure). Both types of O<sub>3</sub> exposure cause damage to agricultural crops, but through very  
30 different mechanisms. Until recently, most research on the mechanism of O<sub>3</sub> damage has used acute  
31 exposure studies. It has become clear that the same cellular and biochemical processes involved in  
32 the response to acute O<sub>3</sub> exposure are not involved in response to chronic O<sub>3</sub> exposure, yet both  
33 cause yield-loss in agriculturally important crops.

34 In addition, new research has highlighted the effects of O<sub>3</sub> on crop quality. Increasing O<sub>3</sub>  
35 concentration decreases nutritive quality of grasses, decreases macro- and micro-nutrient

1 concentrations in fruits and vegetable crops, and decreases cotton fiber quality. These areas of  
2 research require further investigation to determine the mechanism and dose-responses.

3 Evidence is sufficient to conclude that **there is a causal relationship between O<sub>3</sub> exposure**  
4 **and reduced yield and quality of agricultural crops.**

### 9.2.3.3. Factors That Modify Functional and Growth Response

5 Many biotic and abiotic factors, including insects, pathogens, root microbes and fungi,  
6 temperature, water and nutrient availability, and other air pollutants, as well as elevated CO<sub>2</sub>,  
7 influence or alter plant response to O<sub>3</sub>. These modifying factors were comprehensively reviewed in  
8 the 2006 O<sub>3</sub> AQCD. A limited number of studies published since 2006 provide further support for  
9 our understanding of the role of these interactions in modifying O<sub>3</sub>-induced plant responses and are  
10 discussed in Section 9.5.4.

## 9.2.4. Ecosystems and Services

11 Ozone has been found to alter plant physiological processes such as growth, biomass  
12 allocation, reproduction and gas exchange (Section 9.5). Those O<sub>3</sub>-induced effects at the individual  
13 plant scale have the potential to translate to effects at the ecosystem level, and cause changes in  
14 biogeochemical cycling and community composition. Information presented in the associated section  
15 (Section 9.6) was collected at multiple scales, ranging from responses at the population level to the  
16 ecosystem level. The effects of O<sub>3</sub> on ecosystem productivity, C sequestration, water cycling,  
17 nutrient cycling, and community composition are reviewed.

### 9.2.4.1. Productivity and Carbon Sequestration

18 During the previous NAAQS reviews, there were very few studies that investigated the effect  
19 of O<sub>3</sub> exposure on ecosystem productivity and C sequestration. Recent studies from long-term FACE  
20 experiments provided evidence of the association of O<sub>3</sub> exposure and reduced productivity at the  
21 ecosystem level. Elevated O<sub>3</sub> reduced stand-level biomass by 13-23% at Aspen FACE after 7 years  
22 of O<sub>3</sub> exposure (King et al., 2005, [191701](#)), and annual volume growth by 9.5 m<sup>3</sup>/ha at the Kranzberg  
23 Forest (Germany) FACE (Pretzsch et al., 2010, [580435](#)). Studies at the leaf and plant scales showed  
24 that O<sub>3</sub> reduced photosynthesis and plant growth, which provided coherence and biological  
25 plausibility for the decrease in ecosystem productivity. Results across different ecosystem models  
26 were consistent with the FACE experimental evidence, which showed that O<sub>3</sub> reduced ecosystem  
27 productivity.

28 Although O<sub>3</sub> generally causes negative effects on plant growth, the magnitude of the response  
29 varies among plant communities. For example, O<sub>3</sub> had little impact on white fir, but greatly reduced  
30 growth of ponderosa pine in southern California (Weinstein et al., 2005, [179965](#)). Ozone decreased  
31 net primary production (NPP) of most forest types by 7-8% in Mid-Atlantic region, but had small  
32 impacts on spruce-fir forest, which was decreased by only 1% (Pan et al., 2009, [596032](#)). Among

1 crop species, the estimated yield loss for wheat (7-12%) and soybean (6-16%) were higher than rice  
2 (3-4%) and maize (3-5%) (Van Dingenen et al., 2009, [199765](#)).

3 In addition to plant growth, other indicators that are typically estimated by model studies  
4 include net ecosystem CO<sub>2</sub> exchange (NEE), C sequestration, and crop yield. Model simulations  
5 consistently found that O<sub>3</sub> exposure caused negative impacts on those indicators (Section 9.6.2,  
6 Table 9-5), but the severity of these impacts was influenced by multiple interactions of biological  
7 and environmental factors. For example, the largest O<sub>3</sub>-induced crop yield losses occurred in high-  
8 production areas exposed to high O<sub>3</sub> concentrations, such the Midwest and the Mississippi Valley  
9 regions of the U.S. (Van Dingenen et al., 2009, [199765](#)).

10 The suppression of ecosystem C sinks results in more CO<sub>2</sub> accumulation in the atmosphere.  
11 Globally, the indirect radiative forcing, reported in Watts/square meter (W/m<sup>2</sup>), caused by O<sub>3</sub>  
12 exposure through lowering ecosystem C sink (0.62-1.09 W/m<sup>2</sup>) could have an even greater impact  
13 on global warming than the direct radiative forcing of O<sub>3</sub> (0.89 W/m<sup>2</sup>) (Sitch et al., 2007, [093294](#)).  
14 Ozone could also affect regional C budgets through interacting with multiple factors, such as N  
15 deposition, elevated CO<sub>2</sub> and land use history. Model simulations suggested that O<sub>3</sub> partially offset  
16 the growth stimulation caused by elevated CO<sub>2</sub> and N deposition in both Northeast- and Mid-  
17 Atlantic-region forest ecosystems of the U.S. (Ollinger et al., 2002, [180189](#))(Pan et al., 2009,  
18 [596032](#)).

19 The evidence is sufficient to infer that **there is a causal relationship between O<sub>3</sub> exposure**  
20 **and reduced productivity, and a likely causal relationship between O<sub>3</sub> exposure and reduced**  
21 **carbon sequestration in terrestrial ecosystems.**

#### 9.2.4.2. Water Cycling

22 Although the evidence was from a limited number of field and modeling studies, these  
23 findings showed an association of O<sub>3</sub> exposure and the alteration of water cycle at the ecosystem  
24 level. Field studies conducted by McLaughlin et al. (2007, [090348](#))(2007, [090347](#)) suggested that  
25 peak hourly O<sub>3</sub> exposure increased the rate of water loss from several tree species, and led to a  
26 reduction in the late-season modeled stream flow in three forested watersheds in eastern Tennessee.  
27 Evidence of sluggish stomatal responses during O<sub>3</sub> exposure was found in their study and several  
28 other studies (Section 9.6.3), which provided biological plausibility for the observed higher water  
29 loss at the ecosystem level. However, many experiments, mostly based on short-term O<sub>3</sub> exposure,  
30 found that O<sub>3</sub> generally reduced stomatal conductance. The O<sub>3</sub>-induced reduction in stomatal  
31 aperture is the biological assumption for most process-based models. Therefore, results of those  
32 models normally found that O<sub>3</sub> reduced water loss. For example, Felzer (2009, [191460](#)) found that  
33 O<sub>3</sub> damage and N limitation together reduced evapotranspiration and increase runoff.

34 Although the direction of the response differed among studies, the evidence is sufficient to  
35 conclude that **there is likely to be a causal relationship between O<sub>3</sub> exposure and the alteration**  
36 **of ecosystem water production.**

### 9.2.4.3. Below-Ground Processes

1 Since the 2006 O<sub>3</sub> AQCD, more evidence has shown that although the responses are often  
2 species specific, O<sub>3</sub> altered the quality and quantity of C input to soil, microbial community  
3 composition, and C and nutrient cycling. Biogeochemical cycling of below-ground processes is  
4 driven by C input from plants. Studies at the leaf and plant level have provided biologically plausible  
5 mechanisms, such as reduced photosynthetic rates, increased metabolic cost, and reduced root C  
6 allocation (Section 9.6.4) for the association of O<sub>3</sub> exposure and the alteration of below-ground  
7 processes.

8 Results from Aspen FACE and other experimental studies consistently found that O<sub>3</sub> reduced  
9 litter production and altered C chemistry, such as soluble sugars, soluble phenolics, condensed  
10 tannins, lignin, and macro/micro nutrient concentration in litter (Liu et al., 2005, [187005](#))(Parsons et  
11 al., 2008, [191853](#))(Kasurinen et al., 2006, [191269](#)). The changes in substrate quality and quantity  
12 could alter microbial metabolism under elevated O<sub>3</sub>, and therefore soil C and nutrient cycling.  
13 Several studies indicated that O<sub>3</sub> generally suppressed soil enzyme activities (Chung et al., 2006,  
14 [191729](#))(Pritsch et al., 2009, [626808](#)). However, the impact of O<sub>3</sub> on litter decomposition was  
15 inconsistent and varied among species, sites and exposure length. Ozone had small impact on  
16 dynamics of micro and macro nutrients, except for N. Ozone was found to reduce N release from  
17 leaf litter and decrease gross N mineralization, which could potentially decrease N availability to  
18 plants (Holmes et al., 2006, [191372](#))(Liu et al., 2007, [093286](#)).

19 Studies from the Aspen FACE experiment suggested that the response of below-ground  
20 C cycle to O<sub>3</sub> exposure, such as litter decomposition, soil respiration and soil C content, changed  
21 over time. For example, in the early part of the experiment (1998-2003), O<sub>3</sub> had no impact on soil  
22 respiration but reduced the formation rates of total soil C under elevated CO<sub>2</sub>. However, after 10-  
23 11 yr of exposure, O<sub>3</sub> was found to increase soil respiration but have no significant impact on soil  
24 C formation under elevated CO<sub>2</sub> (Section 9.6.4.3).

25 The evidence is sufficient to infer that **there is a causal relationship between O<sub>3</sub> exposure**  
26 **and the alteration of below-ground biogeochemical cycles.**

### 9.2.4.4. Community Composition

27 In the 2006 O<sub>3</sub> AQCD, the impact of O<sub>3</sub> exposure on species competition and community  
28 composition was assessed. Ozone was found to cause a significant decline in ponderosa and Jeffrey  
29 pine in the San Bernardino Mountains in southern California. Ozone exposure also tended to shift  
30 the grass-legume mixtures in favor of grass species (U.S. EPA, 2006, [088089](#)). Since the 2006 O<sub>3</sub>  
31 AQCD, more evidence has shown that O<sub>3</sub> exposure changed the competitive interactions and led to  
32 loss of O<sub>3</sub> sensitive species or genotypes. Studies at plant level found that the severity of O<sub>3</sub> damage  
33 on growth, reproduction and foliar injury varied among species (Section 9.6.5), which provided the  
34 biological plausibility for the alteration of community composition. Additionally, research since the

1 last review has shown that O<sub>3</sub> can alter community composition and diversity of soil microbial  
2 communities.

3 The decline of conifer forests under O<sub>3</sub> exposure was continually observed in several regions.  
4 Ozone damage was believed to be an important causal factor in the dramatic decline of sacred fir in  
5 the valley of Mexico (de Lourdes de Bauer and Hernandez-Tejeda, 2007, [196891](#)), as well as  
6 cembran pine in southern France and Carpathian Mountains (Wieser et al., 2006, [191391](#)). Results  
7 from the Aspen FACE site indicated that O<sub>3</sub> could alter community composition of broadleaf forests  
8 as well. At the Aspen FACE site, O<sub>3</sub> reduced growth and increased mortality of a sensitive aspen  
9 clone, while the O<sub>3</sub> tolerant clone emerged as the dominant clone in the pure aspen community. In  
10 the mixed aspen-birch and aspen-maple communities, O<sub>3</sub> reduced the competitive capacity of aspen  
11 compared to birch and maple (Kubiske et al., 2007, [191336](#)).

12 The tendency for O<sub>3</sub>-exposure to shift the biomass of grass-legume mixtures in favor of grass  
13 species, was reported in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) and has been generally  
14 confirmed by recent studies. However, in a high elevation mature/species-rich grass-legume pasture,  
15 O<sub>3</sub> fumigation showed no significant impact on community composition (Bassin et al., 2007,  
16 [191534](#)).

17 Ozone exposure not only altered community composition of plant species, but also  
18 microorganisms. The shift in community composition of bacteria and fungi has been observed in  
19 both natural and agricultural ecosystems, although no general patterns could be identified (Kanerva  
20 et al., 2008, [191264](#))(Morsky et al., 2008, [191507](#))(Kasurinen et al., 2005, [191245](#)).

21 The evidence is sufficient to conclude that **there is likely a causal relationship between O<sub>3</sub>**  
22 **exposure and the alteration of community composition.**

### 9.2.5. Air Quality Indices

23 Exposure indices are metrics that quantify exposure as it relates to measured plant damage  
24 (i.e., reduced growth). They are summary measures of monitored ambient O<sub>3</sub> concentrations over  
25 time intended to provide a consistent metric for reviewing and comparing exposure-response effects  
26 obtained from various studies. No new information is available since 2006 that alters the basic  
27 conclusions put forth in the 2006 and 1996 O<sub>3</sub> AQCDs (U.S. EPA, 1996, [080827](#))(U.S. EPA, 2006,  
28 [088089](#)). These AQCDs focused on the research used to develop various exposure indices to help  
29 quantify effects on growth and yield in crops, perennials, and trees (primarily seedlings). The  
30 performance of indices was compared through regression analyses of earlier studies designed to  
31 support the estimation of predictive O<sub>3</sub> exposure-response models for growth and/or yield of crops  
32 and tree (seedling) species.

33 The main conclusions from the 1996 and 2006 O<sub>3</sub> AQCDs (U.S. EPA, 1996,  
34 [080827](#))(U.S. EPA, 2006, [088089](#)) regarding an index based on ambient exposure are still valid.  
35 These key conclusions can be restated as follows:

- 36 ■ O<sub>3</sub> effects in plants are cumulative;



### 9.2.5.2. Night-Time Exposures

1 A 12-h (8:00 a.m. to 8:00 p.m.) daylight period for a W126 cumulating exposure was proposed  
2 in 2007 and 2009 following the release of the 2006 O<sub>3</sub> AQCD and was based primarily on evidence  
3 that the conditions for uptake of O<sub>3</sub> into the plant occur mainly during the daytime hours. Plants have  
4 the highest stomatal conductance during the daytime and atmospheric turbulent mixing is greatest  
5 then as well (U.S. EPA, 2006, [088089](#))(Uddling et al., 2010, [387073](#)). Recent reviews of the  
6 literature reported that a large number of species had varying degrees of nocturnal stomatal  
7 conductance (Caird et al., 2007, [199337](#))(Dawson et al., 2007, [670381](#))(Musselman and Minnick,  
8 2000, [011612](#)). In general, stomatal conductance at night is at a much lower rate compared to  
9 daytime conductance (Caird et al., 2007, [199337](#)). For significant nocturnal stomatal flux and O<sub>3</sub>  
10 effects to occur, specific conditions must exist. A susceptible plant with nocturnal stomatal  
11 conductance and low defense must be growing in an area with relatively high night-time O<sub>3</sub> and  
12 appreciable nocturnal turbulence. It is unclear how many areas there are in the U.S. where these  
13 conditions occur. More information is needed in these locations in order to assess the local O<sub>3</sub>  
14 patterns, micrometeorology and responses of potentially vulnerable plant species.

### 9.2.6. Exposure-Response

15 None of the information on effects of O<sub>3</sub> on vegetation published since the 2006 O<sub>3</sub> AQCD has  
16 modified the assessment of quantitative exposure-response relationships that was presented in that  
17 document (U.S. EPA, 2006, [088089](#)). This assessment updates the 2006 exposure-response models  
18 by computing them using the W126 metric, cumulated over 90 days. Almost all of the experimental  
19 research on the effects of O<sub>3</sub> on growth or yield of plants published since 2006 used only two levels  
20 of exposure. In addition, hourly O<sub>3</sub> concentration data that would allow calculations of exposure  
21 using the W126 scale are generally unavailable. However, two long-term experiments, one with a  
22 crop species (soybean), one with a tree species (aspen), have produced data that can be used to  
23 validate the exposure-response models presented in the 2006 O<sub>3</sub> AQCD, and methodology used to  
24 derive them.

25 Quantitative characterization of exposure-response in the 2006 O<sub>3</sub> AQCD was based on  
26 experimental data generated for that purpose by the National Crop Loss Assessment Network  
27 (NCLAN) and EPA National Health and Environmental Effects Research Laboratory, Western  
28 Ecology Division (NHEERL-WED) projects, using OTCs to expose crops and trees seedling to O<sub>3</sub>.  
29 In recent years, yield and growth results for two of the species that had provided extensive exposure-  
30 response information in those projects have become available from studies that used FACE  
31 technology, which is intended to provide conditions much closer to natural environments (Dickson et  
32 al., 2000, [628220](#); Morgan et al., 2004, [072764](#); Morgan et al., 2006, [079186](#); Pregitzer et al., 2008,  
33 [191677](#)). The robust methods that were used previously with exposure measured as SUM06 were  
34 applied to the NCLAN and NHEERL-WED data with exposure measured as W126, in order to  
35 derive single-species median models for soybean and aspen from studies involving different

1 genotypes, years, and locations. The resulting models were used to predict the change in yield of  
2 soybean and biomass of aspen between the two levels of exposure reported in current FACE  
3 experiments. Results from these new experiments were exceptionally close to predictions from the  
4 models. The accuracy of model predictions for two widely different plant species provides support  
5 for the validity of the corresponding multiple-species models for crops and trees in the NCLAN and  
6 NHEERL-WED projects. However, variability among species in those projects indicates that the  
7 range of sensitivity is likely quite wide. This was confirmed by a recent experiment with cottonwood  
8 in a naturally occurring gradient of exposure (Gregg et al., 2006, [186961](#)), which established the  
9 occurrence of species with responses substantially more severe under currently existing conditions  
10 than are predicted by the median model for multiple species.

11 Results from several meta-analyses have provided approximate values for responses of yield  
12 of soybean, wheat, rice and other crops under broad categories of exposure, relative to charcoal-  
13 filtered air (Ainsworth, 2008, [191646](#); Feng et al., 2008, [191453](#); Morgan et al., 2003, [055527](#)).  
14 Likewise, Feng and Kobayashi (2009, [199223](#)) have summarized yield data for six crop species  
15 under various broad comparative exposure categories, while Wittig et al. (2009, [191631](#)) reviewed  
16 263 studies that reported effects on tree biomass. However, these analyses have proved difficult to  
17 compare with exposure-response models, especially given that exposure was not expressed on the  
18 same W126 scale.

## 9.3. Experimental Exposure Methodologies

### 9.3.1. Introduction

19 A variety of methods for studying plant response to O<sub>3</sub> exposures have been developed over  
20 the last several decades. Methodological advancements since 2006 have not fundamentally altered  
21 our understanding of O<sub>3</sub> effects on plants or ecosystems. The majority of methodologies currently  
22 used have been discussed in detail in the 1996 O<sub>3</sub> AQCD (Section 5.2; U.S. EPA, 1996, [080828](#)) and  
23 2006 O<sub>3</sub> AQCD (Section AX9.1; U.S. EPA, 2006, [088089](#)). This section will serve as a short  
24 overview of the methodologies and the reader is referred to the previous O<sub>3</sub> AQCDs for more in-  
25 depth discussion.

### 9.3.2. “Indoor,” Controlled Environment, and Greenhouse Chambers

26 The earliest experimental investigations of the effects of O<sub>3</sub> on plants utilized simple glass or  
27 plastic-covered chambers, often located within greenhouses, into which a flow of O<sub>3</sub>-enriched air or  
28 oxygen could be passed to provide the exposure. The types, shapes, styles, materials of construction,  
29 and locations of these chambers have been numerous. Hogsett et al. (1987, [043465](#)) have  
30 summarized the construction and performance of more elaborate and better instrumented chambers  
31 since the 1960s, including those installed in greenhouses (with or without some control of  
32 temperature and light intensity).

1 One greenhouse chamber approach that continues to yield useful information on the  
2 relationships of O<sub>3</sub> uptake to both physiological and growth effects employs continuous stirred tank  
3 reactors (CSTRs) first described by Heck et al. (1978, [037673](#)). Although originally developed to  
4 permit mass-balance studies of O<sub>3</sub> flux to plants, their use has more recently widened to include  
5 short-term physiological and growth studies of O<sub>3</sub> × CO<sub>2</sub> interactions (Heagle et al., 1994,  
6 [026699](#))(Loats and Rebbeck, 1999, [029709](#))(Rao et al., 1995, [030221](#))(Reinert and Ho, 1995,  
7 [030247](#))(Reinert et al., 1997, [030252](#)), and validation of visible foliar injury on a variety of plant  
8 species (Kline et al., 2009, [196918](#))(Orendovici et al., 2003, [049080](#)). In many cases, supplementary  
9 lighting and temperature control of the surrounding structure have been used to control or modify the  
10 environmental conditions (Heagle et al., 1994, [026699](#)).

11 Many investigations have utilized commercially available controlled environment chambers  
12 and walk-in rooms adapted to permit the introduction of a flow of O<sub>3</sub> into the controlled air-volume.  
13 Such chambers continue to find use in genetic screening and in physiological and biochemical  
14 studies aimed primarily at improving our understanding of modes of action. For example, some of  
15 the studies of the O<sub>3</sub> responses of common plantain (*Plantago major*) populations have been  
16 conducted in controlled environment chambers (Reiling and Davison, 1994, [035373](#))(Whitfield et  
17 al., 1996, [055544](#)).

18 More recently, some researchers have been interested in direct O<sub>3</sub> effects on reproductive  
19 processes, separate from the effects on vegetative processes (Black et al., 2010, [625575](#)). For this  
20 purpose, controlled exposure systems have been employed to expose the reproductive structures of  
21 annual plants to gaseous pollutants independently of the vegetative component (Black et al., 2010,  
22 [625575](#))(Stewart et al., 1996, [036384](#)).

### 9.3.3. Field Chambers

23 In general, field chamber studies are dominated by the use of various versions of the open top  
24 chamber (OTC) design, first described by Heagle et al. (1973, [038348](#)) and Mandl et al. (1973,  
25 [039967](#)). The OTC method continues to be a widely used technique in the U.S. and Europe for  
26 exposing plants to varying levels of O<sub>3</sub>. Most of the new information confirms earlier conclusions  
27 and provides additional support for OTC use in assessing plant species and in developing exposure-  
28 response relationships. Chambers are generally ~3 m in diameter with 2.5-m-high walls. Hogsett et  
29 al. (1987, [043780](#)) described in detail many of the various modifications to the original OTC designs  
30 that appeared subsequently, e.g., the use of larger chambers for exposing small trees (Kats et al.,  
31 1985, [055511](#)) or grapevines (Mandl et al., 1989, [043987](#)), the addition of a conical baffle at the top  
32 to improve ventilation (Kats et al., 1976, [039799](#)), a frustum at the top to reduce ambient air  
33 incursions, and a plastic rain-cap to exclude precipitation (Hogsett et al., 1985, [039383](#)). All versions  
34 of OTCs included the discharge of air via ports in annular ducting or interiorly perforated double-  
35 layered walls at the base of the chambers to provide turbulent mixing and the upward mass flow of  
36 air.

1 Chambered systems, including OTCs, have several advantages. For instance, they can provide  
2 a range of treatment levels including charcoal-filtered (CF), clean-air control, and several above  
3 ambient concentrations for O<sub>3</sub> experiments. Depending on experimental intent, a replicated, clean-air  
4 control treatment is an essential component in many experimental designs. The OTC can provide a  
5 consistent, definable exposure because of the constant wind speed and delivery systems. Statistically  
6 robust concentration-response (C-R) functions can be developed using such systems for evaluating  
7 the implications of various alternative air quality scenarios on vegetation response. Nonetheless,  
8 there are several characteristics of the OTC design and operation that can lead to exposures that  
9 might differ from those experienced by plants in the field. First, the OTC plants are subjected to  
10 constant air flow turbulence, which, by lowering the boundary layer resistance to diffusion, may  
11 result in increased uptake. This may lead to an overestimation of effects relative to areas with less  
12 turbulence (Krupa et al., 1995, [038895](#))(Legge et al., 1995, [040689](#)). Conversely, however, other  
13 research has found that OTC's may slightly change vapor pressure deficit (VPD) in a way that may  
14 decrease the uptake of O<sub>3</sub> into leaves (Piikki et al., 2008, [199265](#)). As with all methods that expose  
15 vegetation to modified O<sub>3</sub> concentrations in chambers, OTCs create internal environments that differ  
16 from ambient air. This so-called “chamber effect” refers to the modification of microclimatic  
17 variables, including reduced and uneven light intensity, uneven rainfall, constant wind speed,  
18 reduced dew formation, and increased air temperatures (Fuhrer, 1994, [055549](#))(Manning and Krupa,  
19 1992, [044155](#)). However, in at least one case where canopy resistance was quantified in OTCs and in  
20 the field, it was determined that gaseous pollutant exposure to crops in OTCs was similar to that  
21 which would have occurred at the same concentration in the field (Unsworth et al., 1984,  
22 [041239](#))(Unsworth et al., 1984, [040024](#)). Because of the standardized methodology and protocols  
23 used in National Crop Loss Assessment Network (NCLAN) and other programs, the database can be  
24 assumed to be internally consistent.

25 While it is clear that OTCs can alter some aspects of the microenvironment and plant growth,  
26 it is important to establish whether or not these differences affect the relative response of a plant to  
27 O<sub>3</sub>. As noted in the 1996 O<sub>3</sub> AQCD (U.S. EPA, 1996, [080828](#)), evidence from a number of  
28 comparative studies of OTCs and other exposure systems suggested that responses were essentially  
29 the same regardless of exposure system used and chamber effects did not significantly affect  
30 response. For example, a study of chamber effects examined the responses of tolerant and sensitive  
31 white clover clones (*Trifolium repens*) to ambient O<sub>3</sub> in greenhouse, open top, and ambient plots  
32 (Heagle et al., 1996, [042660](#)). The response found in OTCs was the same as in ambient plots.

33 Another type of field chamber called a “terracosm” has been developed and used in recent  
34 studies (Lee et al., 2009, [595904](#)). Concern over the need to establish realistic plant-litter-soil  
35 relationships as a prerequisite to studies of the effects of O<sub>3</sub> and CO<sub>2</sub> enrichment on ponderosa pine  
36 (*Pinus ponderosa*) seedlings led Tingey et al. (1996, [055536](#)) to develop closed, partially  
37 environmentally controlled, sun-lit chambers (“terracosms”) incorporating 1-m-deep lysimeters  
38 containing forest soil in which the appropriate horizon structure was retained.

1 Other researchers have recently published studies using another type of out-door chamber  
2 called recirculating Outdoor Plant Environment Chambers (OPECs) (Flowers et al., 2007, [191852](#)).  
3 These closed chambers are approximately 2.44 m×1.52 m with a growth volume of approximately  
4 3.7 m<sup>3</sup> in each chamber. These chambers admit 90% of full sunlight and control temperature,  
5 humidity and vapor pressure (Fiscus et al., 1999, [672964](#)).

#### 9.3.4. Plume and FACE-Type Systems

6 Plume systems are chamberless exposure facilities in which the atmosphere surrounding plants  
7 in the field is modified by the injection of pollutant gas into the air above or around them from  
8 multiple orifices spaced to permit diffusion and turbulence, so as to establish relatively homogeneous  
9 conditions as the individual plumes disperse and mix with the ambient air. They can only be used to  
10 increase the O<sub>3</sub> levels in the ambient air.

11 The most common plume system used in the U.S. is a modification of the free-air carbon-  
12 dioxide/ozone enrichment (FACE) system (Hendrey and Kimball, 1994, [040397](#))(Hendrey et al.,  
13 1999, [042641](#)). Although originally designed to provide chamberless field facilities for studying the  
14 CO<sub>2</sub> effects of climate change, FACE systems have been adapted to include the dispensing of O<sub>3</sub>  
15 (Karnosky et al., 1999, [035307](#)). This method has been employed in Illinois (SoyFACE) to study  
16 soybeans (Morgan et al., 2004, [072764](#))(Rogers et al., 2004, [079201](#)) and in Wisconsin (Aspen  
17 FACE) to study trembling aspen (*Populus tremuloides*), birch (*Betula papyrifera*) and maple (*Acer*  
18 *saccharum*)(Karnosky et al., 1999, [035307](#)). Volk et al. (2003, [055568](#)) also described a similar  
19 system for exposing grasslands that uses 7-m diameter plots. FACE systems discharge the pollutant  
20 gas (O<sub>3</sub> and/or CO<sub>2</sub>) through orifices spaced along an annular ring (or torus) or at different heights on  
21 a ring of vertical pipes. Computer-controlled feedback from the monitoring of gas concentration  
22 regulates the feed rate of enriched air to the dispersion pipes. Feedback of wind speed and direction  
23 information ensures that the discharges only occur upwind of the treatment plots, and that discharge  
24 is restricted or closed down during periods of low wind speed or calm conditions. The diameter of  
25 the arrays and their height (25-30 m) in some FACE systems requires large throughputs of enriched  
26 air per plot, particularly in forest tree systems. The cost of the throughputs tends to limit the number  
27 of enrichment treatments, although Hendrey et al. (1999, [042641](#)) argued that the cost on an enriched  
28 volume basis is comparable to that of chamber systems.

29 Although plume systems make virtually none of the modifications to the physical environment  
30 that are inevitable with chambers, their successful use depends on selecting the appropriate numbers,  
31 sizes, and orientations of the discharge orifices to avoid “hot-spots” resulting from the direct  
32 impingement of jets of pollutant-enriched air on plant foliage (Werner and Fabian, 2002, [053040](#)).  
33 Because mixing is unassisted and completely dependent on wind turbulence and diffusion, local  
34 gradients are inevitable especially in large-scale systems. FACE systems have provisions for shutting  
35 down under low wind speed or calm conditions and for an experimental area that is usually defined  
36 within a generous border in order to strive for homogeneity of the exposure concentrations within the  
37 treatment area. They are also dependent upon continuous computer-controlled feedback of the O<sub>3</sub>

1 concentrations in the mixed treated air and of the meteorological conditions. Plume and FACE  
2 systems also are unable to reduce O<sub>3</sub> levels below ambient in areas where O<sub>3</sub> concentrations are  
3 phytotoxic.

### 9.3.5. Ambient Gradients

4 Ambient O<sub>3</sub> gradients that occur in the U.S. hold potential for the examination of plant  
5 responses over multiple levels of exposure that are occurring. However, few such gradients can be  
6 found that meet the rigorous statistical requirements for comparable site characteristics such as soil  
7 type, temperature, rainfall, radiation, and aspect (Manning and Krupa, 1992, [044155](#)); although with  
8 small plants, soil variability can be avoided by the use of plants in large pots. The use of soil  
9 monoliths transported to various locations along natural O<sub>3</sub> gradients is another possible approach to  
10 overcome differences in soils; however, this approach is also limited to small plants.

11 Studies in the 1970s used the natural gradients occurring in southern California to assess yield  
12 losses of alfalfa and tomato) (Oshima et al., 1976, [038475](#))(Oshima et al., 1977, [038938](#)). A transect  
13 study of the impact of O<sub>3</sub> on the growth of white clover and barley in the U.K. was confounded by  
14 differences in the concurrent gradients of SO<sub>2</sub> and NO<sub>2</sub> pollution (Ashmore et al., 1988, [037038](#)).  
15 Studies of forest tree species in national parks in the eastern U.S. (Winner et al., 1989, [043403](#))  
16 revealed increasing gradients of O<sub>3</sub> and visible foliar injury with increased elevation.

17 Several studies have used the San Bernardino Mountains Gradient Study in southern  
18 California to study the effects of O<sub>3</sub> and N deposition on forests dominated by ponderosa and Jeffrey  
19 pine (Arbaugh et al., 2003, [052925](#))(Miller and Elderman, 1977, [038488](#))(Grulke, 1999,  
20 [052983](#))(Jones and Paine, 2006, [191301](#)). However, it is difficult to separate the effects of N and O<sub>3</sub>  
21 in some instances in these studies (Arbaugh et al., 2003, [052925](#)). An O<sub>3</sub> gradient in Wisconsin has  
22 been used to study foliar injury in a series of trembling aspen clones (*Populus tremuloides*) differing  
23 in O<sub>3</sub> sensitivity (Karnosky et al., 1999, [035307](#))(Maňková et al., 2005, [672965](#)).

24 More recently, some studies have been published that have used natural gradients to study a  
25 variety of endpoints and species. For example, Gregg et al. (2003, [046996](#)) studied cottonwood  
26 saplings grown in an urban to rural gradient of O<sub>3</sub> in the New York City area. The secondary nature  
27 of the reactions of O<sub>3</sub> formation and NO<sub>x</sub> titration reactions within the city center resulted in  
28 significantly higher cumulative O<sub>3</sub> exposures in the rural sites. The results of this gradient study were  
29 similar to those of a parallel OTC study. Also, the U.S. forest service Forest Inventory and Analysis  
30 (FIA) program uses large-scale O<sub>3</sub> exposure patterns across the continental U.S. to study occurrences  
31 of foliar injury due to O<sub>3</sub> exposure (Smith et al., 2003, [044183](#))( Section 9.5.2.3). Finally,  
32 McLaughlin et al. (2007, [090348](#))(2007, [090347](#)) used spatial and temporal O<sub>3</sub> gradients to study  
33 forest growth and water use in the southern Appalachians. These studies found varying O<sub>3</sub> exposures  
34 between years and between sites.

### 9.3.6. Comparative Studies

1 All experimental approaches used to expose plants to O<sub>3</sub> have shortcomings. The use of  
2 laboratory, greenhouse, or field chambers raises concerns for the roles of chamber effects on  
3 micrometeorology. In contrast, plume, FACE and gradient systems suffer from limited exposure  
4 levels, few replicates and an inability to reduce O<sub>3</sub> levels below ambient in areas where O<sub>3</sub>  
5 concentrations are phytotoxic.

6 While it is clear that chambers can alter some aspects of plant growth, it is important to  
7 establish whether or not these differences affect plant response to O<sub>3</sub>. As noted in the 1996 O<sub>3</sub> AQCD  
8 (U.S. EPA, 1996, [080828](#)), evidence from the comparative studies of OTCs and from closed  
9 chamber and O<sub>3</sub>-exclusion exposure systems on the growth of alfalfa (*Medicago sativa*) by Olszyk et  
10 al. (1986, [055530](#)) suggested that, since significant differences were found for fewer than 10% of the  
11 growth parameters measured, the responses were, in general, essentially the same regardless of  
12 exposure system used; and chamber effects did not significantly affect response. In 1988, Heagle et  
13 al. (1988, [043559](#)) concluded: “Although chamber effects on yield are common, there are no results  
14 showing that this will result in a changed yield response to O<sub>3</sub>.” A study of chamber effects examined  
15 the responses of tolerant and sensitive white clover clones (*Trifolium repens*) to ambient O<sub>3</sub> in  
16 greenhouse, open-top, and ambient plots (Heagle et al., 1996, [042660](#)). For individual harvests,  
17 greenhouse O<sub>3</sub> exposure reduced the forage weight of the sensitive clone 7 to 23% more than in  
18 OTCs. However, the response in OTCs was the same as in ambient plots. Several studies have  
19 shown very similar response of yield to O<sub>3</sub> for plants grown in pots or in the ground, suggesting that  
20 even such a significant change in environment does not alter the proportional response to O<sub>3</sub>, at least  
21 as long as the plants are well watered (Heagle, 1979, [039329](#))(Heagle et al., 1983, [039372](#)).

22 A few recent studies have compared results of O<sub>3</sub> experiments between OTCs, FACE  
23 experiments, and gradient studies. For example, a series of studies undertaken at Aspen FACE  
24 (Isebrands et al., 2000, [044174](#))(Isebrands et al., 2001, [036345](#)) showed that O<sub>3</sub>-symptom expression  
25 was generally similar in OTCs, FACE, and ambient-O<sub>3</sub> gradient sites, and supported the previously  
26 observed variation among trembling aspen clones using OTCs (Karnosky et al., 1999,  
27 [035307](#))(Maňková et al., 2005, [672965](#)). In the SoyFACE experiment in Illinois, soybean (Pioneer  
28 93B15 cultivar) yield loss data from a two-year study was published (Morgan et al., 2006, [079186](#)).  
29 This cultivar is a recent selection and, like most modern cultivars, has been selected under an already  
30 high current O<sub>3</sub> exposure. It was found to have average sensitivity to O<sub>3</sub> compared to 22 other  
31 cultivars tested at SoyFACE. In this experiment, ambient hourly O<sub>3</sub> concentrations were increased by  
32 approximately 20% and measured yields were decreased by 15% in 2002 as a result of the increased  
33 O<sub>3</sub> exposure (Morgan et al., 2006, [079186](#)). To compare these results to chamber studies, Morgan et  
34 al. (2006, [079186](#)) calculated the expected yield loss from a linear relationship constructed from  
35 chamber data using 7-h seasonal averages (Ashmore, 2002, [672967](#)). They calculated an 8%  
36 expected yield loss from the 2002 O<sub>3</sub> exposure using that linear relationship. In another study, Gregg  
37 et al. (2003, [046996](#))(2006, [186961](#)) found similar O<sub>3</sub> effects on cottonwood sapling biomass growth

1 and physiology along an ambient O<sub>3</sub> gradient in the New York City area and a parallel OTC study.  
2 Additionally, Section 9.8.3 of this document presents comparisons of exposure-response in from  
3 OTC studies in trees and crops with results from more recent FACE experiments.

## 9.4. Mechanisms Governing Vegetation Response to Ozone

### 9.4.1. Introduction

4 This section focuses on the effects of O<sub>3</sub> stress on plants and their responses to that stress on  
5 the molecular, biochemical and physiological levels. First, the pathway of O<sub>3</sub> uptake into the leaf and  
6 the initial chemical reactions occurring in the substomatal cavity and apoplast will be described  
7 (Section 9.4.2). Once O<sub>3</sub> has entered the substomatal cavity and apoplast, it is thought that the cell  
8 must be able to sense the presence of O<sub>3</sub> or its breakdown products in order to initiate the rapid  
9 changes in gene expression that have been measured in O<sub>3</sub>-treated plants. While an “O<sub>3</sub> sensor” still  
10 remains elusive, much progress has been made in examining several different mechanisms that may  
11 contribute both to sensing the presence of O<sub>3</sub> and its breakdown products, and also transducing a  
12 signal to the nucleus to initiate changes in gene transcription, which will be described in Section  
13 9.4.3.1. The next section focuses on changes in gene expression in response to O<sub>3</sub> exposure, with  
14 particular emphasis on results from transcriptome and proteome analyses (Section 9.4.3.2).  
15 Subsequently, the role of phytohormones such as salicylic acid (SA), ethylene (ET), jasmonic acid  
16 (JA), and abscisic acid (ABA) and their interactions in both signal transduction and determining  
17 plant response to O<sub>3</sub> is discussed in Section 9.4.3.3. After O<sub>3</sub> uptake and sensing, plants can respond  
18 to the oxidative stress to minimize damage. These mechanisms of detoxification, with particular  
19 emphasis on antioxidant enzymes and metabolites, are reviewed in Section 9.4.4. The next section  
20 focuses on the effects of O<sub>3</sub> on primary and secondary metabolism in plants, looking at  
21 photosynthesis, respiration and several secondary metabolites, some of which may also act as  
22 antioxidants and protect the plant from oxidative stress (Section 9.4.5). The last section focuses on  
23 the mechanisms underlying changes in stomatal function (Section 9.4.6). For many of these topics,  
24 information from the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) has been summarized, as this  
25 information is still valid and supported by more recent findings. For other topics, such as genomics  
26 and proteomics, which have arisen due to the availability of new technologies, the information is  
27 based solely on new publications with no reference to the 2006 O<sub>3</sub> AQCD.

28 As Section 9.4 focuses on mechanisms underlying vegetation response to O<sub>3</sub>, the conditions  
29 that are used to study these mechanisms are often artificial and do not necessarily reflect conditions  
30 that a plant may be exposed to in an agricultural setting or natural ecosystem. The goal of many of  
31 these studies is to elicit a plant response to O<sub>3</sub> in a relatively short period of time and not always to  
32 simulate ambient O<sub>3</sub> exposures. Therefore, plants are often exposed to unrealistically high O<sub>3</sub>  
33 concentrations for several hours or days (acute exposure), and only in a few cases to ambient or

1 slightly elevated O<sub>3</sub> concentrations for longer time periods (chronic exposure). Additionally, the  
2 plant species utilized in these studies are often not agriculturally important or commonly found as  
3 part of natural ecosystems. Model organisms such as *Arabidopsis thaliana* are frequently used as  
4 they are easy to work with, and mutants or transgenic plants are easy to develop or have already been  
5 developed. Furthermore, the *Arabidopsis* genome has been sequenced, and much is known about the  
6 molecular basis of many biochemical and cellular processes.

7 Many of the studies described in this section focus on changes in the expression of genes in  
8 O<sub>3</sub>-treated plants. However, changes in gene expression (i.e., either up- or down-regulation of gene  
9 expression) do not always translate into changes in protein quantity and/or activity, as there are many  
10 levels of post-transcriptional and post-translational modifications which impact protein quantity and  
11 activity. Frequently, these studies do not evaluate whether the observed changes in gene expression  
12 lead to changes at the protein level and, therefore, it is not always clear how relevant the changes in  
13 gene expression are in determining plant response to O<sub>3</sub>.

14 The advent of new technologies, such as those employed in genomics and proteomics, has  
15 allowed for a more comprehensive analysis of the many molecular and biochemical mechanisms of  
16 plant response to O<sub>3</sub> and how all these responses interact with or affect each other to determine the  
17 ultimate response of plants to a stressor such as O<sub>3</sub>. While the studies of transcriptome changes are  
18 very valuable, further work needs to be done to evaluate whether the transcriptome changes result in  
19 concomitant changes in the proteome. A few recent studies have evaluated proteome changes in  
20 response to O<sub>3</sub>, and those results are also discussed in Section 9.4.3.2.

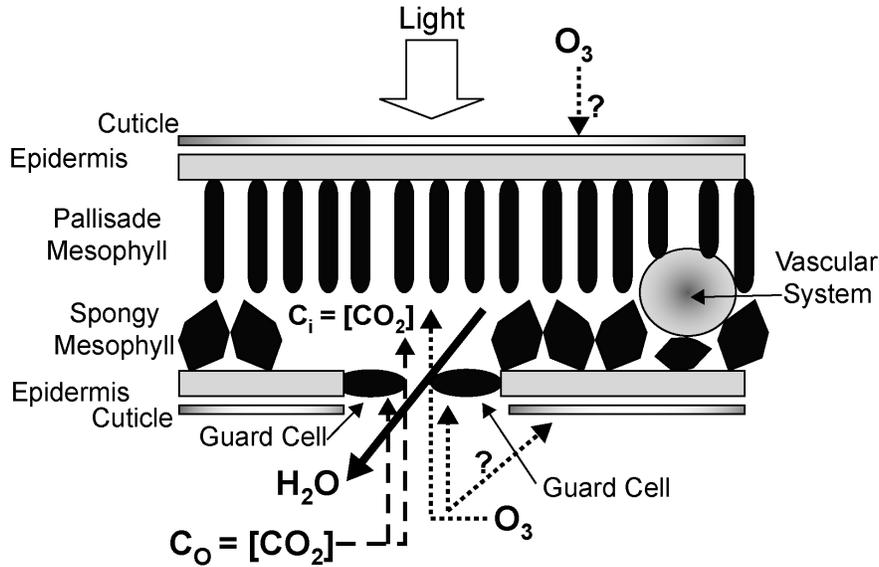
21 The most significant change in this section in relation to the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006,  
22 [088089](#)) is the increased emphasis on the understanding of molecular mechanisms underlying plant  
23 responses to O<sub>3</sub>, as a significant number of the newer studies that were evaluated for this section  
24 focus on changes in gene expression in plants exposed to elevated O<sub>3</sub>. Conclusions from the 2006 O<sub>3</sub>  
25 AQCD have been supported by these new studies, and the advent of new technologies has allowed  
26 for a more comprehensive understanding of the mechanisms governing plant response to O<sub>3</sub>.

27 In summary, the goal of many of these new studies reported on in this section was to increase  
28 knowledge of the mechanisms of plant response to O<sub>3</sub> by using artificial exposure conditions and  
29 model organisms. This information adds to the understanding of the basic biology of plant response  
30 to oxidative stress in the absence of any other potential stressors. The results of these studies are  
31 important and valid, even though they may not always directly translate into effects observed in  
32 other plants under more realistic exposure conditions. They represent one step in the process of  
33 comprehensively understanding plant responses to oxidative stress, which then need to be followed  
34 up with additional experiments using other plant species exposed to O<sub>3</sub> under more natural  
35 conditions.

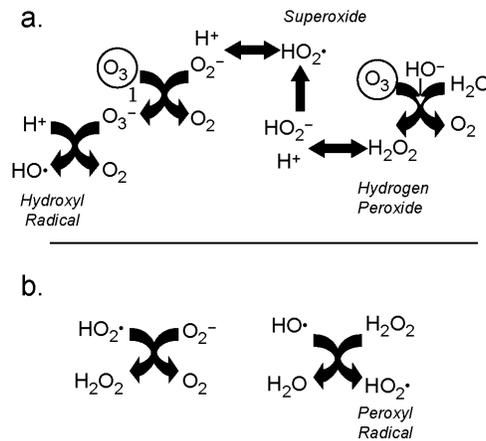
## 9.4.2. Ozone Uptake into the Leaf

1 AX9.2.3 of the 2006 O<sub>3</sub> AQCD clearly described the process by which O<sub>3</sub> enters plant leaves  
2 through open stomata (U.S. EPA, 2006, [088089](#)). This information continues to be valid and is only  
3 summarized here.

4 Ozone moves into the leaf interior by diffusing through open stomata, and environmental  
5 conditions which promote high rates of gas exchange will favor the uptake of the pollutant by the  
6 leaf. Factors that may limit uptake include boundary layer resistance and the size of the stomatal  
7 aperture (Figure 9-2) (U.S. EPA, 2006, [088089](#)). Once inside the substomatal cavity, O<sub>3</sub> is thought to  
8 rapidly react with the aqueous apoplast to form breakdown products known as reactive oxygen  
9 species (ROS), such as hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), superoxide (O<sub>2</sub><sup>-</sup>), hydroxyl radicals (HO<sup>•</sup>) and  
10 peroxy radicals (HO<sub>2</sub><sup>•</sup>) (Figure 9-3). Hydrogen peroxide is not only a toxic breakdown product of O<sub>3</sub>,  
11 but has been shown to function as a signaling molecule, which is activated in response to both biotic  
12 and abiotic stressors. The role of H<sub>2</sub>O<sub>2</sub> in signaling was described in detail in the 2006 O<sub>3</sub> AQCD  
13 (U.S. EPA, 2006, [088089](#)). Additional organic molecules present in the apoplast or cell wall, such as  
14 those containing double bonds or sulfhydryls that are sensitive to oxidation, could also be converted  
15 to oxygenated molecules after interacting with O<sub>3</sub> (Figure 9-4). These reactions are not only pH  
16 dependent but are also influenced by the presence of other molecules in the apoplast (U.S. EPA,  
17 2006, [088089](#)). The 2006 O<sub>3</sub> AQCD provided a comprehensive summary of what is known about the  
18 possible interactions of O<sub>3</sub> with other biomolecules (U.S. EPA, 2006, [088089](#)). It is in the apoplast  
19 that initial detoxification reactions by antioxidant metabolites and enzymes take place, and these  
20 initial reactions are critical to reduce concentrations of the oxidative breakdown products of O<sub>3</sub>;  
21 these reactions are described in more detail in Section 9.4.4 of this document.

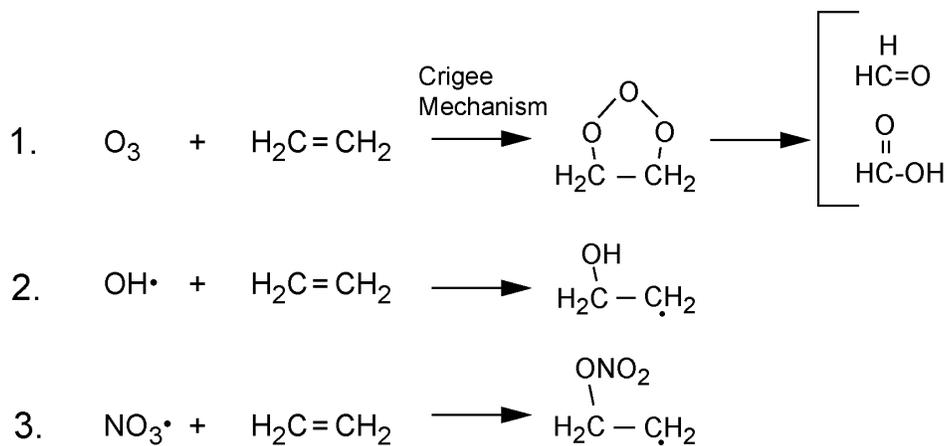


**Figure 9-2.** The microarchitecture of a dicot leaf. While details among species vary, the general overview remains the same. Light that drives photosynthesis generally falls upon the upper (adaxial) leaf surface. Carbon dioxide and ozone enter through the stomata on the lower (abaxial) leaf surface, while water vapor exits through the stomata (transpiration).

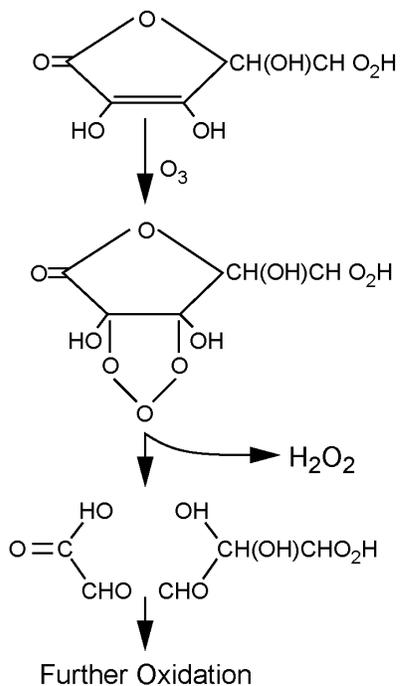


**Figure 9-3.** Possible reactions of ozone within water. (a) Ozone reacts at the double bonds to form carbonyl groups. (b) Under certain circumstances, peroxides are generated.

a.



b.



Source: Adapted from Mudd (1996, [052795](#))

**Figure 9-4. The Crigee mechanism of ozone attack of a double bond. (a) The typical Crigee mechanism is shown in which several reactions paths from the initial product is shown. (b) Typical reaction of ascorbic acid with ozone.**

### 9.4.3. Cellular to Systemic Responses

#### 9.4.3.1. Ozone Sensing 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 with the  
3 perception and integration of responses to the stress. Many of these studies have been conducted  
4 using *Arabidopsis* or tobacco plants, for which a variety of mutants are available and/or which can be  
5 easily genetically modified to generate either loss-of-function or over-expressing genotypes. Several  
6 comprehensive review articles provide an overview of what is known of O<sub>3</sub>-induced signal  
7 transduction processes and how they may help to explain differential sensitivity of plants to the  
8 pollutant (Kangasjarvi et al., 2005, [180341](#))(Ludwikow and Sadowski, 2008, [191426](#))(Baier et al.,  
9 2005, [186866](#)). Additionally, analysis of several studies of transcriptome changes has also allowed  
10 for the compilation of these data to determine an initial time-course for O<sub>3</sub>-induced activation of  
11 various signaling compounds (Kangasjarvi et al., 2005, [180341](#)).

12 A number of different mechanisms for plant sensing of O<sub>3</sub> have been proposed; however, there  
13 is still much that is not known about this process. Ozone and/or the ROS breakdown products could  
14 be sensed by an apoplastic receptor protein, which would either be directly modified by O<sub>3</sub> or ROS  
15 or which might sense O<sub>3</sub> or ROS modifications in other apoplastic components (Kangasjarvi et al.,  
16 2005, [180341](#))(Baier et al., 2005, [186866](#)). Some of the earliest events that occur in plant response to  
17 O<sub>3</sub> have been described in the guard cells of stomata. Reactive oxygen species were observed in the  
18 chloroplasts of guard cells in the O<sub>3</sub> tolerant Col-0 *Arabidopsis thaliana* ecotype plants within  
19 5 minutes of plant exposure to 350 ppb O<sub>3</sub> (Joo et al., 2005, [191307](#)). Reactive oxygen species from  
20 the breakdown of O<sub>3</sub> in the apoplast are believed to activate GTPases (G-proteins), which, in turn,  
21 activate several intracellular sources of ROS, including ROS derived from the chloroplasts.  
22 G-proteins are also believed to play a role in activating membrane-bound NADPH oxidases to  
23 produce ROS and, as a result, propagate the oxidative burst to neighboring cells (Joo et al., 2005,  
24 [191307](#)). Therefore, G-proteins are recognized as important molecules involved in plant responses to  
25 O<sub>3</sub> and may play a role in perceiving ROS from the breakdown of O<sub>3</sub> in the apoplast (Booker et al.,  
26 2004, [020581](#))(Kangasjarvi et al., 2005, [180341](#)).

27 A change in the redox state of the plant and the oxidation of sensitive molecules in itself may  
28 represent a means of perception and signaling of oxidative stress in plants. Disulfide-thiol  
29 conversions in proteins and the redox state of the glutathione pool are likely to be important  
30 components of redox sensing and signal transduction (Foyer and Noctor, 2005, [191555](#))(Foyer and  
31 Noctor, 2005, [631198](#)).

32 Calcium (Ca<sup>2+</sup>) has also been implicated in the transduction of signals to the nucleus in  
33 response to oxidative stress. The influx of Ca<sup>2+</sup> from the apoplast into the cell occurs early in plant  
34 response to O<sub>3</sub>, and it is thought to play a role in regulating the activity of protein kinases, which are  
35 discussed below (Hamel et al., 2005, [191214](#))(Baier et al., 2005, [186866](#)). Calcium channel blockers

1 inhibited O<sub>3</sub>-induced activation of protein kinases in tobacco suspension cells exposed to 500 ppb O<sub>3</sub>  
2 for 10 minutes, indicating that the opening of Ca<sup>2+</sup> channels is an important upstream signaling event  
3 or that the as yet unknown upstream process has a requirement for Ca<sup>2+</sup> (Samuel et al., 2000,  
4 [625706](#)).

5 Once ROS are generated by NADPH oxidase, signals are further transmitted to the nucleus to  
6 initiate changes in gene expression associated with plant defense responses. Integral to these signal  
7 cascades are mitogen-activated protein kinases (MAPK), which phosphorylate proteins and activate  
8 various cellular responses (Hamel et al., 2005, [191214](#)). Mitogen-activated protein kinases are  
9 induced in several different plant species in response to O<sub>3</sub> exposure, including tobacco (Samuel et  
10 al., 2005, [199316](#)), Arabidopsis (Ludwikow et al., 2004, [595939](#)), the shrub *Phillyrea latifolia*  
11 (Paolacci et al., 2007, [191422](#)) and poplar (Hamel et al., 2005, [191214](#)). In tobacco, the MAPK that  
12 is induced by plant exposure to 500 ppb O<sub>3</sub> is a salicylic acid (SA) induced protein kinase (SIPK),  
13 which was found to positively regulate O<sub>3</sub>-induced ethylene (ET) production and negatively regulate  
14 SA accumulation (Samuel et al., 2005, [199316](#)). In poplar suspension cells exposed to 500 ppb O<sub>3</sub>,  
15 O<sub>3</sub>-induced activation of two distinct MAP kinases was dependent on ROS formation and the  
16 activity of Ca<sup>2+</sup> channels (Hamel et al., 2005, [191214](#)). Arabidopsis mutants with suppressed activity  
17 of MAPK3 and MAPK6 (an ortholog of SIPK in tobacco) were more susceptible to exposure to  
18 500 ppb O<sub>3</sub>, as evidenced by tissue death resembling the hypersensitive response (Miles et al., 2005,  
19 [191648](#)). Similar results of increased susceptibility to 500 ppb O<sub>3</sub> were found in tobacco lines either  
20 over-expressing SIPK or with suppressed SIPK function. The authors concluded that these tobacco  
21 lines were unable to cope with increased oxidative stress due to the alteration of the normal  
22 O<sub>3</sub>-induced MAPK signal transduction process (Samuel and Ellis, 2002, [625703](#)). The Arabidopsis  
23 MAPK3 and MAPK6 are also differentially induced in Col-0 and the O<sub>3</sub>-sensitive Arabidopsis  
24 mutant radical induced cell death (*rcd1*) exposed to 250-300 ppb O<sub>3</sub> for 6 hours, indicating a role for  
25 these kinases in plant response to oxidative stress (Overmyer et al., 2005, [191596](#)). Similarly,  
26 components of the MAPK cascades were down-regulated in the sensitive Wassilewskija (Ws)  
27 Arabidopsis ecotype after exposure to 300 ppb O<sub>3</sub> for 6 h, suggesting that the sensitive ecotypes may  
28 not activate these defense responses (Mahalingam et al., 2006, [191221](#)). Expression of MAPK5 was  
29 also reduced in the Ws ecotype in response to chronic O<sub>3</sub> exposures; Ws Arabidopsis plants were  
30 exposed to O<sub>3</sub> concentrations 20-25% above ambient for 8-12 days in the SoyFACE site (Li et al.,  
31 2006, [191332](#)).

32 The cysteine-rich RLKs (CRKs), which are part of the receptor-like/Pelle kinase (RLKs)  
33 group, are thought to be involved in the regulation of defense responses and cell death in Arabidopsis  
34 (Wrzaczek et al., 2010, [644190](#)). CRKs were up-regulated by treatments that resulted in apoplastic  
35 ROS production, such as O<sub>3</sub> (250 ppb O<sub>3</sub> for 6 hours) and pathogen treatments, but either remained  
36 unchanged or were down-regulated by treatments resulting in ROS production in other cellular  
37 compartments, such as the mitochondria or chloroplasts. Although their function remains unclear, it  
38 has been postulated that a conserved cysteine motif in the CRKs could serve as a sensor for redox  
39 modifications in the cell resulting from ROS production (Wrzaczek et al., 2010, [644190](#)).

1 In conclusion, experimental evidence suggests that there may be several different mechanisms  
2 involved in sensing the presence of O<sub>3</sub> or its breakdown products. These mechanisms may vary by  
3 species or developmental stage of the plant or may co-exist and be activated by different exposure  
4 conditions. Calcium and protein kinases are likely involved in the transduction of the initial signal to  
5 the nucleus and other cellular compartments to initiate the changes in gene transcription discussed in  
6 Section 9.4.3.2.

### 9.4.3.2. Gene Expression Changes in Response to Ozone

7 The advent of DNA microarray technology has allowed for the study of gene expression in  
8 cells on a large scale. Rather than assessing changes in gene expression of individual genes, DNA  
9 microarrays facilitate the evaluation of entire transcriptomes, providing a comprehensive picture of  
10 alterations in gene expression. In addition, these studies have provided more insight into the complex  
11 interactions between molecules and signal pathways, which result in the regulation of plant  
12 responses to stresses such as O<sub>3</sub> (Ludwikow and Sadowski, 2008, [191426](#)). Transcriptome analysis  
13 of O<sub>3</sub>-treated plants has been performed in several species, including *Arabidopsis thaliana* (Tosti et  
14 al., 2006, [191425](#))(Heidenreich et al., 2005, [191260](#))(Li et al., 2006, [191332](#))(Mahalingam et al.,  
15 2005, [191693](#))(Tamaoki et al., 2003, [080053](#)), pepper (*Capsicum annuum*) (Lee and Yun, 2006,  
16 [191592](#)), clover (*Medicago truncatula*) (Puckette et al., 2008, [191698](#)), *Phillyrea latifolia* (Paolacci  
17 et al., 2007, [191422](#)), and European beech (*Fagus sylvatica*) (Olbrich et al., 2005, [191697](#))(Olbrich  
18 et al., 2009, [596020](#))(Olbrich et al., 2010, [625424](#)). In some cases, researchers compared  
19 transcriptomes of two or more cultivars, ecotypes or mutants that differed in their sensitivity to O<sub>3</sub>  
20 (Lee and Yun, 2006, [191592](#))(Tamaoki et al., 2003, [080053](#))(Li et al., 2006, [191332](#))(Puckette et al.,  
21 2008, [191698](#))(Rizzo et al., 2007, [191447](#)). Species, O<sub>3</sub> exposure conditions (concentration, duration  
22 of exposure) and sampling times varied significantly in these studies. However, functional  
23 classification of the genes that were either up- or down-regulated by plant exposure to O<sub>3</sub> exhibited  
24 common trends. Genes involved in plant defense, signaling and those associated with the synthesis  
25 of plant hormones and secondary metabolism were generally up-regulated, while those related to  
26 photosynthesis and general metabolism were generally down-regulated in O<sub>3</sub>-treated plants (Tosti et  
27 al., 2006, [191425](#))(Olbrich et al., 2005, [191697](#))(Tamaoki et al., 2003, [080053](#))(Lee and Yun, 2006,  
28 [191592](#))(Puckette et al., 2008, [191698](#))(Li et al., 2006, [191332](#)).

29 Analysis of the transcriptome has been used to evaluate differences in gene expression  
30 between O<sub>3</sub> sensitive and tolerant plants. In pepper, 67% of the 180 genes studied that were affected  
31 by O<sub>3</sub> were differentially regulated in the sensitive and tolerant cultivars. At both 0 hours and  
32 48 hours after a 3-day exposure at 150 ppb, O<sub>3</sub> responsive genes were either up- or down-regulated  
33 more markedly in the sensitive than in the tolerant cultivar (Lee and Yun, 2006, [191592](#)).  
34 Transcriptome analysis also revealed differences in timing and magnitude of changes in gene  
35 expression between sensitive and tolerant clovers. Acute exposure (300 ppb O<sub>3</sub> for 6 hours) led to the  
36 production of an oxidative burst in both clovers (Puckette et al., 2008, [191698](#)). However, the  
37 sensitive Jemalong cultivar exhibited a sustained ROS burst and a concomitant down-regulation of

1 defense response genes at 12 hours after the onset of exposure, while the tolerant JE 154 accession  
2 showed much more rapid and large-scale transcriptome changes than the Jemalong cultivar (Puckette  
3 et al., 2008, [191698](#)).

4 Arabidopsis ecotypes WS and Col-0 were exposed to  $1.2 \times$  ambient O<sub>3</sub> concentrations for  
5 8-12 days at the SoyFACE site (Li et al., 2006, [191332](#)). The sensitive WS ecotype showed a far  
6 greater number of changes in gene expression in response to this low-level O<sub>3</sub> exposure than the  
7 tolerant Col-0 ecotype. Exposure of the WS ecotype to 300 ppb O<sub>3</sub> for 6 hours showed a rapid  
8 induction of genes leading to cell death, such as proteases, and down-regulation or inactivation of  
9 cell signaling genes, demonstrating an ineffective defense response in this O<sub>3</sub> sensitive ecotype  
10 (Mahalingam et al., 2006, [191221](#)).

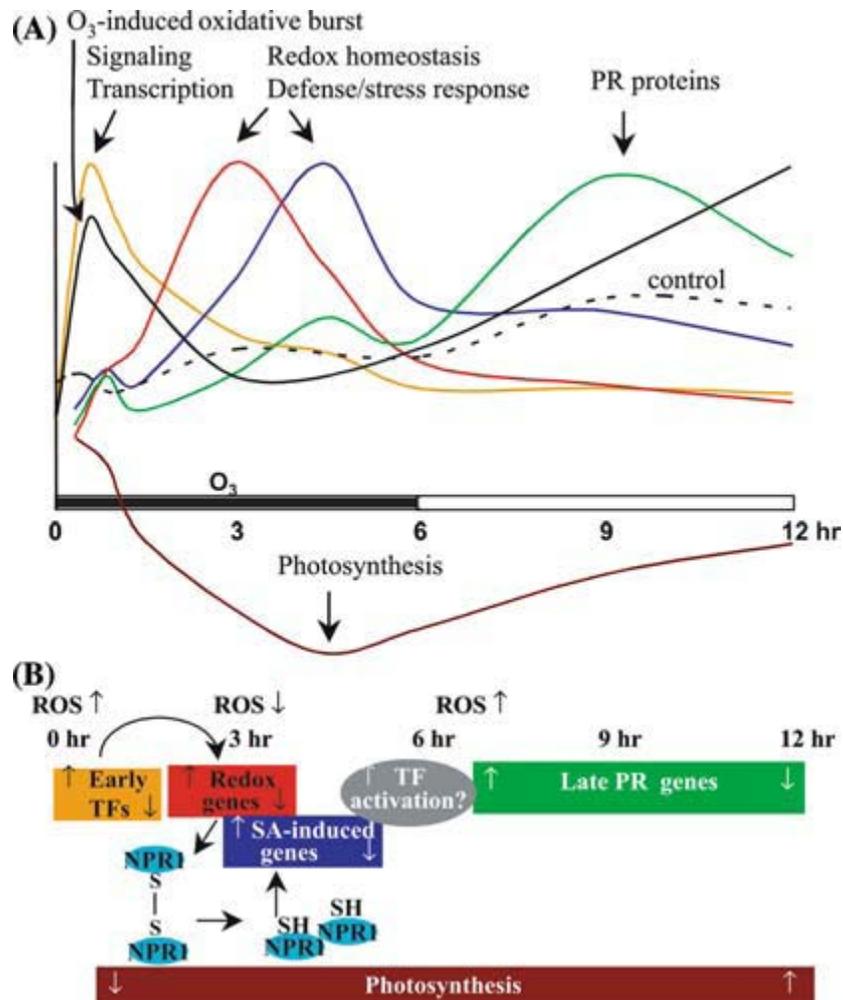
11 The temporal response of plants to O<sub>3</sub> exposure was evaluated in the Arabidopsis Col-0  
12 ecotype during a 6-h exposure at 350 ppb O<sub>3</sub> and for 6 hours after the exposure was completed.  
13 Results of this study, shown in Figure 9-5, indicate that genes associated with signal transduction and  
14 regulation of transcription were in the class of early up-regulated genes, while genes associated with  
15 redox homeostasis and defense/stress response were in the class of late up-regulated genes  
16 (Mahalingam et al., 2005, [191693](#)).

17 A few studies have been conducted to evaluate transcriptome changes in response to longer  
18 term chronic O<sub>3</sub> exposures in woody plant species. Longer term exposures resulted in the up-  
19 regulation of genes associated with secondary metabolites, including isoprenoids, polyamines and  
20 phenylpropanoids in 2-year-old seedlings of the Mediterranean shrub *Phillyrea latifolia* exposed to  
21 110 ppb O<sub>3</sub> for 90 days (Paolacci et al., 2007, [191422](#)). In 3-year-old European beech saplings  
22 exposed to O<sub>3</sub> for 20 months, with monthly average twice ambient O<sub>3</sub> concentrations ranging from  
23 11 to 80 ppb, O<sub>3</sub>-induced changes in gene transcription were similar to those observed for  
24 herbaceous species, including genes associated with plant stress response, primary metabolism,  
25 hormone synthesis, cell structure and premature senescence (Olbrich et al., 2009, [596020](#)). In  
26 another study, the magnitude of these transcriptional changes was far greater in beech saplings than  
27 in adult trees exposed to the same O<sub>3</sub> concentrations for the same time period, indicating that adult  
28 trees may be less responsive to this stressor than younger plants (Olbrich et al., 2010, [625424](#)).

29 These results have been substantiated by results from proteome analysis in rice, poplar, wheat,  
30 and soybean. Exposure of soybean to 120 ppb O<sub>3</sub> for 12 h/day for 3 days in growth chambers  
31 resulted in decreases in the quantity of proteins associated with photosynthesis, while proteins  
32 involved with antioxidant defense and C metabolism increased (Ahsan et al., 2010, [644189](#)). Young  
33 poplar plants exposed to 120 ppb O<sub>3</sub> in a growth chamber for 35 days also showed significant  
34 changes in proteins involved in C metabolism (Bohler et al., 2007, [199408](#)). Declines in enzymes  
35 associated with C fixation, the Calvin cycle and photosystem II were measured, while ascorbate  
36 peroxidase and enzymes associated with glucose catabolism increased in abundance. Two-week-old  
37 rice seedlings exposed to varying levels of O<sub>3</sub> (4, 40, 80, 120 ppb) in a growth chamber for 9 days  
38 showed reductions in expression of proteins associated with photosynthesis and energy metabolism,  
39 and increases in some antioxidant and defense related proteins (Feng et al., 2008, [191626](#)). A

1 subsequent study of O<sub>3</sub>-treated rice seedlings (exposed to 200 ppb O<sub>3</sub> for 24 h) focusing on the  
2 integration of transcriptomics and proteomics, supported and further enhanced these results (Cho et  
3 al., 2008, [603254](#)). The authors found that of the 22,000 genes analyzed from the rice genome, 1,535  
4 were differentially regulated by O<sub>3</sub>. Those genes were functionally categorized as transcription  
5 factors, MAPK cascades, those encoding for enzymes involved in the synthesis of JA, ET, shikimate,  
6 tryptophan and lignin, and those involved in glycolysis, citric acid cycle, oxidative respiration and  
7 photosynthesis. The authors determined that the proteome and metabolome analysis supported the  
8 results of the transcriptome changes described above (Cho et al., 2008, [603254](#)). This type of study,  
9 which ties together results from changes in gene expression, protein quantity and activity, and  
10 metabolite levels, provides the most complete picture of the molecular and biochemical changes  
11 occurring in plants exposed to a stressor such as O<sub>3</sub>. Sarkar et al. (2010, [657214](#)) compared two  
12 cultivars of wheat grown in OTCs at several O<sub>3</sub> concentrations, including filtered air, ambient O<sub>3</sub>  
13 (mean concentration 47 ppb), ambient + 10 ppb and ambient + 20 ppb for 5 h/day for 50 days.  
14 Declines in the rate of photosynthesis and stomatal conductance were related to decreases in proteins  
15 involved in C fixation and electron transport, and evidence of increased proteolysis of photosynthetic  
16 proteins such as the large subunit of ribulose-1,6-bisphosphate carboxylase/oxygenase (Rubisco).  
17 Enzymes that take part in energy metabolism, such as ATP synthesis, were also down-regulated,  
18 while defense/stress related proteins were induced with O<sub>3</sub> treatment. In comparing the two wheat  
19 cultivars, Sarkar et al. (2010, [657214](#)) found that while the qualitative changes in protein expression  
20 between the two cultivars was similar, the magnitude of these changes differed between the sensitive  
21 and tolerant wheat cultivars.

22 All of these studies describe common trends for changes in gene and protein expression which  
23 occur in a variety of plant species in response to O<sub>3</sub>. While genes associated with C assimilation and  
24 general metabolism are down-regulated, genes associated with signaling, catabolism, and defense are  
25 up-regulated. The magnitude of these changes in gene and protein expression appears to be related to  
26 plant sensitivity or tolerance to O<sub>3</sub>.



Source: Used with permission from Springer, Mahalingam et al. (2005, [191693](#)).

**Figure 9-5** Composite diagram of major themes in the temporal evolution of the genetic response to ozone stress. (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 up-regulated genes (yellow, peaks at 0.5-1 hours), and the 3 hours (blue), 4.5 hours (red) and 9-12 hours (green) late up-regulated genes and for the down-regulated genes coding for photosynthesis proteins (brown). (B) Diagrammatic representation of redox regulation of the oxidative stress response.

### 9.4.3.3. Role of Phytohormones in Plant Response to Ozone

1 Many studies of O<sub>3</sub> effects on plants have analyzed the importance of plant hormones such as  
 2 SA, ET and JA in determining plant response to O<sub>3</sub>; some of the roles of these hormones were  
 3 described in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). Transcriptome analysis and the use of a  
 4 variety of mutants have allowed for further elucidation of the complex interactions between SA, ET,  
 5 JA and the role of abscisic acid (ABA) in mediating plant response to O<sub>3</sub> (Ludwikow and Sadowski,  
 6 2008, [191426](#)). In addition to their roles in signaling pathways, phytohormones also appear to

1 regulate, and be regulated by, the MAPK signaling cascades described previously. Most evidence  
2 suggests that while ET and SA are needed to develop O<sub>3</sub>-induced leaf lesions, JA acts  
3 antagonistically to SA and ET to limit the lesions (Figure 9-6) (Kangasjarvi et al., 2005, [180341](#)).

4 The rapid production of ET in response to O<sub>3</sub> has been described in many plant species and  
5 has been further characterized through the use of a variety of mutants that either over-produce or are  
6 insensitive to ET. Production of stress ET in O<sub>3</sub>-treated plants, which is thought to be a wounding  
7 response, was found to be correlated to the degree of injury development in leaves (U.S. EPA, 2006,  
8 [088089](#)). More recent studies have supported these conclusions and have also focused on the  
9 interactions occurring between several oxidative-stress induced phytohormones. Yoshida et al.  
10 (2009, [191385](#)) determined that ET likely amplifies the oxidative signal generated by ROS, thereby  
11 promoting lesion formation. By analyzing the O<sub>3</sub>-induced transcriptome of several Arabidopsis  
12 mutants of the Col-0 ecotype, Tamaoki et al. (2003, [080053](#)) determined that at 12 hours after  
13 initiating the O<sub>3</sub> exposure (200 ppb for 12 hours), the ET and JA signaling pathways were the main  
14 pathways used to activate plant defense responses, with a lesser role for SA. The authors also  
15 demonstrated that low levels of ET production could stimulate the expression of defense genes,  
16 rather than promoting cell death when ET production is high. Tosti et al. (2006, [191425](#)) supported  
17 these findings by showing that O<sub>3</sub> not only activates the biosynthetic pathways of ET, JA and SA, but  
18 also increases the expression of genes related to the signal transduction pathways of these  
19 phytohormones in O<sub>3</sub>-treated Arabidopsis plants (300 ppb O<sub>3</sub> for 6 hours). Conversely, in the O<sub>3</sub>  
20 sensitive Ws ecotype, its sensitivity may, in part, be due to intrinsically high ET levels leading to SA  
21 accumulation, and the high ET and SA may act to repress JA-associated genes, which would serve to  
22 inhibit the spread of lesions (Mahalingam et al., 2006, [191221](#)). Ogawa et al. (2005, [191653](#)) found  
23 that an O<sub>3</sub>-induced increase in SA leads to the formation of leaf lesions in tobacco plants exposed to  
24 200 ppb O<sub>3</sub> for 6 hours. Furthermore, several genes encoding for enzymes in the biosynthetic  
25 pathway of SA were suppressed in transgenic tobacco plants with reduced levels of O<sub>3</sub>-induced ET  
26 production, suggesting that SA levels are controlled by ET in the presence of O<sub>3</sub>.

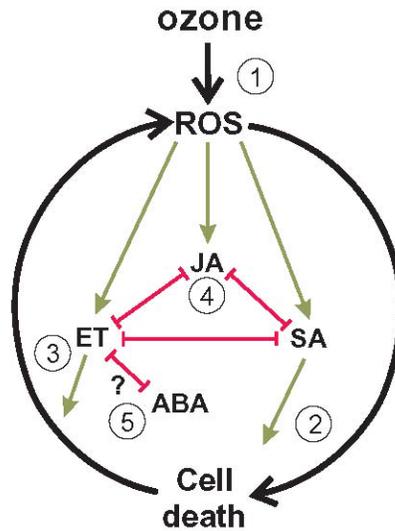
27 Exposure of the Arabidopsis mutant *rcd1* to acute doses of O<sub>3</sub> (250 ppb O<sub>3</sub> for 8 h/day for  
28 3 days) resulted in programmed cell death (PCD) and the formation of leaf lesions. Salicylic acid  
29 was required for the initiation of PCD in these mutants, and increased ET synthesis resulted in  
30 amplification of cell death, while JA was thought to contain the spreading of lesions (Overmyer et  
31 al., 2000, [036361](#)). In addition, the O<sub>3</sub>-treated *rcd1* mutants showed higher SA and JA accumulation  
32 as compared to the Col-0 ecotype. High SA levels could be involved in amplifying cell death in these  
33 mutants. Jasmonic acid, which is thought to accumulate as a direct result of cell death, may represent  
34 an autocatalytic mechanism for limiting cell death, by which the increased cell death observed in the  
35 *rcd1* mutant would determine the high amount of JA needed to contain lesion formation (Overmyer  
36 et al., 2005, [191596](#)). In cotton plants exposed to a range of O<sub>3</sub> concentrations (0-120 ppb) and  
37 methyl jasmonate (MeJA), Grantz et al. (2010, [625419](#)) determined that endogenous applications of  
38 MeJA did not protect plants from chronic O<sub>3</sub> exposure.

1           There are distinct patterns of gene expression when evaluating early and later O<sub>3</sub> responsive  
2 genes (Mahalingam et al., 2005, [191693](#)). While ET and JA pathways were stimulated rapidly after  
3 Arabidopsis Col-0 exposure to O<sub>3</sub>, at 48 hours postexposure, JA and ET synthesis in O<sub>3</sub>-treated  
4 Arabidopsis were reduced, while the synthesis of SA was stimulated (D'Haese et al., 2006, [191448](#)).

5           Abscisic acid has been investigated for its role in regulating stomatal aperture and also for its  
6 contribution to signaling pathways in the plant. The role of ABA and the interaction between ABA  
7 and H<sub>2</sub>O<sub>2</sub> in O<sub>3</sub>-induced stomatal closure was described in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006,  
8 [088089](#)). More recently, it was determined that synthesis of ABA was induced in O<sub>3</sub>-treated  
9 Arabidopsis plants (250-350 ppb O<sub>3</sub> for 6 hours), with a more pronounced induction in several O<sub>3</sub>  
10 sensitive rcd mutants as compared to the wildtype Col-0 (Overmyer et al., 2008, [191283](#)). Ludwikow  
11 et al. (2009, [199440](#)) used Arabidopsis ABI1td mutants, in which a key negative regulator of ABA  
12 action (abscisic acid insensitive1 protein phosphatase 2C) has been knocked out, to examine O<sub>3</sub>  
13 responsive genes in this mutant compared to the Arabidopsis Col-0. Results of this study indicate a  
14 role for ABI1 in negatively regulating the synthesis of both ABA and ET in O<sub>3</sub>-treated plants  
15 (350 ppb O<sub>3</sub> for 9 hours). Additionally, ABI1 may stimulate JA-related gene expression, providing  
16 evidence for an antagonistic interaction between ABA and JA signaling pathways (Ludwikow et al.,  
17 2009, [199440](#)).

18           Nitric oxide (NO) has also been shown to play a role in regulating O<sub>3</sub>-induced gene expression  
19 in plants. However, little is known to date about NO and its role in the complex interactions of  
20 molecules in response to O<sub>3</sub>. Exposure of tobacco to O<sub>3</sub> (150 ppb for 5 hours) stimulated NO and  
21 NO-dependent ET production, while NO production itself did not depend on the presence of ET  
22 (Ederli et al., 2006, [191479](#)). Analysis of O<sub>3</sub>-treated Arabidopsis indicated the possibility of a dual  
23 role for NO in the initiation of cell death and later lesion containment (Ahlfors et al., 2009, [191533](#)).

24           While much work remains to be done to better elucidate how plants sense O<sub>3</sub> and how signals  
25 are communicated to the nucleus to generate plant responses to oxidative stress, it is clear that the  
26 mechanism for O<sub>3</sub> sensing and signal transduction is very complex. Many of the phytohormones and  
27 other signaling molecules thought to be involved in these processes are interactive and depend upon  
28 a variety of other factors, which could be either internal or external to the plant. This results in a  
29 highly dynamic and complex system, capable of generating a variety of plant responses to oxidative  
30 stress.



Source: Used with permission from Blackwell Publishing Ltd., Kangasjarvi et al. (2005, [180341](#)).

**Figure 9-6. The oxidative cell death cycle.** ①Ozone-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.

#### 9.4.4. Detoxification

##### 9.4.4.1. Overview of Ozone-Induced Defense Mechanisms

1 Plants are exposed to an oxidizing environment on a continual basis, and many reactions that  
 2 are part of the basic metabolic processes, such as photosynthesis and respiration, generate ROS. As a  
 3 result, there is an extensive and complex mechanism in place to detoxify these oxidizing radicals,  
 4 including both enzymes and metabolites, which are located in several locations in the cell and also in  
 5 the apoplast of the cell. As O<sub>3</sub> enters the leaf through open stomata, the first point of contact of O<sub>3</sub>  
 6 with the plant is thought to be in the apoplast, where it breaks down to form oxidizing radicals such  
 7 as H<sub>2</sub>O<sub>2</sub>, O<sub>2</sub><sup>-</sup>, HO· and HO<sub>2</sub>. Another source of oxidizing radicals is an oxidative burst, generated by  
 8 a membrane-bound NADPH oxidase enzyme, which is thought to be part of the plant's defense  
 9 system against pathogens (Schraudner et al., 1998, [056358](#)). Antioxidant metabolites and enzymes  
 10 located in the apoplast are thought to form a first line of defense by detoxifying O<sub>3</sub> and/or the ROS  
 11 that are formed as breakdown products of O<sub>3</sub> (Section 9.4.2.). However, even with the presence of  
 12 several antioxidants, including ascorbate, the redox buffering capacity of the apoplast is far less than

1 that of the cytoplasm, as it lacks the regeneration systems necessary to retain a reduced pool of  
2 antioxidants (Foyer and Noctor, 2005, [631198](#)).

3 Redox homeostasis is regulated by the presence of a pool of antioxidants, which are typically  
4 found in a reduced state and detoxify ROS produced by oxidases or electron transport components.  
5 As ROS increase due to environmental stress such as O<sub>3</sub>, the antioxidant pool will no longer be able  
6 to maintain its reduced state (Foyer and Noctor, 2005, [631198](#)). As such, not only the quantity and  
7 types of antioxidant enzymes and metabolites present, but also the cellular ability to regenerate those  
8 antioxidants are important considerations in mechanisms of plant tolerance to oxidative stress  
9 (Dizengremel et al., 2008, [191587](#)). Molecules such as glutathione (GSH), thioredoxins and NADPH  
10 play very important roles in this regeneration process; additionally, alterations in C metabolism will  
11 be necessary to supply the needed reducing power for antioxidant regeneration (Dizengremel et al.,  
12 2008, [191587](#)). Increases in the activity of catabolic pathways allow the cell to generate more  
13 NADPH (Section 9.4.5).

#### 9.4.4.2. Role of Antioxidants in Plant Defense Responses

14 Ascorbate has been the focus of many different studies as an antioxidant metabolite that  
15 protects plants from exposure to O<sub>3</sub>. It is found in several cellular locations, including the  
16 chloroplast, the cytosol and the apoplast (Noctor and Foyer, 1998, [657213](#)). Ascorbate is synthesized  
17 in the cell and transported to the apoplast. Apoplastic ascorbate can be oxidized to dehydroascorbate  
18 (DHA) with exposure to O<sub>3</sub> and is then transported back to the cytoplasm. Here, DHA is reduced to  
19 ascorbate by the enzyme dehydroascorbate reductase (DHAR) and reduced GSH, which is part of the  
20 ascorbate-glutathione cycle (Noctor and Foyer, 1998, [657213](#)). Many studies have focused on  
21 evaluating whether ascorbate is the determining factor in differential sensitivity of plants to O<sub>3</sub>.  
22 Cheng et al. (2007, [191499](#)) exposed two soybean cultivars to elevated O<sub>3</sub> (77 ppb) and filtered air  
23 for 7 h/day for 6 days. The differences in sensitivity between the two cultivars could not be  
24 explained by differential O<sub>3</sub> uptake or by the fraction of reduced ascorbate present in the apoplast.  
25 However, total antioxidant capacity of the apoplast was twofold higher in the tolerant Essex cultivar  
26 as compared to the sensitive Forrest cultivar, indicating that there may be other compounds in the  
27 leaf apoplast that scavenge ROS. D'Haese et al. (2005, [191551](#)) exposed the NC-S (sensitive) and  
28 NC-R (resistant) clones of white clover (*Trifolium repens*) to 60 ppb O<sub>3</sub> for 7 h/day for 5 days in  
29 environmental chambers. Surprisingly, the NC-S clone had a higher constitutive concentration of  
30 apoplastic ascorbate with a higher redox status than the NC-R clone. However, the redox status of  
31 symplastic GSH was higher in NC-R, even though the concentration of GSH was not higher than in  
32 NC-S. In addition, total symplastic antioxidative capacity was not a determining factor in differential  
33 sensitivity between these two clones. Severino et al. (2007, [199293](#)) also examined the role of  
34 antioxidants in the differential sensitivity of the two white clover clones by growing them in the field  
35 for a growing season and then exposing them to elevated O<sub>3</sub> (100 ppb for 8 h/day for 10 days) in  
36 OTC at the end of the field season. The NC-R clone had greater quantities of total ascorbate and total  
37 antioxidants than the NC-S clone at the end of the experiment. While the second study indicates a

1 possible relationship between O<sub>3</sub> tolerance and ascorbate levels, the first study indicates that there  
2 are other factors besides ascorbate that determine plant tolerance to O<sub>3</sub>. In snap bean, plants of the O<sub>3</sub>  
3 tolerant Provider cultivar had greater total ascorbate and more ascorbate in the apoplast than the  
4 sensitive S156 cultivar after exposure to 71 ppb O<sub>3</sub> for 10 days in OTC (Burkey et al., 2003,  
5 [630251](#)). While most of the apoplastic ascorbate was in the oxidized form, the ratio of reduced  
6 ascorbate to total ascorbate was higher in Provider than S156, indicating that Provider is better able  
7 to maintain this ratio to maximize plant protection from oxidative stress.

8 While the quantities of antioxidant metabolites such as ascorbate are an important indicator of  
9 plant tolerance to O<sub>3</sub>, the ability of the plant to recycle oxidized ascorbate efficiently plays a large  
10 role in determining the plant's ability to deal with a sustained exposure to oxidative stress. Tobacco  
11 plants over-expressing DHAR were better protected from exposure to either chronic (100 ppb O<sub>3</sub>  
12 4 h/day for 30 days) or acute (200 ppb O<sub>3</sub> for 2 hours) conditions than control plants and those with  
13 reduced expression of DHAR. The DHAR over-expressing plants exhibited an increase in guard cell  
14 ascorbic acid, leading to a decrease in stomatal responsiveness to O<sub>3</sub> and an increase in stomatal  
15 conductance and O<sub>3</sub> uptake. Despite this, the presence of higher levels of ascorbic acid led to a lower  
16 oxidative load and a higher level of photosynthetic activity in the DHAR over-expressing plants  
17 (Chen and Gallie, 2005, [191465](#)). A subsequent study with tobacco plants over-expressing DHAR  
18 confirmed some of these results. Levels of ascorbic acid were higher in the transgenic tobacco  
19 plants, and they exhibited greater tolerance to O<sub>3</sub> exposure (200 ppb O<sub>3</sub>) as demonstrated by higher  
20 photosynthetic rates in the transgenic plants as compared to the control plants (Eltayeb et al., 2006,  
21 [191377](#)). Over-expression of monodehydroascorbate reductase (MDAR) in tobacco plants also  
22 showed enhanced stress tolerance in response to O<sub>3</sub> exposure (200 ppb O<sub>3</sub>), with higher rates of  
23 photosynthesis and higher levels of reduced ascorbic acid as compared to controls (Eltayeb et al.,  
24 2007, [191553](#)). Results of these studies show the importance of ascorbic acid as a detoxification  
25 mechanism, but more importantly emphasize that the recycling of oxidized ascorbate and  
26 maintenance of a reduced pool of ascorbate is critical in determining plant tolerance to oxidative  
27 stress.

28 The roles of other antioxidant metabolites and enzymes, including GSH, catalase (CAT), and  
29 superoxide dismutase (SOD), were comprehensively reviewed in the 2006 O<sub>3</sub> AQCD (U.S. EPA,  
30 2006, [088089](#)). Additional studies have supported the findings reported in that document. Superoxide  
31 dismutase (SOD) and peroxidase (POD) activities were measured in both the tolerant Bel B and  
32 sensitive Bel W3 tobacco cultivars exposed to ambient O<sub>3</sub> concentrations for 2 weeks 3 times  
33 throughout a growing season (Borowiak et al., 2009, [191247](#)). Tulip poplar (*Liriodendron tulipifera*)  
34 trees exposed to increasing O<sub>3</sub> concentrations (from 100 to 300 ppb O<sub>3</sub> during a 2-week period)  
35 showed increases in activities of SOD, ascorbate peroxidase (APX), glutathione reductase (GR),  
36 MDAR, DHAR, CAT and POD in the 2-week period, although individual enzyme activities  
37 increased at different times during the 2-week period (Ryang et al., 2009, [191267](#)).

38 Longer, chronic O<sub>3</sub> exposures in trees revealed some distinctive patterns of increases in SOD  
39 and APX activity that were measured in *Quercus mongolica* after 45 days of plant exposure to

1 80 ppb O<sub>3</sub>, which were followed by declines in the activities and quantities of these enzymes after  
2 75 days of exposure (Yan et al., 2010, [628514](#)). Similarly, activities of SOD, APX, DHAR, MDAR,  
3 and GR increased in *Gingko biloba* trees during the first 50 days of exposure to 80 ppb O<sub>3</sub>, followed  
4 by decreases in activity below control values after 50 days of exposure (He et al., 2006, [199430](#)).  
5 Soybean plants exposed to 70 or 100 ppb O<sub>3</sub> for 4 h/day over the course of a growing season showed  
6 elevated POD activity and a decrease in CAT activity at 40 and 60 days after germination (Singh et  
7 al., 2010, [386275](#)).

8 Antioxidant enzymes appear to increase in quantity in O<sub>3</sub>-treated plants as a defense  
9 mechanism against oxidative stress. However, it appears that plants cannot maintain these elevated  
10 levels of antioxidant enzymes for an extended period of time, likely due to the high metabolic costs  
11 involved. Therefore, plants exposed to chronic O<sub>3</sub> conditions may show more symptoms of exposure  
12 as defensive mechanisms are down-regulated over time.

### 9.4.5. Effects on Primary and Secondary Metabolism

#### 9.4.5.1. Light and Dark Reactions of Photosynthesis

13 Declines in the rate of photosynthesis and stomatal conductance in O<sub>3</sub>-treated plants have been  
14 documented for many different plant species (U.S. EPA, 2006, [088089](#))(Booker et al., 2009, [191569](#))  
15 (Wittig et al., 2007, [191695](#)). Much of the literature regarding O<sub>3</sub> effects on photosynthesis has  
16 focused on C assimilation; however, more recently, attention has also been focused on deleterious  
17 effects on the light reactions. Chlorophyll fluorescence provides a useful measure of changes to the  
18 photosynthetic process from exposure to oxidative stress. Decreases in the Fv/Fm ratio (a measure of  
19 the maximum efficiency of Photosystem II) in dark adapted leaves indicate a decline in the  
20 efficiency of the PSII photosystems and a concomitant increase in non-photochemical quenching  
21 (Guidi and Degl'Innocenti, 2008, [191571](#))(Scebba et al., 2006, [191219](#)). Changes in these parameters  
22 have been correlated to differential sensitivity of plants to the pollutant. In a study to evaluate the  
23 response of 4 maple species to O<sub>3</sub> (exposed to an 8-h avg of 51 ppb for ambient and 79 ppb for  
24 elevated treatment in OTC), the 2 species which were most sensitive based on visible injury and  
25 declines in CO<sub>2</sub> assimilation also showed the greatest decreases in Fv/Fm in symptomatic leaves. In  
26 asymptomatic leaves, CO<sub>2</sub> assimilation decreased significantly but there was no significant decline  
27 in Fv/Fm (Calatayud et al., 2007, [191411](#)). Degl'Innocenti et al. (2007, [191350](#)) measured  
28 significant decreases in Fv/Fm in young and symptomatic leaves of a resistant tomato genotype (line  
29 93.1033/1) in response to O<sub>3</sub> exposure (150 ppb O<sub>3</sub> for 3 hours in a growth chamber), but only minor  
30 decreases in asymptomatic leaves with no associated changes in net photosynthetic rate. In the O<sub>3</sub>  
31 sensitive tomato cultivar Cuor Di Bue, the Fv/Fm ratio did not change, while the photosynthetic rate  
32 declined significantly in asymptomatic leaves (Degl'Innocenti et al., 2007, [191350](#)). In two soybean  
33 cultivars, Fv/Fm also declined significantly with plant exposure to O<sub>3</sub> (Singh et al., 2009, [199427](#)). It

1 appears that in asymptomatic leaves, photoinhibition, as indicated by a decrease in Fv/Fm, is not the  
2 main reason for a decline in photosynthesis.

3 An evaluation of photosynthetic parameters of two white clover (*Trifolium repens* cv. Regal)  
4 clones that differ in their O<sub>3</sub> sensitivity revealed that O<sub>3</sub> (40-110 ppb O<sub>3</sub> for 7 h/day for 5 days)  
5 increased the coefficient of non-photochemical quenching (q<sub>NP</sub>) in both the resistant (NC-R) and  
6 sensitive (NC-S) clones, however q<sub>NP</sub> was significantly lower for the sensitive clone (Crous et al.,  
7 2006, [199321](#)). Sensitive Acer clones had a lower coefficient of non-photochemical quenching,  
8 while exposure to O<sub>3</sub> increased q<sub>NP</sub> in both sensitive and tolerant clones (Calatayud et al., 2007,  
9 [191411](#)). While exposure to O<sub>3</sub> also increased q<sub>NP</sub> in tomato, there were no differences in the  
10 coefficient of photochemical quenching between cultivars thought to be differentially sensitive to O<sub>3</sub>.  
11 (Degl'Innocenti et al., 2007, [191350](#)). Higher q<sub>NP</sub> as a result of exposure to O<sub>3</sub> indicates a reduction  
12 in the proportion of absorbed light energy being used to drive photochemistry. A lower coefficient of  
13 non-photochemical quenching in O<sub>3</sub> sensitive plants could indicate increased vulnerability to ROS  
14 generated during exposure to oxidative stress (Crous et al., 2006, [199321](#)).

15 Several measures of the light reactions of photosynthesis are sensitive to exposure to O<sub>3</sub>,  
16 however, photosynthetic C assimilation is generally considered to be more affected by pollutant  
17 exposure, resulting in an overall decline in photosynthesis (Heath, 2008, [195632](#))(Fiscus et al., 2005,  
18 [079155](#))(Guidi and Degl'Innocenti, 2008, [191571](#)). Loss of C assimilation capacity has been shown  
19 to result primarily from declines in the quantity of Rubisco (Calatayud et al., 2007, [191411](#))(Singh et  
20 al., 2009, [199427](#)). Experimental evidence suggests that both decreases in Rubisco synthesis and  
21 enhanced degradation of the protein contribute to the measured reduction in its quantity (U.S. EPA,  
22 2006, [088089](#)). Reduced C assimilation has been linked to reductions in biomass and yield (Keutgen  
23 et al., 2005, [191295](#))(He et al., 2007, [199789](#))(Novak et al., 2007, [194630](#))(Gregg et al., 2006,  
24 [186961](#)), (Wang et al., 2009, [199303](#)).

25 Most of the research on O<sub>3</sub> effects on photosynthesis has focused on C3 (Calvin cycle) plants  
26 because C4 (Hatch-Slack) plants have lower stomatal conductance and therefore assumed to be less  
27 sensitive to O<sub>3</sub> stress. However, a few studies have been conducted to evaluate the effects of O<sub>3</sub> on  
28 C4 photosynthesis. In older maize leaves, Leitao et al. (2007, [191456](#))(2007, [191263](#)) found that the  
29 activity, quantity and transcript levels of both Rubisco and phosphoenolpyruvate carboxylase (PEPc)  
30 decreased as a function of rising O<sub>3</sub> concentration. In younger maize leaves, the quantity, activity,  
31 and transcript levels of the carboxylases were either increased or unaffected in plants exposed to  
32 40 ppb O<sub>3</sub> for 7 h/day for 28-33 days, but decreased at 80 ppb (Leitao et al., 2007, [191263](#))(Leitao et  
33 al., 2007, [199379](#)).

#### 9.4.5.2. Respiration and Dark Respiration

34 While much research emphasis regarding O<sub>3</sub> effects on plants has focused on the negative  
35 impacts on C assimilation, other studies have measured impacts on catabolic pathways such as  
36 respiration and photorespiration. Generally, respiration has been found to increase in plants exposed  
37 to O<sub>3</sub>. Bean plants exposed to ambient (average 12-h mean 43 ppb) and twice ambient (average 12-h

1 mean 80 ppb) O<sub>3</sub> showed increases in respiration. When mathematically partitioned, the maintenance  
2 coefficient of respiration was significantly increased by O<sub>3</sub> exposure, while the growth coefficient of  
3 respiration was not affected (Amthor, 1988, [041870](#)). Loblolly pines were exposed to ambient (12-h  
4 daily mean was 45 ppb) and twice ambient (12 hours daily mean was 86 ppb) O<sub>3</sub> for 12 h/day for  
5 approximately seven months per year for 3 and 4 years. While photosynthetic activity declined with  
6 the age of the needles and increasing O<sub>3</sub> concentration, enzymes associated with respiration showed  
7 higher levels of activity with increasing O<sub>3</sub> concentration (Dizengremel et al., 1994, [187217](#)). In  
8 their review on the role of metabolic changes in plant redox status after O<sub>3</sub> exposure, Dizengremel et  
9 al. (2009, [199424](#)) summarized multiple studies in which several different tree species were exposed  
10 to O<sub>3</sub> concentrations ranging from ambient to 200 ppb O<sub>3</sub> for at least several weeks. In all cases, the  
11 activity of enzymes, including phosphofructokinase, pyruvate kinase and fumarase, which are part of  
12 several catabolic pathways, were increased in response to O<sub>3</sub> exposure.

13 Photorespiration is a light-stimulated process which consumes O<sub>2</sub> and releases CO<sub>2</sub>. While it  
14 has been regarded as a wasteful process, more recent evidence suggests that it may play a role in  
15 photoprotection during photosynthesis (Bagard et al., 2008, [191593](#)). The few studies that have been  
16 conducted on O<sub>3</sub> effects on photorespiration suggest that rates of photorespiration decline  
17 concomitantly with rates of photosynthesis. Soybean plants were exposed to ambient (daily averages  
18 43-58 ppb) and 1.5 ambient O<sub>3</sub> (daily averages 63-83 ppb) O<sub>3</sub> in OTCs for 12 h/day for 4 months.  
19 Rates of photosynthesis and photorespiration and photorespiratory enzyme activity declined only at  
20 the end of the growing season and did not appear to be very sensitive to O<sub>3</sub> exposure (Booker et al.,  
21 1997, [026425](#)). Young hybrid poplars exposed to 120 ppb O<sub>3</sub> for 13 h/day for 35 days in phytotron  
22 chambers showed that effects on photorespiration and photosynthesis were dependent upon the  
23 developmental stage of the leaf. While young leaves were not impacted, reductions in photosynthesis  
24 and photorespiration were measured in fully expanded leaves (Bagard et al., 2008, [191593](#)).

### 9.4.5.3. Secondary Metabolism

25 Transcriptome analysis of Arabidopsis plants has revealed modulation of several genes  
26 involved in plant secondary metabolism (Ludwikow and Sadowski, 2008, [191426](#)). Phenylalanine  
27 ammonia lyase (PAL) has been the focus of many studies involving plant responses to O<sub>3</sub> due to its  
28 importance in linking the phenylpropanoid pathway of plant secondary metabolism to primary  
29 metabolism in the form of the shikimate pathway. Genes encoding several enzymes of the  
30 phenylpropanoid pathway and lignin biosynthesis were up-regulated in transcriptome analysis of  
31 Arabidopsis plants (Col-0) exposed to 350 ppb O<sub>3</sub> for 6 hours, while 2 genes involved in flavonoid  
32 biosynthesis were down-regulated (Ludwikow et al., 2004, [595939](#)). Exposure of Arabidopsis  
33 (Col-0) to lower O<sub>3</sub> concentrations (150 ppb for 8 h/day for 2 days) resulted in the induction of 11  
34 transcripts involved in flavonoid synthesis. In their exposure of 2-year-old Mediterranean shrub  
35 *Phillyrea latifolia* to 110 ppb O<sub>3</sub> for 90 days, Paolacci et al. (2007, [191422](#)) identified four clones  
36 that were up-regulated and corresponded to genes involved in the synthesis of secondary  
37 metabolites, such as isoprenoids, polyamines and phenylpropanoids. Up-regulation of genes

1 involved in isoprene synthesis was also observed in *Medicago trunculata* exposed to 300 ppb O<sub>3</sub> for  
2 6 hours, while genes encoding enzymes of the flavonoid synthesis pathway were either up- or down-  
3 regulated (Puckette et al., 2008, [191698](#)). Exposure of red clover to 1.5 × ambient O<sub>3</sub> (average  
4 concentrations of 32.4 ppb) for up to 9 weeks in an open field exposure system resulted in increases  
5 in leaf total phenolic content. However, the types of phenolics that were increased in response to O<sub>3</sub>  
6 exposure differed depending upon the developmental stage of the plant. While almost all of the 31  
7 different phenolic compounds measured increased in quantity initially during the exposure, after  
8 3 weeks the quantity of isoflavones decreased while other phenolics increased (Saviranta et al., 2010,  
9 [102177](#)). Exposure of beech saplings to ambient and 2 × ambient O<sub>3</sub> concentrations over 2 growing  
10 seasons resulted in the induction of several enzymes which contribute to lignin formation, while  
11 enzymes involved in flavonoid biosynthesis were down-regulated (Olbrich et al., 2009, [596020](#)).  
12 Exposure of tobacco Bel W3 to 160 ppb O<sub>3</sub> for 5 hours showed up-regulation of almost all genes  
13 encoding for enzymes which are part of the prechorismate pathway (Janzik et al., 2005, [191581](#)).  
14 Isoprenoids can serve as antioxidant compounds in plants exposed to oxidative stress (Paolacci et al.,  
15 2007, [191422](#)).

16 The prechorismate pathway is the pathway leading to the formation of chorismate, a precursor  
17 to the formation of the aromatic amino acids tryptophan, tyrosine and phenylalanine. These amino  
18 acids are precursors for the formation of many secondary aromatic compounds, and, therefore, the  
19 prechorismate pathway represents a branch-point in the regulation of metabolites into either primary  
20 or secondary metabolism (Janzik et al., 2005, [191581](#)). Exposure of the O<sub>3</sub> sensitive Bel W3 tobacco  
21 cultivar at 160 ppb for 5 hours showed an increase in transcript levels of most of the genes encoding  
22 enzymes of the prechorismate pathway. However, shikimate kinase (SK) did not show any change in  
23 transcript levels and only one of three isoforms of DAHPS (3-deoxy-D-arabino-heptulosonate-7-  
24 phosphate synthase), the first enzyme in this pathway, was induced by O<sub>3</sub> exposure (Janzik et al.,  
25 2005, [191581](#)). Differential induction of DAHPS isoforms was also observed in European beech  
26 after 40 days of exposure to 150-190 ppb O<sub>3</sub>. At this time point in the beech experiment, transcript  
27 levels of shikimate pathway enzymes, including SK, were generally strongly induced after an only  
28 weak initial induction after the first 40 days of exposure. Both soluble and cell-wall bound phenolic  
29 metabolites showed only minimal increases in response to O<sub>3</sub> for the duration of the exposure period  
30 (Alonso et al., 2007, [199289](#)). Total leaf phenolics decreased with leaf age in *Populus nigra* exposed  
31 to 80 ppb O<sub>3</sub> for 12 h/day for 14 days. Ozone increased the concentration of total leaf phenolics in  
32 newly expanded leaves, with the most significant increases occurring in compounds such as  
33 quercetin glycoside, which has a high antioxidant capacity (Fares et al., 2010, [628522](#)). While O<sub>3</sub>  
34 exposure induced the activity of several phenylpropanoid pathway enzymes, the degree of induction  
35 differed in the two poplar clones exposed to 60 ppb for 5 h/day for 15 days. In the tolerant I-214  
36 clone, PAL activity increased ninefold in O<sub>3</sub>-treated plants as compared to controls, while there was  
37 no significant difference in PAL activity in the sensitive Eridano clone (Di Baccio et al., 2008,  
38 [199850](#)).

1 Polyamines such as putrescine, spermidine and spermine play a variety of roles in plants and  
2 have been implicated in plant defense responses to both abiotic and biotic stresses. They exist in both  
3 a free form and conjugated to hydroxycinnamic acids. Investigations on the role of polyamines have  
4 found that levels of putrescine increase in response to oxidative stress. This increase stems largely  
5 from the increase in the activity of arginine decarboxylase (ADC), a key enzyme in the synthesis of  
6 putrescine (Groppa and Benavides, 2008, [191616](#)). Langebartels et al. (1991, [043506](#)) described  
7 differences in putrescine accumulation in O<sub>3</sub>-treated tobacco plants exposed to several O<sub>3</sub>  
8 concentrations, ranging from 0-400 ppb for 5-7 hours. A large and rapid increase in putrescine  
9 occurred in the tolerant Bel B cultivar and only a small increase in the Bel W3 cultivar, which  
10 occurred only after the formation of necrotic leaf lesions. Van Buuren et al. (2002, [631199](#)) further  
11 examined the role of polyamines in these two tobacco cultivars during an acute (130 ppb O<sub>3</sub> for 7 h  
12 in a growth chamber) exposure. They found that while free putrescine accumulated in undamaged  
13 tissue of both cultivars, conjugated putrescine predominantly accumulated in tissues undergoing cell  
14 death after plant exposure to O<sub>3</sub> (van Buuren et al., 2002, [631199](#)). The authors suggest that while  
15 free putrescine may not play a role in conferring tolerance in the Bel B cultivar, conjugated  
16 putrescine may play a role in O<sub>3</sub>-induced programmed cell death in Bel W3 plants.

17 Isoprene is emitted by some plant species and represents the predominant biogenic source of  
18 hydrocarbon emissions in the atmosphere (Guenther et al., 2006, [607080](#)). In the atmosphere, the  
19 oxidation of isoprene by hydroxyl radicals can enhance O<sub>3</sub> formation in the presence of NO<sub>x</sub>,  
20 thereby impacting the O<sub>3</sub> concentration that plants are exposed to. While isoprene emission varies  
21 widely between species, and it has been proposed to stabilize membranes and provide those plant  
22 species that produce it with a mechanism of thermotolerance (Sharkey et al., 2008, [191492](#)). It has  
23 also been suggested that isoprene may act as an antioxidant compound to scavenge O<sub>3</sub> (Loreto and  
24 Velikova, 2001, [657212](#)). Recent studies using a variety of plant species have shown conflicting  
25 results in trying to understand the effects of O<sub>3</sub> on isoprene emission. Acute doses of O<sub>3</sub> (300 ppb for  
26 3 h) stimulated isoprene emissions in detached leaves of *Phragmites australis* (Velikova et al., 2005,  
27 [199410](#)). Similarly, isoprene emissions were stimulated in *Populus nigra* after exposure to 100 ppb  
28 O<sub>3</sub> for 5 days continuously (Fares et al., 2008, [191683](#)). Isoprene emission in attached leaves of  
29 *Populus alba*, which were exposed to 150 ppb O<sub>3</sub> for 11 h/day for 30 days inside cuvettes, was  
30 inhibited, while isoprene emission and transcript levels of isoprene synthase mRNA were increased  
31 in the leaves exposed to ambient O<sub>3</sub> (40 ppb), which were located above the leaves enclosed in the  
32 exposure cuvettes (Fares et al., 2006, [191455](#)). Exposure of 2 genotypes of hybrid poplar to 120 ppb  
33 O<sub>3</sub> for 6 h/day for 8 days resulted in a significant reduction in isoprene emission in the O<sub>3</sub>-sensitive  
34 but not the tolerant genotype (Ryan et al., 2009, [191299](#)). Similarly, O<sub>3</sub> treatment (80 ppb 12 h/day  
35 for 14 days) of *Populus nigra* showed that isoprene emission was reduced in the treated plants  
36 relative to the control plants (Fares et al., 2010, [628522](#)). Based on results of this and other studies,  
37 Fares et al. (2010, [628522](#)) concluded that the isoprenoid pathway may be induced in plants exposed  
38 to acute O<sub>3</sub> doses, while at lower doses isoprene emission may be inhibited. Vickers et al. (2009,  
39 [191497](#)) developed transgenic tobacco plants with the isoprene synthase gene from *Populus alba* and

1 exposed them to 120 ppb O<sub>3</sub> for 6 h/day for 2 days. They determined that the wildtype plants showed  
2 significantly more O<sub>3</sub> damage, including the development of leaf lesions and a decline in  
3 photosynthetic rates, than the transgenic, isoprene-emitting plants. Transgenic plants also  
4 accumulated less H<sub>2</sub>O<sub>2</sub> and had lower levels of lipid peroxidation following exposure to O<sub>3</sub> than the  
5 wildtype plants (Vickers et al., 2009, [191497](#)). These results indicate that isoprene may have a  
6 protective role for plants exposed to oxidative stress.

#### 9.4.6. Changes in Stomatal Function

7 There has been some debate as to whether O<sub>3</sub>-induced reductions in photosynthesis result from  
8 changes in stomatal conductance or direct effects on C assimilation. A review of the literature  
9 suggests there may be species-specific differences in how O<sub>3</sub> affects photosynthesis through either  
10 direct or indirect mechanisms. Recent studies utilizing a new simultaneous O<sub>3</sub> exposure/gas  
11 exchange device have demonstrated that exposure of Arabidopsis plants to 150 ppb O<sub>3</sub> resulted in a  
12 60-70% decline in stomatal conductance within 9-12 minutes of beginning the exposure. Twenty to  
13 thirty minutes later, stomatal conductance had returned to its initial value, even with continuing  
14 exposure to O<sub>3</sub>, indicating a rapid direct effect of O<sub>3</sub> on stomatal function (Kollist et al., 2007,  
15 [191539](#)). The contributions of stomatal versus non-stomatal factors in reducing net photosynthesis  
16 have been investigated in a number of tree species. *Ginkgo biloba* trees exposed to ambient O<sub>3</sub>  
17 (40 ppb) and elevated O<sub>3</sub> (80 ppb) in OTCs for 90 days were investigated over the course of seven  
18 months. Initially, stomatal limitation restricted C assimilation and, along with higher rates dark  
19 respiration, served to protect against oxidative stress. However, as the season progressed, declines in  
20 C assimilation resulted from direct oxidative damage to the photosynthetic apparatus (He et al.,  
21 2007, [199789](#)). In other studies focusing on O<sub>3</sub> effects on adult trees, including *Quercus mongolica*  
22 (exposed to 80 ppb O<sub>3</sub> for 9 h/day for 4 months in OTCs) and *Fagus sylvatica* (exposed to the  
23 2 × ambient concentrations, with a mean of 57 ppb O<sub>3</sub> for 6 months in a free air fumigation system)  
24 O<sub>3</sub>-induced reductions in stomatal conductance were accompanied by a decrease in intercellular CO<sub>2</sub>  
25 concentration, indicating that stomatal closure did not result from high internal CO<sub>2</sub> but rather from a  
26 direct effect of O<sub>3</sub> on the guard cells (Wang et al., 2009, [199303](#))(Kitao et al., 2009, [191331](#)). In a  
27 related study, *Populus deltoides* grown in rural areas showed a greater O<sub>3</sub>-induced decline in biomass  
28 allocation than those grown in urban areas (with means in O<sub>3</sub> concentrations ranging from 20-36 ppb  
29 in urban areas and 36-47 ppb in rural areas). This decline in biomass was determined to result from  
30 significantly higher rates of stomatal conductance in the rural trees, indicating a loss of stomatal  
31 control (Gregg et al., 2006, [186961](#)). An investigation of the differences between O<sub>3</sub>-sensitive and  
32 insensitive cutleaf coneflower (*Rudbeckia laciniata* var. *digitata*) revealed differences in stomatal  
33 behavior (Grulke et al., 2007, [186963](#)). Cutleaf coneflower plants growing in Great Smoky Mountain  
34 National Park (exposed to mean O<sub>3</sub> concentration of 42 ppb from mid-May through mid-September)  
35 showed variable stomatal responses to changes in environmental conditions, such as light and vapor  
36 pressure deficit. It is likely that the O<sub>3</sub>-sensitive coneflower plants have a set of traits, such as a

1 sluggish stomatal response to changes in light intensity, which predispose them to being more  
2 sensitive to O<sub>3</sub> exposure (Grulke et al., 2007, [186963](#))(Paoletti and Grulke, 2010, [628561](#)).

3 Feng et al. (2007, [191641](#)) determined that reductions in net photosynthesis in O<sub>3</sub>-exposed  
4 winter wheat (*Triticum aestivum*), exposed to a mean concentration of either 52 or 105 ppb O<sub>3</sub> for  
5 6 weeks in OTCs, likely occurred as a result of both stomatal and non-stomatal factors. Other studies  
6 suggest that O<sub>3</sub> impacts net photosynthesis only through non-stomatal factors. A direct effect of O<sub>3</sub>  
7 on C fixation as described above would lead to a buildup of internal CO<sub>2</sub>, resulting in a reductions in  
8 stomatal conductance through stomatal closure. In *Acer opalus*, a significant reduction in light-  
9 saturated photosynthesis was accompanied by significant increases in internal CO<sub>2</sub> concentration and  
10 decreases in water use efficiency without appreciable changes in stomatal conductance (Calatayud et  
11 al., 2007, [191411](#)). A similar decrease in photosynthesis, accompanied by an increase in internal CO<sub>2</sub>  
12 concentration, was measured in soybean plants exposed to O<sub>3</sub>. Singh et al. (2009, [199427](#)) attributed  
13 the declines in photosynthesis to direct damage to the photosynthetic apparatus rather than to  
14 stomatal limitations.

## 9.5. Nature of Effects on Vegetation

### 9.5.1. Introduction

15 Ambient O<sub>3</sub> concentrations have long been known to cause visible symptoms, decreases in  
16 photosynthetic rates, decreases in growth, and decreases in the yield of plants (U.S. EPA, 1978,  
17 [040586](#))(U.S. EPA, 1986, [017607](#))(U.S. EPA, 1996, [080828](#))(U.S. EPA, 2006, [088089](#)). Numerous  
18 studies have related O<sub>3</sub> exposure to plant responses, with most effort focused on the yield of crops  
19 and the growth of tree seedlings. Most experiments exposed individual plants grown in pots or soil  
20 under controlled conditions to known concentrations of O<sub>3</sub> for a segment of daylight hours for some  
21 portion of the plant's life span (Section 9.3). This section focuses on the responses of plants to  
22 seasonal or multi-year exposures to known amounts of O<sub>3</sub>. Quantitative responses include changes in  
23 growth and biomass allocation, changes in reproduction, onset of visible foliar injury, and changes in  
24 leaf gas exchange. The response of a plant species or variety to O<sub>3</sub> exposure depends upon many  
25 factors, including biochemical and physiological status (Section 9.4), genetic characteristics, and  
26 previous and current exposure to other stressors (Section 9.5.4.). Because of the available  
27 information, most of this section focuses on the response of individual plants, especially tree  
28 seedlings and crops, with limited discussion of mixtures of herbaceous species. Responses at the  
29 ecosystem scale are discussed in Section 9.6.

30 This section will focus mainly on studies published since the release of the 2006 O<sub>3</sub> AQCD  
31 (U.S. EPA, 2006, [088089](#)). However, because much O<sub>3</sub> research was conducted prior to the 2006 O<sub>3</sub>  
32 AQCD, the present discussion of vegetation response to O<sub>3</sub> exposure is largely based on the  
33 conclusions of the 1978, 1986, 1996, and 2006 O<sub>3</sub> AQCDs (U.S. EPA, 1978, [040586](#))(U.S. EPA,  
34 1986, [017607](#))(U.S. EPA, 1996, [080828](#))(U.S. EPA, 2006, [088089](#)).

## 9.5.2. Effects on Woody and Herbaceous Vegetation

### 9.5.2.1. Growth and Biomass Allocation

1 The previous O<sub>3</sub> AQCDs concluded that there is strong evidence that exposure to O<sub>3</sub> decreases  
2 growth in numerous plant species. Studies published since the last review support those conclusions  
3 and are summarized below.

4 In a recently published meta-analysis, Wittig et al. (2009, [191631](#)) quantitatively compiled  
5 peer reviewed studies from the past 40 years on the effect of current and future O<sub>3</sub> exposures on the  
6 physiology and growth of forest species. Wittig et al. (2009, [191631](#)) reported that current ambient  
7 O<sub>3</sub> concentrations (~40 ppb) significantly decreased annual total biomass growth (7%) across 263  
8 studies. However, this effect could be greater (11 to 17%) in areas that have higher O<sub>3</sub> concentrations  
9 and as background O<sub>3</sub> increases in the future (Wittig et al., 2009, [191631](#)). This meta-analysis  
10 demonstrates the coherence of O<sub>3</sub> effects across numerous studies and species using a variety of  
11 experimental techniques.

12 In two companion papers, McLaughlin et al. (2007, [090348](#))(2007, [090347](#)) investigated the  
13 effects of ambient O<sub>3</sub> on tree growth and hydrology at forest sites in the southern Appalachian  
14 Mountains. The authors reported the cumulative effects of ambient levels of O<sub>3</sub> decreased seasonal  
15 stem growth by 30-50% for most trees species in a high O<sub>3</sub> year in comparison to a low O<sub>3</sub> year  
16 (McLaughlin et al., 2007, [090348](#)). The authors also report that high ambient O<sub>3</sub> concentrations can  
17 disrupt whole-tree water use and in turn reduce late-season streamflow (McLaughlin et al., 2007,  
18 [090347](#)); see Section 9.6.3 for more on water cycling.

19 Since the 2006 O<sub>3</sub> AQCD, several new studies based on the Aspen FACE “free air” O<sub>3</sub> and  
20 CO<sub>2</sub> exposure experiment in a forest in Wisconsin were published (Darbah et al., 2007,  
21 [093288](#))(Darbah et al., 2008, [196890](#))(King et al., 2005, [191701](#))(Kubiske et al., 2006,  
22 [093284](#))(Kubiske et al., 2007, [191336](#))(Riikonen et al., 2008, [191258](#)). King et al. (2005, [191701](#))  
23 found that O<sub>3</sub> fumigation over the first seven years of stand development reduced total biomass  
24 relative to the control by 23, 13, and 14% in the aspen, aspen-birch, and aspen-maple communities,  
25 respectively. Over the same time period, Kubiske et al. (2006, [093284](#)) observed that elevated O<sub>3</sub>  
26 decreased tree heights, diameters, and main stem volumes in the aspen community by 11, 16, and  
27 20%, respectively. In addition, Kubiske et al. (2007, [191336](#)) reported that elevated O<sub>3</sub> may change  
28 the intra- and inter-species competition. For example, O<sub>3</sub> treatments increased the rate of conversion  
29 from a mixed aspen-birch community to a birch dominated community. In another study at this site,  
30 Percy et al. (2007, [093287](#)) suggested that negative growth effects were seen below the previous 8-h  
31 O<sub>3</sub> standard level of 0.084 ppm, but the informativeness of the study was diminished by severe  
32 methodological problems.

33 Several studies at the Aspen FACE site also considered other growth-related effects of elevated  
34 O<sub>3</sub>. Darbah et al. (2007, [093288](#))(2008, [196890](#)) reported that O<sub>3</sub> treatments decreased paper birch  
35 seed weight and seed germination and that this would likely lead to a negative impact of

1 regeneration for that species. Riikonen et al. (2008, [191258](#)) found that elevated O<sub>3</sub> decreased the  
2 amount of starch in birch buds by 16%, and reduced aspen bud size, which may have been related to  
3 the observed delay in spring leaf development. The results suggest that elevated O<sub>3</sub> concentrations  
4 have the potential to alter C metabolism of overwintering buds, which may have carry-over effects in  
5 the subsequent growing season (Riikonen et al., 2008, [191258](#)).

6 Effects on growth of understory vegetation were also investigated at Aspen FACE. Bandeff et  
7 al. (2006, [191733](#)) found that the effects of elevated CO<sub>2</sub> and O<sub>3</sub> on understory species composition,  
8 total and individual species biomass, N content, and <sup>15</sup>N recovery were a result of overstory  
9 community responses to those treatments; however, there were no apparent direct treatment effects  
10 due to high variability of the data. Total understory biomass increased with increasing light and was  
11 greatest under the open canopy of the aspen/maple community, as well as the more open canopy of  
12 the elevated O<sub>3</sub> treatments (Bandeff et al., 2006, [191733](#)). Similarly, data from a study by Awmack et  
13 al. (2007, [191415](#)) suggest that elevated CO<sub>2</sub> and O<sub>3</sub> may have indirect growth effects on red  
14 (*Trifolium pratense*) and white (*Trifolium repens*) clover in the understory via overstory community  
15 effects; however, no direct effects of elevated O<sub>3</sub> were observed.

16 Overall, the studies at the Aspen FACE experiment are consistent with many of the OTC  
17 studies that were the foundation of previous O<sub>3</sub> NAAQS reviews. These results strengthen our  
18 understanding of O<sub>3</sub> 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 endpoint for an assessment of the risk of O<sub>3</sub>  
21 exposure can be defined as yield or growth, e.g., production of grain. For plants grown in mixtures  
22 such as hayfields, and natural or semi-natural grasslands (including native nonagricultural species),  
23 endpoints other than production of biomass may be important. Such endpoints include biodiversity  
24 or species composition, and effects may result from competitive interactions among plants in mixed-  
25 species communities. Most of the available data on non-crop herbaceous species are for grasslands  
26 with many of the recent studies conducted in Europe. See Section 9.6.5 for a review of the recent  
27 literature on O<sub>3</sub> effects on competition and biodiversity in grasslands.

## Root Growth

28 Although O<sub>3</sub> does not penetrate soil, it could alter root development by decreasing  
29 C assimilation via photosynthesis (Andersen, 2003, [041673](#)). The response of root development to  
30 O<sub>3</sub> exposure depends on available photosynthate and could vary over time. Many biotic and abiotic  
31 factors, such as community dynamics and drought stress, have been found to affect root production  
32 under elevated O<sub>3</sub>. An earlier study at the AspenFACE experiment found that elevated O<sub>3</sub> reduced  
33 coarse root and fine roots biomass in young stands of paper birch and trembling aspen (King et al.,  
34 2001, [041751](#)). However, this reduction disappeared several years later. Ozone significantly  
35 increased fine-root (<1.0 mm) in the aspen community (Pregitzer et al., 2008, [191677](#)). This increase  
36 in fine root production was due to changes in community composition, such as better survival of the  
37 O<sub>3</sub>-tolerant aspen genotype, birch, and maple, rather than changes in C allocation at the individual

1 tree level (Pregitzer et al., 2008, [191677](#))(Zak et al., 2007, [191239](#)). In an adult European  
2 beech/Norway spruce forest in Germany, drought was found to nullify the O<sub>3</sub>-driven stimulation of  
3 fine root growth. Ozone stimulated fine-root production of beech during the humid year, but had no  
4 significant impact on fine root production in the dry year (Nikolova et al., 2010, [626810](#))(Matyssek  
5 et al., 2010, [628553](#)).

6 Using a non-destructive method, Vollsnes et al. (2010, [625576](#)) studied the in vivo root  
7 development of subterranean clover (*Trifolium subterraneum*) before, during and after short-term O<sub>3</sub>  
8 exposure. It was found that O<sub>3</sub> reduced root tip formation, root elongation, the total root length, and  
9 the ratios between below- and above-ground growth within one week after exposure. Those effects  
10 persisted for up to three weeks; however, biomass and biomass ratios were not significantly altered  
11 at the harvest five weeks after exposure.

12 Ozone has been shown to have negative (Jones et al., 2010, [567354](#)), non-significant (Phillips  
13 et al., 2009, [199802](#))(Andersen et al., 2010, [628559](#)) and positive effects (Pregitzer et al., 2008,  
14 [191677](#))(Grebenc and Kraigher, 2007, [191265](#)) on root biomass and root: shoot ratio. While the  
15 findings of individual studies were mixed, several recent meta-analyses have generally indicated that  
16 O<sub>3</sub> reduced C allocated to roots. In one meta-analysis, Grantz et al. (2006, [191545](#)) estimated the  
17 effect of O<sub>3</sub> on the root:shoot allometric coefficient (k), the ratio between the relative growth rate of  
18 the root and shoot. The results showed that O<sub>3</sub> reduced k by 5.6%, and the largest decline was  
19 observed in slow-growing plants. In another meta-analysis including 263 publications, Wittig et al.  
20 (2009, [191631](#)) found that current O<sub>3</sub> exposure had no significant impacts on root biomass and  
21 root:shoot ratio when compared to pre-industrial O<sub>3</sub> exposure. However, if O<sub>3</sub> concentrations rose to  
22 81-101 ppb (projected O<sub>3</sub> levels in 2100), both root biomass and root:shoot ratio were found to  
23 significantly decrease. Gymnosperms and angiosperms differed in their responses, with  
24 gymnosperms being less sensitive to elevated O<sub>3</sub>. In two other meta-analyses, Wang et al. (2010,  
25 [387478](#)) found elevated O<sub>3</sub> reduced biomass allocation to roots by 8.3% at ambient CO<sub>2</sub> and 6.0% at  
26 elevated CO<sub>2</sub>, and Morgan et al. (2003, [055527](#)) found O<sub>3</sub> reduced root dry weight of soybean.

### 9.5.2.2. Reproduction

27 Studies during recent decades have demonstrated O<sub>3</sub> effects on different stages of plant  
28 reproduction. The impacts of O<sub>3</sub> on reproductive development, as reviewed by Black et al. (2000,  
29 [036322](#)), can occur by influencing (1) age at which flowering occurs, particularly in long-lived trees  
30 that often have long juvenile periods of early growth without flower and seed production; (2) flower  
31 bud initiation and development; (3) pollen germination and pollen tube growth; and (4) seed, fruit, or  
32 cone yields and seed quality (Table 9-2) (U.S. EPA, 2006, [088089](#)).

33 Several recent studies since the 2006 O<sub>3</sub> AQCD further demonstrate the effects of O<sub>3</sub> on  
34 reproductive processes in herbaceous and woody plant species. Rämö et al. (2007, [191441](#)) exposed  
35 several meadow species to elevated O<sub>3</sub> (40-50 ppb) and CO<sub>2</sub> (+100 ppm), both individually and  
36 combined, over three growing seasons in ground-planted mesocosms, using OTCs. Elevated O<sub>3</sub>

1 delayed flowering of *Campanula rotundifolia* and *Vicia cracca*. Ozone also reduced the overall  
2 number of produced flowers and decreased fresh weight of individual *Fragaria vesca* berries.

3 Black et al. (2007, [191558](#)) exposed *Brassica campestris* to 70 ppb for two days during late  
4 vegetative growth or ten days during most of the vegetative phase. The two-day exposure had no  
5 effect on growth or reproductive characteristics, while the 10 day exposure reduced vegetative  
6 growth and reproductive site number on the terminal raceme, emphasizing the importance of  
7 exposure duration and timing. Mature seed number and weight per pod were unaffected due to  
8 reduced seed abortion, suggesting that, although O<sub>3</sub> affected reproductive processes, indeterminate  
9 species such as *B. campestris* possess enough compensatory flexibility to avoid reduced seed  
10 production (Black et al., 2007, [191558](#)).

11 In the determinate species, *Plantago major*, Black et al. (2010, [625575](#)) found that O<sub>3</sub> can  
12 have direct effects on reproductive development in populations of differing sensitivity. Only the first  
13 flowering spike was exposed to 120 ppb O<sub>3</sub> for 7 hours per day on 9 successive days (corresponding  
14 to flower development) while the leaves and second spike were exposed to charcoal-filtered air.  
15 Exposure of the first spike to O<sub>3</sub> affected seed number per capsule on both spikes even though spike  
16 two was not exposed. The combined seed weight of spikes one and two was increased by 19% in the  
17 two resistant populations, suggesting an overcompensation for injury; whereas, a decrease of 21%  
18 was observed in the most sensitive population (Black et al., 2010, [625575](#)).

19 A study by Darbah et al. (2007, [093288](#))(2008, [196890](#)) of paper birch (*Betula papyrifera*)  
20 trees at the Aspen FACE site in Rhinelander, WI investigated the effects of elevated O<sub>3</sub> and/or CO<sub>2</sub>  
21 on reproductive fitness. Elevated O<sub>3</sub> increased flowering, but decreased seed weight and germination  
22 success rate of seeds from the exposed trees. These results suggest that O<sub>3</sub> can dramatically affect  
23 flowering, seed production, and seed quality of paper birch, ultimately affecting its reproductive  
24 fitness (Darbah et al., 2007, [093288](#))(Darbah et al., 2008, [196890](#)).

**Table 9-2. Ozone effects on plant reproductive processes (derived from Table AX9-22 of the 2006 ozone AQCD)**

Species	Condition Measures	References
Apocynun androsaemifolium	Flowering time	Bergweiler and Manning (1999, <a href="#">036321</a> )
Buddleia davidii	Flowering time	Findley et al. (1997, <a href="#">036337</a> )
Rubus cuneifolius	Pollen germination	Chappelka (2002, <a href="#">052946</a> )
Plantago major	Pollen tube elongation	Stewart (1998, <a href="#">094233</a> )
Fragaria x ananassa	Fruit yield	Drogoudi and Ashmore (2001, <a href="#">052959</a> ); Drogoudi and Ashmore (2000, <a href="#">042517</a> )
Plantago major	Seed yield	Lyons and Barnes (1998, <a href="#">036354</a> ); Pearson et al. (1996, <a href="#">053074</a> ); Reiling and Davison (1992, <a href="#">043591</a> ); Whitfield et al. (1997, <a href="#">036397</a> )
Understory herbs	Seed yield	Harward and Treshow (1975, <a href="#">038366</a> )

Source: Adapted from 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#))

### 9.5.2.3. Visible Foliar Injury

1 Visible foliar injury resulting from exposure to O<sub>3</sub> has been well characterized and  
2 documented over several decades on many tree, shrub, herbaceous, and crop species (U.S. EPA,  
3 2006, [088089](#))(U.S. EPA, 1996, [080827](#))(U.S. EPA, 1984, [029711](#))(U.S. EPA, 1978, [040586](#)).  
4 Visible foliar injury symptoms are considered diagnostic as they have been verified experimentally  
5 in exposure-response studies, using exposure methodologies such as CSTRs, OTCs, and free-air  
6 fumigation (see Section 9.3 for more detail on exposure methodologies). Several pictorial atlases and  
7 guides have been published, providing details on diagnosis and identification of O<sub>3</sub>-induced visible  
8 foliar injury on many plant species throughout North America (Penn State, 1987, [626971](#))(Flagler,  
9 1998, [025525](#)) and Europe (Sánchez et al., 2001, [626980](#))(Sánchez et al., 2001, [626980](#))(Innes et al.,  
10 2001, [048954](#)). Typical visible injury symptoms on broad-leaved plants include: stippling, flecking,  
11 surface bleaching, bifacial necrosis, pigmentation (e.g., bronzing), chlorosis, and/or premature  
12 senescence. Typical visible injury symptoms for conifers include: chlorotic banding, tip burn,  
13 flecking, chlorotic mottling, and/or premature senescence of needles. Although common patterns of  
14 injury develop within a species, these foliar lesions can vary considerably between and within  
15 taxonomic groups. Furthermore, the degree and extent of visible foliar injury development varies  
16 from year to year and site to site (Chappelka et al., 2007, [093290](#))(Orendovici-Best et al., 2008,  
17 [196940](#))(Smith et al., 2003, [044183](#)), even among co-members of a population exposed to similar O<sub>3</sub>  
18 levels, due to the influence of co-occurring environmental and genetic factors. Nevertheless,  
19 Chappelka et al. (2007, [093290](#)) reported that the average incidence of O<sub>3</sub>-induced foliar injury was  
20 73% on milkweed in the Great Smokey Mountain National Park in the years 1992-1996.

21 Although the majority of O<sub>3</sub>-induced visible foliar injury occurrence has been observed on  
22 seedlings and small plants, many studies have reported visible injury of mature coniferous trees,  
23 primarily in the western U.S. (Arbaugh et al., 1998, [040297](#)) and to mature deciduous trees in eastern  
24 North America (Chappelka et al., 1999, [041860](#); Chappelka et al., 1999, [052952](#); Hildebrand et al.,

1 1996, [042670](#); Schaub et al., 2005, [191608](#); Somers et al., 1998, [044010](#); Vollenweider et al., 2003,  
2 [051157](#)).

3 It is important to note that visible foliar injury occurs only when sensitive plants are exposed  
4 to elevated O<sub>3</sub> concentrations in a predisposing environment. A major confounding factor for O<sub>3</sub>-  
5 induced visible foliar injury is the amount of soil moisture available to a plant during the year that  
6 the visible foliar injury is being assessed. This is because lack of soil moisture generally decreases  
7 stomatal conductance of plants and, therefore, limits the amount of O<sub>3</sub> entering the leaf that can  
8 cause injury (Grulke et al., 2003, [042637](#))(Matyssek et al., 2006, [191481](#))(Panek, 2004,  
9 [079202](#))(Panek and Goldstein, 2001, [030190](#))(Temple et al., 1992, [043349](#))(Temple et al., 1988,  
10 [043237](#)). Consequently, many studies have shown that dry periods in local areas tend to decrease the  
11 incidence and severity of O<sub>3</sub>-induced visible foliar injury; therefore, the incidence of visible foliar  
12 injury is not always higher in years and areas with higher O<sub>3</sub>, especially with co-occurring drought  
13 (Smith et al., 2003, [044183](#)). Other factors such as leaf age influence the severity of symptom  
14 expression with older leaves showing greater injury severity (Zhang et al., 2010, [628555](#)).

15 Although visible injury is a valuable indicator of the presence of phytotoxic concentrations of  
16 O<sub>3</sub> in ambient air, it is not always a reliable indicator of other negative effects on vegetation. The  
17 significance of O<sub>3</sub> injury at the leaf and whole plant levels depends on how much of the total leaf  
18 area of the plant has been affected, as well as the plant's age, size, developmental stage, and degree  
19 of functional redundancy among the existing leaf area. Previous O<sub>3</sub> AQCDs have noted the difficulty  
20 in relating visible foliar injury symptoms to other vegetation effects such as individual plant growth,  
21 stand growth, or ecosystem characteristics (U.S. EPA, 2006, [088089](#))(U.S. EPA, 1996,  
22 [080827](#))(U.S. EPA, 1996, [080827](#)). As a result, it is not presently possible to determine, with  
23 consistency across species and environments, what degree of injury at the leaf level has significance  
24 to the vigor of the whole plant. However, in some cases, visible foliar symptoms have been  
25 correlated with decreased vegetative growth (Benoit et al., 1982, [039778](#); Karnosky et al., 1996,  
26 [036347](#); Peterson et al., 1987, [042148](#); Somers et al., 1998, [044010](#)) and with impaired reproductive  
27 function (Black et al., 2000, [036322](#); Chappelka, 2002, [052946](#)). Conversely, the lack of visible  
28 injury does not always indicate a lack of phytotoxic concentrations of O<sub>3</sub> or a lack of non-visible O<sub>3</sub>  
29 effects (Gregg et al., 2003, [046996](#); Gregg et al., 2006, [186961](#)).

## **Biomonitoring**

30 The use of biological indicators to detect phytotoxic levels of O<sub>3</sub> is a longstanding and  
31 effective methodology (Chappelka and Samuelson, 1998, [093687](#); Manning and Krupa, 1992,  
32 [044155](#)). A plant bioindicator can be defined as a vascular or nonvascular plant exhibiting a typical  
33 and verifiable response when exposed to a plant stress such as an air pollutant (Manning, 2003,  
34 [053773](#)). To be considered a good indicator species, plants must (1) exhibit a distinct, verified  
35 response; (2) have few or no confounding disease or pest problems; and (3) exhibit genetic stability  
36 (U.S. EPA, 2006, [088089](#)). Such sensitive plants can be used to detect the presence of a specific air  
37 pollutant such as O<sub>3</sub> in the ambient air at a specific location or region and, as a result of the

1 magnitude of their response, provide unique information regarding specific ambient air quality.  
2 Bioindicators can be either introduced sentinels, such as the widely used tobacco (*Nicotiana*  
3 *tabacum*) variety Bel W3 (Calatayud et al., 2007, [191568](#); Gombert et al., 2006, [089309](#); Heggestad,  
4 1991, [042533](#); Kostka-Rick and Hahn, 2005, [199428](#); Laffray et al., 2007, [191384](#); Nali et al., 2007,  
5 [191478](#)) or detectors, which are sensitive native plant species (e.g., tall milkweed [*Asclepias*  
6 *exaltata*]; Chappelka et al., 2007, [093290](#); Souza et al., 2006, [191658](#)). The approach is especially  
7 useful in areas where O<sub>3</sub> monitors are not operated (Manning, 2003, [053773](#)). For example, in  
8 remote wilderness areas where instrument monitoring is generally not available, the use of  
9 bioindicator surveys in conjunction with the use of passive samplers (Krupa et al., 2001, [040430](#))  
10 may be a useful methodology (Manning, 2003, [053773](#)). However, the method requires expertise or  
11 training in recognizing those signs and symptoms uniquely attributable to exposure to O<sub>3</sub> as well as  
12 in their quantitative assessment.

13 Since the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), new sensitive plant species have been  
14 identified from field surveys and verified in controlled exposure studies (Kline et al., 2008, [191591](#);  
15 Kline et al., 2009, [196918](#)). Several multiple-year field surveys have also been conducted at National  
16 Wildlife Refuges in Maine, Michigan, New Jersey, and South Carolina (Davis, 2007, [093291](#); Davis,  
17 2007, [093292](#); Davis, 2009, [199287](#); Davis and Orendovici, 2006, [093293](#)).

18 The USDA Forest Service through the Forest Health Monitoring Program (FHM) (1990 -  
19 2001) and currently the Forest Inventory and Analysis (FIA) Program has been collecting data  
20 regarding the incidence and severity of visible foliar injury on a variety of O<sub>3</sub> sensitive plant species  
21 throughout the U.S. (Coulston et al., 2003, [041871](#))(Smith et al., 2003, [044183](#)). The plots where  
22 these data are taken are known as biosites. These biosites are located throughout the country and  
23 analysis of visible foliar injury within these sites follows a set of established protocols. For more  
24 details, see <http://www.nrs.fs.fed.us/fia/topics/ozone/> (USDA, 2011, [677550](#)). The network has  
25 provided evidence of O<sub>3</sub> concentrations high enough to induce visible symptoms on sensitive  
26 vegetation. From repeated observations and measurements made over a number of years, specific  
27 patterns of areas experiencing visible O<sub>3</sub> injury symptoms can be identified. Coulston et al. (2003,  
28 [041871](#)) used information gathered over a 6-year period (1994-1999) from the network to identify  
29 several species that were sensitive to O<sub>3</sub> over a regional scale including sweetgum (*Liquidambar*  
30 *styraciflua*), loblolly pine (*Pinus taeda*), and black cherry (*Prunus serotina*). In a study of the west  
31 coast of the U.S, Campbell et al. (2007, [602360](#)) reported O<sub>3</sub> injury in 25-37% of biosites in  
32 California forested ecosystems from 2000-2005.

33 A study by Kohut (2007, [093289](#)) assessed the risk of O<sub>3</sub>-induced visible foliar injury on  
34 bioindicator plants (NPS, 2006, [677536](#)) in 244 national parks in support of the National Park  
35 Service's Vital Signs Monitoring Network (NPS, 2007, [677537](#)). The risk assessment was based on a  
36 simple model relating response to the interaction of the plant, the level of O<sub>3</sub> exposure, and the  
37 exposure environment. Kohut (2007, [093289](#)) concluded that the risk of visible foliar injury was  
38 high in 65 parks (27%), moderate in 46 parks (19%), and low in 131 parks (54%). Some of the well-  
39 known parks with a high risk of O<sub>3</sub>-induced visible foliar injury include Gettysburg, Valley Forge,

1 Delaware Water Gap, Cape Cod, Fire Island, Antietam, Harpers Ferry, Manassas, Wolf Trap Farm  
2 Park, Mammoth Cave, Shiloh, Sleeping Bear Dunes, Great Smoky Mountains, Joshua Tree, Sequoia  
3 and Kings Canyon, and Yosemite.

#### 9.5.2.4. Leaf Gas Exchange

4 In general, there is strong experimental evidence over several decades of research that  
5 exposure to O<sub>3</sub> reduces photosynthesis and alters stomatal conductance in a wide variety of plant  
6 species (Wittig et al., 2007, [191695](#)) and these effects have been discussed in detail in previous O<sub>3</sub>  
7 AQCDs (U.S. EPA, 2006, [088089](#))(U.S. EPA, 1996, [080827](#)). Recent studies related to these effects  
8 are discussed in several sections within this document; therefore, this section refers to those sections  
9 for a more in depth discussion.

10 Ozone effects on photosynthesis were presented Section 9.4.5.1, with a focus on recent studies  
11 on the effects of O<sub>3</sub> on light reactions. Changes in stomatal function in response to O<sub>3</sub> exposure were  
12 discussed in Section 9.4.6. In addition, the implications of changes in stomatal control for water  
13 cycling are discussed in Section 9.6.3. Leaf gas exchange as it relates to effects based air quality  
14 exposure indices and dose modeling is discussed throughout Section 9.7.

#### 9.5.3. Agricultural Crops

15 The detrimental effect of O<sub>3</sub> on crop production has been recognized since the 1960's and a  
16 large body of research has stemmed from that recognition. Previous O<sub>3</sub> AQCDs have extensively  
17 reviewed this body of literature (U.S. EPA, 2006, [088089](#)). Table 9-3 summarizes recent  
18 experimental studies of O<sub>3</sub> effects on agricultural crops, exclusive of growth and yield. Growth and  
19 yield results are summarized in Table 9-16.

20 Ozone diffuses into the leaf apoplast via the stomata where it is rapidly converted into other  
21 ROS that signal a diverse metabolic response (Kangasjarvi et al., 2005, [180341](#))(Long and Naidu,  
22 2002, [038179](#)). The mechanism of O<sub>3</sub> sensing and cellular response is detailed in Section 9.4.3.1.  
23 Ozone stress has been characterized as either acute or chronic, depending on the O<sub>3</sub> concentration  
24 and the exposure duration (Fiscus et al., 2005, [079155](#)). While the actual concentration and duration  
25 threshold for O<sub>3</sub> damage varies from species to species and sometimes even among genotypes of the  
26 same species (Ariyaphanphitak et al., 2005, [191349](#))(Biswas et al., 2008, [191428](#))(Dalstein and Vas,  
27 2005, [191570](#))(Guidi et al., 2009, [199825](#))(Keutgen et al., 2005, [191295](#))(Sawada and Kohno, 2009,  
28 [199426](#)), it is commonly accepted that acute damage results from a very high concentration of O<sub>3</sub>  
29 (>150 ppb) over a short period of time, and chronic O<sub>3</sub> damage results from a lower concentration of  
30 exposure over a longer period of time. In general, acute O<sub>3</sub> damage has been well characterized and  
31 mimics the biochemical defense response of plants to pathogen attack (Kangasjarvi et al., 2005,  
32 [180341](#))(Overmyer et al., 2003, [053537](#)). In contrast, the mechanism leading to chronic O<sub>3</sub> damage  
33 is less well-characterized but hallmark physiological symptoms include: decreased photosynthetic  
34 productivity, decreased Rubisco activity and chlorophyll content, lower stomatal conductance, leaf

1 chlorosis, accelerated senescence and a general decrease in green leaf area and plant productivity  
2 (Ashmore et al., 2006, [191557](#)). Despite the knowledge gap pertaining to the mechanism of O<sub>3</sub>  
3 damage, a number of comprehensive reviews and meta-analyses have recently been published  
4 discussing both the current understanding of the quantitative effects of O<sub>3</sub> concentration on a variety  
5 of crop species and the potential focus areas for biotechnological improvement to a future growing  
6 environment that will include higher O<sub>3</sub> concentrations (Ainsworth, 2008, [191646](#))(Booker et al.,  
7 2009, [191569](#))(Feng et al., 2008, [191453](#))(Grantz et al., 2006, [191545](#))(Hayes et al., 2007,  
8 [196911](#))(Mills et al., 2007, [180221](#))(Morgan et al., 2003, [055527](#))(Van Dingenen et al., 2009,  
9 [199765](#)). Since the 2006 O<sub>3</sub> AQCD, exposure-response indices for a variety of crops have been  
10 suggested (Mills et al., 2007, [180221](#)) and many reports have investigated the effects of O<sub>3</sub>  
11 concentration on seed or fruit quality to extend the knowledge base beyond yield quantity. This  
12 section will outline the key findings from these papers as well as highlight some of the recent  
13 research addressing the endpoints such as yields and crop quality.

14 Genetic variability is not the only factor that determines the crop response to O<sub>3</sub>-damage.  
15 Ozone concentrations throughout a growing-season is not homogeneous and other environmental  
16 conditions, such as elevated CO<sub>2</sub> concentrations, drought, cold or nutrient availability may alleviate  
17 or exacerbate the oxidative stress response to a given O<sub>3</sub> concentration. This section will also  
18 highlight recent literature that focuses on O<sub>3</sub> damage to crops as influenced by other environmental  
19 factors.

### 9.5.3.1. Yield

20 It is well known that yield is negatively impacted in many crop species in response to high O<sub>3</sub>  
21 concentrations. However the threshold for damage varies from species to species. Reproductive  
22 organs such as seeds may be particularly sensitive to injury or biomass reductions due to O<sub>3</sub>, as  
23 reviewed by Black et al. (2000, [036322](#)). Numerous analyses of experiments conducted in OTCs and  
24 with naturally occurring gradients demonstrate that the effects of O<sub>3</sub> exposure vary depending on the  
25 growth stage of the plant. Plants grown for seed or grain are often most sensitive to exposure during  
26 the seed or grain-filling period (Lee et al., 1988, [594572](#))(Pleijel et al., 1998, [053021](#))(Soja et al.,  
27 2000, [030388](#))(Younglove et al., 1994, [044162](#)). AX9.5.4.1 of the 2006 O<sub>3</sub> AQCD summarized many  
28 previous studies on crop yield (U.S. EPA, 2006, [088089](#)).

29 The effect of O<sub>3</sub> exposure on U.S. crops remains an important area of research and several  
30 studies have been published on this topic since the 2006 O<sub>3</sub> AQCD (Tables 9-3 and 9-16). For  
31 example, one study with cotton in a crop-weed interaction study (Grantz and Shrestha, 2006,  
32 [191702](#)) utilizing OTCs suggests that ambient O<sub>3</sub> concentrations (12-h avg: 79.9 ppb) decreased  
33 cotton biomass by 25% and 1.5 × ambient O<sub>3</sub> concentration (12-h avg: 122.7 ppb) decreased cotton  
34 biomass by 75% compared to charcoal filtered control (12-h avg: 12.8 ppb). Further, this study  
35 suggests that the weed, yellow nutsedge, was less sensitive to increasing O<sub>3</sub> concentration which  
36 would increase weed competition (Grantz and Shrestha, 2006, [191702](#)). In a study of peanuts in  
37 North Carolina, near ambient and elevated exposures of O<sub>3</sub> reduced photosynthesis and yield

1 compared to very low O<sub>3</sub> conditions (Booker et al., 2007, [191370](#))(Burkey et al., 2007, [191371](#)). In  
2 another study, Grantz and Vu (2009, [195237](#)) reported that sugarcane biomass growth significantly  
3 declined under O<sub>3</sub> exposure.

4 The average yield loss reported across a number of meta-analytic studies have been published  
5 recently for soybean (Morgan et al., 2003, [055527](#)), wheat (Feng et al., 2008, [191453](#)), rice  
6 (Ainsworth, 2008, [191646](#)), semi-natural vegetation (Hayes et al., 2007, [196911](#)), potato, bean and  
7 barley (Feng and Kobayashi, 2009, [199223](#)). The meta-analytic technique allows for the objective  
8 development of a quantitative consensus of the effects of a treatment across a wide body of literature  
9 and therefore provides an average response ratio compiled from these sources. Further, this  
10 technique allows for a compilation of data across a range of O<sub>3</sub>-fumigation techniques, durations and  
11 concentrations in order to assemble the existing literature in a meaningful manner.

12 Morgan et al. (2003, [055527](#)) reported an average seed yield loss for soybean of 24%  
13 compared to charcoal filtered air across all O<sub>3</sub> concentrations used in the 53 compiled studies. The  
14 decrease in seed yield appeared to be the product of nearly equal decreases (7-12%) in seed weight,  
15 seed number and pod number. As would be expected, the lowest O<sub>3</sub> concentration (30-59 ppb)  
16 resulted in the smallest yield losses, approximately 8%, while the highest O<sub>3</sub> concentration  
17 (80-120 ppb ) resulted in the largest yield losses, approximately 35% (Morgan et al., 2003, [055527](#)).  
18 Further, the oil/protein ratio within the soybean seed was altered due to growth at elevated O<sub>3</sub>  
19 concentrations, with a decrease in oil content. The studies included in this meta-analysis all used  
20 enclosed fumigation systems or growth chambers which may have altered the coupling of the  
21 atmosphere to the lower plant canopy (McLeod and Long, 1999, [688834](#)). Utilizing the Soybean  
22 Free Air gas Concentration Enrichment Facility (SoyFACE; [www.soyface.illinois.edu](http://www.soyface.illinois.edu)), Morgan et al.  
23 (2006, [079186](#)) report a 20% seed yield loss due to a 23% increase in average daytime O<sub>3</sub>  
24 concentration (56-69 ppb) within a single soybean cultivar across two growing seasons in Illinois,  
25 supporting the results from the meta-analysis. A further breakdown of the effects of current O<sub>3</sub>  
26 concentrations (AOT40 of 4.7 ppm-h) on bean seed quality (*Phaseolus vulgaris*) has identified that  
27 growth at current O<sub>3</sub> concentrations compared to charcoal-filtered air raised total lipids, total crude  
28 protein and dietary fiber content (Iriti et al., 2009, [195635](#)). An increase in total phenolics was also  
29 observed, however the individual phenolics compounds responded differently, with significant  
30 decreases in anthocyanin content. The seeds from ambient O<sub>3</sub> exposed plants also displayed  
31 increased total antioxidant capacity compared to charcoal-filtered air controls (Iriti et al., 2009,  
32 [195635](#)). Betzelberger et al. (2010, [644183](#)) has recently utilized the SoyFACE facility to compare  
33 the impact of elevated O<sub>3</sub> concentrations across 10 soybean cultivars to investigate intraspecific  
34 variability of the O<sub>3</sub> response to find physiological or biochemical markers for eventual O<sub>3</sub> tolerance  
35 breeding efforts (Betzelberger et al., 2010, [644183](#)). They report an average 17% decrease in yield  
36 across all 10 cultivars across two growing seasons due to a doubling of ambient O<sub>3</sub> concentrations,  
37 with a the individual cultivar responses ranging from -7% to -36%. The dose-response functions  
38 derived for these 10 modern cultivars were similar to the response functions derived from the

1 NCLAN studies conducted in the 1980's (Heagle, 1989, [093985](#)) suggesting there has not been any  
2 inadvertent selection for more O<sub>3</sub>-tolerant cultivars in recent history.

3 A meta-analysis has also been performed on studies investigating the effects of O<sub>3</sub>  
4 concentrations on wheat (Feng et al., 2008, [191453](#)). Across 23 studies included, elevated O<sub>3</sub>  
5 concentrations (ranging from a 7-h daily average of 31-200 ppb) decreased grain yield by 29%.  
6 Winter wheat and spring wheat did not differ in their responses; however the response in both  
7 varieties to increasing O<sub>3</sub> concentrations resulted in successively larger decreases in yield, from a  
8 20% decrease in 42 ppb to 60% in 153 ppb O<sub>3</sub>. These yield losses were mainly caused by a  
9 combination of decreases in individual grain weight (-18%), ear number per plant (-16%), and grain  
10 number per ear (-11%). Further, the grain starch concentration decreased by 8% and the grain protein  
11 yield decreased by 18% due to growth at elevated O<sub>3</sub> concentrations as well. However, increases in  
12 grain calcium and potassium levels were reported (Feng et al., 2008, [191453](#)).

13 A recent meta-analysis found that growth at elevated O<sub>3</sub> concentrations negatively impacts  
14 nearly every aspect of rice performance as well (Ainsworth, 2008, [191646](#)). While rice is not a major  
15 crop in the U.S., it provides a staple food for over half of the global population (IRRI, 2002, [688833](#))  
16 and the effects of rising O<sub>3</sub> concentrations on rice yields merits consideration. On average, rice  
17 yields decreased 14% in 62 ppb O<sub>3</sub> compared to charcoal-filtered air. This yield loss was largely  
18 driven by a 20% decrease in grain number (Ainsworth, 2008, [191646](#)).

19 Feng and Kobayashi (2009, [199223](#)) have recently compiled yield data for six major crop  
20 species, potato, barley, wheat, rice, bean and soybean and grouped the O<sub>3</sub> treatments used in those  
21 studies into three categories: baseline O<sub>3</sub> concentrations (<26 ppb), current ambient 7- or 12-h daily  
22 O<sub>3</sub> concentrations (31-50 ppb), and future ambient 7- or 12-h daily O<sub>3</sub> concentrations (51-75 ppb).  
23 Using these categories, they have effectively characterized the effects of current O<sub>3</sub> concentrations  
24 and the effects of future O<sub>3</sub> concentrations compared to the baseline O<sub>3</sub> concentrations. At current O<sub>3</sub>  
25 concentrations, which ranged from 41-49 ppb in the studies included, soybean (-7.7%), bean  
26 (-19.0%), barley (-8.9%), wheat (-9.7%), rice (-17.5%) and potato (-5.3%) all reported yield losses  
27 compared to the baseline O<sub>3</sub> concentrations (<26 ppb). At future O<sub>3</sub> concentrations, averaging  
28 63 ppb, soybean (-21.6%), bean (-41.4%), barley (-14%), wheat (-28%), rice (-17.5%) and potato  
29 (-11.9%) all reported significantly larger yield losses compared to the losses at current O<sub>3</sub>  
30 concentrations (<26 ppb) (Feng and Kobayashi, 2009, [199223](#)).

31 An extensive review of OTC literature has determined the AOT40 critical level that causes a  
32 5% yield reduction across a variety of agricultural and horticultural species (Mills et al., 2007,  
33 [180221](#)). They classify the species into three groups: sensitive, moderate and tolerant. The sensitive  
34 crops, including watermelon, beans, cotton, wheat, turnip, onion, soybean, lettuce, and tomato,  
35 respond with a 5% reduction in yield under a 3-month AOT40 of 6 ppm-h. Watermelon was the most  
36 sensitive with a critical level of 1.6 ppm-h. The moderately sensitive crops, including sugar beet,  
37 oilseed rape, potato, tobacco, rice, maize, grape and broccoli, responded with a 5% reduction in yield  
38 between 8.6 and 20 ppm-h. The crops classified as tolerant, including strawberry, plum and barley,  
39 responded with a 5% yield reduction between 62-83.3 ppm-h (Mills et al., 2007, [180221](#)).

1 Feng and Kobayashi (2009, [199223](#)) compared their response-exposure results to those  
2 published by Mills et al. (2007, [180221](#)) and found the ranges of yield loss to be similar for soybean,  
3 rice and bean. However, Feng and Kobayashi reported smaller yield losses for potato and wheat and  
4 larger yield losses for barley compared to the dose-response functions published by Mills et al.  
5 (2007, [180221](#)), which they attributed to their more lenient criteria for literature inclusion.

6 While the studies investigating the impact of various O<sub>3</sub> concentrations on yield are important  
7 and aid in determining the vulnerability of various crops to a variety of O<sub>3</sub> concentrations, there is  
8 still uncertainty as to how these crops will respond under field conditions with interacting  
9 environmental factors such as temperature, soil moisture, CO<sub>2</sub> concentration, and soil fertility  
10 (Booker et al., 2009, [191569](#)). Further, there appears to be a distinct developmental and genotype  
11 dependant influence on plant sensitivity to O<sub>3</sub> that has yet to be fully investigated across O<sub>3</sub>  
12 concentrations in a field setting.

13 Because O<sub>3</sub> is heterogeneous in both time and space and O<sub>3</sub> monitoring stations are  
14 predominantly near urban areas, the O<sub>3</sub> impacts on current crop yields are difficult to estimate.  
15 Fishman et al. (2010, [644259](#)) have used satellite observations to estimate O<sub>3</sub> concentrations in the  
16 contiguous tri-state area of Iowa, Illinois and Indiana and have combined that information with other  
17 measured environmental variables to model the historical impact of O<sub>3</sub> concentrations on soybean  
18 yield across the 2002-2006 growing seasons. When soybean yield across Iowa, Indiana and Illinois  
19 was modeled as a function of seasonal temperature, soil moisture and O<sub>3</sub> concentrations, O<sub>3</sub> had the  
20 largest contribution to the variability in yield for the southern-most latitudes included in the dataset.  
21 Fishman et al. (2010, [644259](#)) determined that O<sub>3</sub> concentrations significantly reduced soybean yield  
22 by -0.38 to -1.63% ppb/v across the 5 years. This value is consistent with previous chamber studies  
23 (NCLAN; Heagle, 1989, [093985](#)) and results from SoyFACE (Morgan et al., 2006, [079186](#)).  
24 Satellite estimates of tropospheric O<sub>3</sub> concentrations exist globally (Fishman et al., 2008, [193927](#)),  
25 therefore utilizing this historical modeling approach is feasible across a wider geographical area,  
26 longer time-span and perhaps for more crop species.

### 9.5.3.2. Crop Quality

27 In general, it appears that increasing O<sub>3</sub> concentrations above current ambient concentrations  
28 can cause species dependant biomass losses, decreases in root biomass and nutritive quality,  
29 accelerated senescence and shifts in biodiversity. A study conducted with highbush blackberry has  
30 demonstrated decreased nutritive quality with increasing O<sub>3</sub> concentration despite no change in  
31 biomass among a charcoal-filtered control, an ambient O<sub>3</sub> and a 2 × ambient O<sub>3</sub> treatment (Ditchkoff  
32 et al., 2009, [192230](#)). A study conducted with sedge using control (30 ppb), low (55 ppb), medium  
33 (80 ppb) and high (105 ppb) O<sub>3</sub> treatments has demonstrated decreased root biomass and accelerated  
34 senescence in the medium and high O<sub>3</sub> treatments (Jones et al., 2010, [567354](#)). Alfalfa showed no  
35 biomass changes across two years of double ambient O<sub>3</sub> concentrations (AOT40 of 13.9 ppm-h)  
36 using FACE fumigation (Maggio et al., 2009, [191645](#)). However a modeling study has demonstrated  
37 that 84% of the relative feed value in high-yielding alfalfa was due to the variability in mean O<sub>3</sub>

1 concentration from 1998-2002 (Lin et al., 2007, [196925](#)). Further, in a managed grassland FACE  
2 system, the reduction in total biomass harvest over five years decreased twice as fast in the elevated  
3 treatment (AOT40 of 13-59 ppm-h) compared to ambient (AOT40 of 1-20.7 ppm-h). Compared with  
4 the ambient control, loss in annual dry matter yield was 23% after 5 year. Further, there was  
5 significant changes in the functional categories growing in each plot with legumes showing the  
6 strongest negative response (Volk et al., 2006, [191434](#)). This study suggests a shift in biodiversity  
7 away from nitrogen-fixers in managed grasslands. An OTC study conducted with *Trifolium*  
8 *subterraneum* exposed to filtered (<15 ppb), ambient, and 40 ppb above ambient O<sub>3</sub> demonstrates  
9 decreases in biomass in the highest O<sub>3</sub> treatment as well as 10-20% decreased nutritive quality which  
10 was mainly attributed to accelerated senescence (Sanz et al., 2005, [196963](#)). A study conducted with  
11 Eastern gamagrass and big bluestem in OTCs suggests that big bluestem is not sensitive to O<sub>3</sub>, but  
12 gamagrass displayed decreased nutritive quality, due to higher lignin content and decreased N, in the  
13 2 × ambient O<sub>3</sub> treatment (Lewis et al., 2006, [191542](#)).

**Table 9-3. Summary of recent studies of ozone effects on crops (exclusive of growth and yield)**

Species Facility Location	Exposure Duration	Ozone Exposure <sup>a</sup> (Additional treatment)	Variable(s) measured	percent change from CF <sup>b</sup> (percent change from ambient)	Reference
Alfalfa ( <i>Medicago sativa</i> cv. Beaver)	1, 2 or 4 days	3, 5 or 7 h/day 85 ppb	Relative feed value	n.s *high variability among treatment groups (N/A)	Muntifering et al. (2006, <a href="#">191270</a> )
Growth chambers		(Exposure duration)			
Bean ( <i>Phaseolus vulgaris</i> l. cv Borlotto)	4 months	Seasonal AOT40: CF = 0.5 ppm-h; Ambient = 4.6 ppm-h	Seed lipid, Protein content	+28.5 (N/A) +7.88 (N/A)	Iriti et al. (2009, <a href="#">195635</a> )
OTC, ground-planted		(N/A)	Fiber content	+14.54 (N/A)	
Curno, Italy					
Big Blue Stem ( <i>Andropogon gerardii</i> )	4 months	12-h avg: CF = 14 ppb; Ambient = 29 ppb; Elevated = 71 ppb	Relative feed value	n.s. (n.s.)	Lewis et al. (2006, <a href="#">191542</a> )
OTC		(N/A)			
Alabama, U.S.					
<i>Brassica napus</i>	4 days	CF & 176 ppb for 4 h/day	Glucosinolates	-41 (N/A)	Gielen et al. (2006, <a href="#">191271</a> )
Growth chambers		(N/A)			
Belgium					
<i>Brassica napus</i> cv. Westar	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. (2009, <a href="#">191338</a> )
Growth chambers					
Finland					
Eastern Gamagrass ( <i>Tripsacum dactyloides</i> )	4 months	12-h avg: CF = 14 ppb; Ambient = 29 ppb; Elevated = 71 ppb	Relative feed value	-17 (-12)	Lewis et al. (2006, <a href="#">191542</a> )
OTC		(N/A)			
Alabama, U.S.					
Lettuce ( <i>Lactuca sativa</i> )	30 days	12-h mean: CF = 10.2 ppb; NF = 30.1 ppb; NF+O <sub>3</sub> = 62.7 ppb	Lipid peroxidation; Root length	+77 (+38) -22 (-14)	Calatayud et. al. (2002, <a href="#">684222</a> )
OTC		(4 cultivars)			
Carcaixent Experimental Station, Spain					
Peanut ( <i>Arachis hypogaea</i> )	3 yr	12-h avg: CF = 22 ppb; Ambient = 46 ppb; Elevated = 75 ppb	Harvest biomass	-40 (-10)	Booker et al. (2007, <a href="#">191370</a> )
OTC		(CO <sub>2</sub> : 375 ppm; 548 ppm; 730 ppm)			
Raleigh, NC; U.S.					
<i>Poa pratensis</i>	3 yr; 4-5 wk 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, <a href="#">191437</a> )
OTC					
Braunschweig, Germany					
Potato ( <i>Solanum tuberosum</i> cv. Bintje)	2 yr	CF = 10 ppb; Ambient = 25 ppb; Ambient(+) = (36 ppb); Ambient(++ ) = (47 ppb)	[K], [Ca], [Mg], [P], [N] per dry weight of tubers *dose-response regression, report significant positive or negative slope with increasing [O <sub>3</sub> ]	[N] [P] [Ca] n.s.; [K] & [Mg] sig + (N/A)	Piikki et al. (2007, <a href="#">191451</a> )
OTC		(N/A)			
Sweden & Finland					

Species Facility Location	Exposure Duration	Ozone Exposure <sup>a</sup> (Additional treatment)	Variable(s) measured	percent change from CF <sup>b</sup> (percent change from ambient)	Reference
Potato ( <i>Solanum tuberosum</i> cv. Indira)	8 wk	CF = 10 ppb; Ambient = 50 ppb; 2xAmbient = 100 ppb	Pathogen infestation using % necrosis	+52 (n.s.)	Plessl et al. (2007, <a href="#">196952</a> )
Climate chambers Germany		(CO <sub>2</sub> : 400 ppm & 700 ppm)			
Soybean OTC	3 yr	AOT40: CF = 0 ppm-h; Ambient = 3.4 ppm-h; Elevated = 9.0 ppm-h	Daily evapotranspiration	-28 (-14)	Jaude et al. (2008, <a href="#">191222</a> )
Italy		(Well-watered & water-stressed)			
Soybean ( <i>Glycine max</i> cv. 93B15)	3 yr May-Oct	AOT40: Ambient = 5-22 ppm-h; Elevated = 20-43 ppm-h	Photosynthesis in new leaves,	N/A (n.s.)	Bernacchi et al. (2006, <a href="#">158001</a> )
SoyFACE Urbana, IL; U.S.		(CO <sub>2</sub> : 550 ppm; environmental variability)			
Soybean ( <i>Glycine max</i> cv. 93B15)	4 months	8-h avg: Ambient = 38.5 ppb; Elevated = 52 ppb	Herbivory defense-related genes	N/A (N/A)	Casteel et al. (2008, <a href="#">191696</a> )
SoyFACE Urbana, IL; U.S.		(Herbivory)			
Soybean ( <i>Glycine max</i> cv. Essex)	2 yr	12-h avg: CF = 21 ppb; 1.5xAmbient = 74 ppb	Post-harvest residue	N/A (-15.46)	Booker et al. (2005, <a href="#">079151</a> )
OTC, ground-planted Raleigh, NC; U.S.		(CO <sub>2</sub> : 370 ppm & 714 ppm)			
Soybean ( <i>Glycine max</i> cv. Essex)	2x3 months	12-h avg: CF = 18 ppb); Elevated = 72 ppb)	Water-use efficiency	n.s. (N/A)	Booker et al. (Booker et al., 2004, <a href="#">079138</a> )
OTCs, 21 L pots Raleigh, NC; U.S.		(CO <sub>2</sub> : 367 & 718)			
Soybean ( <i>Glycine max</i> ) 10 cultivars)	2 yr	8-h avg (ppb): Ambient = 46.3 & 37.9; Elevated = 82.5 & 61.3	Total antioxidant capacity	N/A (+19)	Betzelberger et al. (2010, <a href="#">644183</a> )
SoyFACE Urbana, IL; U.S.		(Cultivar comparisons)			
Spring Wheat ( <i>Triticum aestivum</i> cv. Minaret; Satu; Drabant; Dragon)	7 yr	Seasonal AOT40s ranged from 0 to 16 ppm-h	Seed protein content; 1,000-seed weight regressed across all experiments	N/A (Significant negative correlation)	Piikki et al. (2008, <a href="#">199812</a> )
OTCs Belgium, Finland, & Sweden		(N/A)		N/A (Significant negative correlation)	
Strawberry ( <i>Fragaria x ananassa</i> Duch. Cv. Korona & Elsanta)	2 months	8-h avg: CF = 0 ppb; Elevated = 78 ppb	Total leaf area	-16 (N/A)	Keutgen et al. (2005, <a href="#">191295</a> )
Growth chambers Bonn, Germany		(N/A)			
Sweet Potato	4 wk	8-h avg: CF = 0 ppb; Ambient < 40 ppb; Elevated = 255 ppb	Tuber weight	-14 (-11.5)	Keutgen et al. (2008, <a href="#">191690</a> )
Growth Chambers Bonn, Germany		(N/A)			

Species Facility Location	Exposure Duration	Ozone Exposure <sup>a</sup> (Additional treatment)	Variable(s) measured	percent change from CF <sup>b</sup> (percent change from ambient)	Reference
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)	Calvo, et al. (2005, <a href="#">191570</a> )
<i>Trifolium repens</i> & <i>Trifolium pretense</i> Aspen FACE Rhineland, WI; U.S.	3 months	3-mo daylight avg: Ambient = 34.8 ppb; 1.2xAmbient = 42.23 ppb  (CO <sub>2</sub> : 560 ppm)	Lignin;  Dry-matter digestibility	N/A (+19.3)  N/A (-4.2)	Muntifering et al. (2006, <a href="#">191270</a> )

<sup>a</sup>Ozone exposure in ppb unless otherwise noted.

<sup>b</sup>CF = Carbon-filtered air.

NF = Non-filtered air.

## 9.5.4. Factors that Modify Functional and Growth Response

1 Many biotic and abiotic factors, including insects, pathogens, root microbes and fungi,  
2 temperature, water and nutrient availability, and other air pollutants, as well as elevated CO<sub>2</sub>,  
3 influence or alter plant response to O<sub>3</sub>. These modifying factors were comprehensively reviewed in  
4 AX9.3 of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) and thus, this section serves mainly as a  
5 brief summary of the previous findings. A limited number of new studies published since the 2006  
6 O<sub>3</sub> AQCD add to our understanding of the role of these interactions in modifying O<sub>3</sub>-induced plant  
7 responses. Many of these modifying factors and interactions are integrated into discussions  
8 elsewhere in this chapter and the reader is directed to those sections.

### 9.5.4.1. Genetics

9 It is well known that species vary greatly in their responsiveness to O<sub>3</sub>. Even within a given  
10 species, individual genotypes or populations can also vary significantly with respect to O<sub>3</sub> sensitivity  
11 (see section AX 9.3.2 of the 2006 AQCD; U.S. EPA, 2006, [088089](#)). Therefore, caution should be  
12 taken when considering a species' degree of sensitivity to O<sub>3</sub>. Plant response to O<sub>3</sub> is determined by  
13 genes that are directly related to oxidant stress and to an unknown number of genes that are not  
14 specifically related to oxidants, but instead control leaf and cell wall thickness, stomatal  
15 conductance, and the internal architecture of the air spaces. It is rarely the case that single genes are  
16 responsible for O<sub>3</sub> tolerance. Studies using molecular biological tools and transgenic plants have  
17 positively verified the role of various genes and gene products in O<sub>3</sub> tolerance and are continuing to  
18 increase the understanding of O<sub>3</sub> toxicity and differences in O<sub>3</sub> sensitivity. See Section 9.4.3.2 of this  
19 document for a discussion of recent studies related to gene expression changes in response to O<sub>3</sub>.

### 9.5.4.2. Environmental Biological Factors

1 As stated in the 2006 O<sub>3</sub> AQCD, the biological factors within the plant's environment that may  
2 directly or indirectly influence its response to O<sub>3</sub> in a positive or negative manner encompass insects  
3 and other animal pests, diseases, weeds, and other competing plant species. Ozone may influence the  
4 severity of a disease or infestation by a pest or weed, either by direct effects on the causal species, or  
5 indirectly by affecting the host, or both. In addition, the interaction between O<sub>3</sub>, a plant, and a pest,  
6 pathogen, or weed may influence the response of the target host species to O<sub>3</sub> (U.S. EPA, 2006,  
7 [088089](#)). Several recent studies on the effects of O<sub>3</sub> on insects via their interactions with plants are  
8 discussed in Section 9.6.6.1. In addition, O<sub>3</sub> has also been shown to alter soil fauna communities  
9 (Section 9.6.6.2).

10 In contrast to detrimental biological interactions, there are mutually beneficial relationships or  
11 symbioses involving higher plants and bacteria or fungi. These include (1) the nitrogen-fixing  
12 species *Rhizobium* and *Frankia* that nodulate the roots of legumes and alder and (2) the mycorrhizae  
13 that infect the roots of many crop and tree species, all of which may be affected by exposure of the  
14 host plants to O<sub>3</sub>. Some discussion of mycorrhizae can be found in Section 9.6.4.

15 In addition to the interactions involving animal pests, O<sub>3</sub> also has indirect effects on higher  
16 herbivorous animals, e.g., livestock, due to O<sub>3</sub>-induced changes in feed quality. Recent studies on the  
17 effects of O<sub>3</sub> on nutritive quality of plants are discussed in Sections 9.5.3 and 9.6.6.3.

18 Intra- and interspecific competition are also important factors in determining vegetation  
19 response to O<sub>3</sub>. Plant competition involves the ability of individual plants to acquire the  
20 environmental resources needed for growth and development: light, water, nutrients, and space.  
21 Intraspecific competition involves individuals of the same species, typically in monoculture crop  
22 situations, while interspecific competition refers to the interference exerted by individuals of  
23 different species on each other when they are in a mixed culture. This topic was previously reviewed  
24 in AX9.3.3.4 of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). Recent studies on competition and its  
25 implications for community composition are discussed in Section 9.6.5.

### 9.5.4.3. Physical Factors

26 Physical or abiotic factors play a large role in modifying plant response to O<sub>3</sub>, and have been  
27 extensively discussed in previous O<sub>3</sub> AQCDs (U.S. EPA, 1996, [080828](#))(U.S. EPA, 2006, [088089](#)).  
28 This section summarizes those findings as well as recent studies published since the last review.

29 Although some studies have indicated that O<sub>3</sub> impact significantly increases with increased  
30 ambient temperature (Ball et al., 2000, [026354](#))(Mills et al., 2000, [030098](#)), other studies have  
31 indicated that temperature has little effect (Balls et al., 1996, [026370](#))(Fredericksen et al., 1996,  
32 [026653](#)). A recent study by Riikonen et al. (2009, [195664](#)) at the Ruohoniemi open air exposure field  
33 in Kuopio, Finland found that the effects of temperature and O<sub>3</sub> on total leaf area and photosynthesis  
34 of *Betula pendula* were counteractive. Elevated O<sub>3</sub> reduced the saplings' ability to utilize the warmer  
35 growth environment by increasing the stomatal limitation for photosynthesis and by reducing the

1 redox state of ascorbate in the apoplast in the combination treatment as compared to temperature  
2 alone (Riikonen et al., 2009, [195664](#)).

3 Temperature affects the rates of all physiological processes based on enzyme catalysis and  
4 diffusion; each process and overall growth (the integral of all processes) has a distinct optimal  
5 temperature range. It is important to note that a plant's response to changes in temperature will  
6 depend on whether it is growing near its optimum temperature for growth or near its maximum  
7 temperature (Rowland-Bamford, 2000, [030257](#)). However, temperature is very likely an important  
8 variable affecting plant O<sub>3</sub> response in the presence of the elevated CO<sub>2</sub> levels contributing to global  
9 climate change. In contrast, some evidence suggests that O<sub>3</sub> exposure sensitizes plants to low  
10 temperature stress (Colls and Unsworth, 1992, [026469](#)) and, also, that O<sub>3</sub> decreases below-ground  
11 carbohydrate reserves, which may lead to responses in perennial species ranging from rapid demise  
12 to impaired growth in subsequent seasons (i.e., carry-over effects) (Andersen et al., 1997, [052923](#)).

13 Light, a component of the plant's physical environment, is an essential "resource" of energy  
14 content that drives photosynthesis and C assimilation. It has been suggested that increased light  
15 intensity may increase the O<sub>3</sub> sensitivity of light-tolerant species while decreasing that of shade-  
16 tolerant species, but this appears to be an oversimplification with many exceptions. Several studies  
17 suggest that the interaction between O<sub>3</sub> sensitivity and light environment is complicated by the  
18 developmental stage as well as the light environment of individual leaves in the canopy (Chappelka  
19 and Samuelson, 1998, [093687](#))(Topa et al., 2001, [035398](#))(Kitao et al., 2009, [191331](#)).

20 Although the relative humidity of the ambient air has generally been found to increase the  
21 adverse effects of O<sub>3</sub> by increasing stomatal conductance (thereby increasing O<sub>3</sub> flux into the leaves),  
22 abundant evidence also indicates that the ready availability of soil moisture results in greater O<sub>3</sub>  
23 sensitivity (Mills, 2002, [035322](#)). The partial "protection" against the adverse effects of O<sub>3</sub> afforded  
24 by drought has been observed in field experiments (Low et al., 2006, [191396](#)) and modeled in  
25 computer simulations (Broadmeadow and Jackson, 2000, [021325](#)). Conversely, O<sub>3</sub> may enhance the  
26 negative effects of O<sub>3</sub> on plants (Grulke et al., 2003, [052984](#))(Pollastrini et al., 2010, [644392](#)). There  
27 is also some evidence that O<sub>3</sub> can predispose plants to drought stress (Maier-Maercker, 1998,  
28 [029961](#)). Hence, the nature of the response is largely species-specific and will depend to some extent  
29 upon the sequence in which the stressors occur.

#### 9.5.4.4. Interactions with other Pollutants

##### Ozone-Nitrogen Interactions

30 Elevated O<sub>3</sub> exposure and N deposition often co-occur as major pollutant types. However, the  
31 interactions of O<sub>3</sub> exposure and N deposition on vegetation are complex and less well understood  
32 compared to their independent effects. Consistent with the conclusion of the 2006 O<sub>3</sub> AQCD  
33 (U.S. EPA, 2006, [088089](#)), studies published since the last review indicated that the interactive  
34 effects of N and O<sub>3</sub> varied among species and ecosystems (Table 9-4). This section will focus on O<sub>3</sub>  
35 and N interactions at the plant scale. Responses at the ecosystem scale are discussed in Section 9.6.

1 Nitrogen deposition could stimulate relative growth rate (RGR), and lead to increased stomatal  
2 conductance. Therefore, plants might become more susceptible to O<sub>3</sub> exposure. Alternatively, N  
3 deposition may increase the availability of photosynthates for use in detoxification and plants could  
4 become more tolerant to O<sub>3</sub> (Bassin et al., 2007, [196879](#)). Only a few recent studies have  
5 investigated the interactive effects of O<sub>3</sub> and N in the U.S. Grulke et al. (2005, [199433](#)) measured  
6 stomatal conductance of California black oak (*Quercus kelloggii*) at a long-term N-enrichment site  
7 located in the San Bernardino Mountains, which is accompanied by high O<sub>3</sub> exposure (80 ppb,  
8 24-h avg. over a six month growing season). The authors found that N amendment led to poor  
9 stomatal control in full sun in midsummer of the average precipitation years, but enhanced stomatal  
10 control in shade leaves of California black oak. In an OTC study, Handley and Grulke (2008,  
11 [191485](#)) found that O<sub>3</sub> lowered photosynthetic ability and water-use efficiency, and increased leaf  
12 chlorosis and necrosis of California black oak. Nitrogen fertilization tended to reduce plant  
13 sensitivity to O<sub>3</sub> exposure; however, the interaction was not statistically significant.

14 Studies conducted outside the U.S. are also summarized in Table 9-4. Generally, the responses  
15 were species specific. The O<sub>3</sub>-induced reduction in photosynthetic rate and biomass loss were greater  
16 in the relatively high N treatment for watermelon (*Citrillus lanants*) (Calatayud et al., 2006, [191482](#))  
17 and Japanese beech (*Fagus crenata*) seedlings (Yamaguchi et al., 2007, [191438](#)). However, there  
18 was no significant interactive effect of O<sub>3</sub> and N on biomass production for *Quercus serrata*  
19 seedlings (Watanabe et al., 2007, [191474](#)), young Norway spruce (*Picea abies*) trees (Thomas et al.,  
20 2005, [075930](#)), and young European beech (*Fagus sylvatica*) trees (Thomas et al., 2006, [191362](#)).

**Table 9-4. Response of plants to the interactive effects of elevated ozone exposure and N 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, <a href="#">199433</a> )
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 <sub>3</sub> exposure; however the interaction was not statistically significant.	Handley and Grulke (2008, <a href="#">191485</a> )
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 nitrogen levels alleviated the negative impact of O <sub>3</sub> on root starch concentrations	Thomas et al.(2005, <a href="#">195930</a> )
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	Nitrogen addition amplified the negative effects of O <sub>3</sub> on leaf area and shoot elongation.	Thomas et al.(2006, <a href="#">191362</a> )
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 <sub>3</sub> treatment.	Bassin et al.(2007, <a href="#">191534</a> )
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 <sub>3</sub> and N interactive effects on leaf chlorophyll concentration, leaf weight and change in <sup>18</sup> O, and the patterns were not consistent.	Bassin et al.(2009, <a href="#">191333</a> )
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 <sub>3</sub> treatment.	Bassin et al.(2007, <a href="#">191534</a> )
Spain	watermelon ( <i>Citrillus lanants</i> )	O <sub>3</sub> free (AOT40 of 0 ppm-h), ambient (AOT40 of 5.1-6.3 ppm-h) and elevated O <sub>3</sub> (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 <sub>3</sub> on Chl a fluorescence parameters, lipid peroxidation, and the total yield.	Calatayud et al.(2006, <a href="#">191482</a> )
Spain	<i>Trifolium striatum</i>	Filtered (24-h avg. of 8-22 ppb); ambient (29-34 ppb), elevated O <sub>3</sub> (35-56 ppb)	10, 30, and 60 kg N/ ha/yr	Ozone reduced total aerial biomass. N fertilization counterbalanced O <sub>3</sub> -induced effects only when plants were exposed to moderate O <sub>3</sub> levels (ambient) but not under elevated O <sub>3</sub> concentrations.	Sanz et al. (2007, <a href="#">199245</a> )
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 <sub>3</sub> -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, <a href="#">191438</a> )
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 <sub>3</sub> and N load on the growth and net photosynthetic rate were detected.	Watanabe et al.(2007, <a href="#">191474</a> )

### Ozone-Carbon Dioxide Interactions

1 Several decades of research has shown that exposure to elevated CO<sub>2</sub> increases photosynthetic  
2 rates (Tissue et al., 1999, [029011](#))(Bernacchi et al., 2006, [158001](#))(Will and Ceulemans, 1997,  
3 [679719](#))(Tissue et al., 1997, [679718](#))(Bernacchi et al., 2005, [679713](#)), decreases stomatal  
4 conductance (Bernacchi et al., 2006, [158001](#))(Ainsworth and Rogers, 2007, [092940](#))(Paoletti et al.,  
5 2007, [199365](#))(Medlyn et al., 2001, [679716](#))(Leakey et al., 2006, [679714](#)) and generally increases  
6 the growth of plants(McCarthy et al., 2010, [679715](#))(Norby et al., 2005, [679717](#)). This is in contrast  
7 to the decrease on photosynthesis and growth in many plants that are exposed to elevated O<sub>3</sub>. The

1 interactive effects on vegetation have been the subject of research in the past two decades because  
2 the implications on productivity and water use of ecosystems. This area of research was covered  
3 thoroughly in AX9.3.8.1 of the 2006 O<sub>3</sub> AQCD and much of the conclusions made then are still  
4 relevant (U.S. EPA, 2006, [088089](#)).

5 The bulk of the available evidence shows that, under the various experimental conditions used  
6 (which almost exclusively employed abrupt or “step” increases in CO<sub>2</sub> concentration, as discussed  
7 below), increased CO<sub>2</sub> levels (ambient + 200 to 400 ppm) may protect plants from the adverse  
8 effects of O<sub>3</sub> on growth. This protection may be afforded in part by CO<sub>2</sub> acting together with O<sub>3</sub> in  
9 inducing stomatal closure, thereby reducing O<sub>3</sub> uptake, and in part by CO<sub>2</sub> reducing the negative  
10 effects of O<sub>3</sub> on Rubisco and its activity in CO<sub>2</sub>-fixation. Although both CO<sub>2</sub>-induced and  
11 O<sub>3</sub>-induced decreases in stomatal conductance have been observed primarily in short-term studies,  
12 recent data show a long-term and sustained reduction in stomatal conductance under elevated CO<sub>2</sub>  
13 for a number of species (Ainsworth and Long, 2005, [042647](#))(Ellsworth et al., 2004,  
14 [080092](#))(Gunderson et al., 2002, [080097](#)). Instances of increased stomatal conductance have also  
15 been observed in response to O<sub>3</sub> exposure, suggesting partial stomatal dysfunction after extended  
16 periods of exposure (Maier-Maercker, 1998, [029961](#))(Grulke et al., 2007, [186963](#))(Paoletti and  
17 Grulke, 2010, [628561](#)).

18 Important caveats must be raised with regard to the findings presented in published research.  
19 The first caveat concerns the distinctly different natures of the exposures to O<sub>3</sub> and CO<sub>2</sub> experienced  
20 by plants in the field. Changes in the ambient concentrations of these gases have very different  
21 dynamics. In the context of climate change, CO<sub>2</sub> levels increase relatively slowly (globally  
22 2 ppm/year) and may change little over several seasons of growth. On the other hand, O<sub>3</sub> presents a  
23 fluctuating stressor with considerable hour-to-hour, day-to-day and regional variability (Polle and  
24 Pell, 1999, [093689](#)). Almost all of the evidence presented comes from experimentation involving  
25 plants subjected to an abrupt step increase to a higher, steady CO<sub>2</sub> concentration. In contrast, the O<sub>3</sub>  
26 exposure concentrations usually varied from day to day. Luo and Reynolds (1999, [035319](#)), Hui et  
27 al. (2002, [035288](#)), and Luo (2001, [035318](#)) noted the difficulties in predicting the likely effects of a  
28 gradual CO<sub>2</sub> increase from experiments involving a step increase or those using a range of CO<sub>2</sub>  
29 concentrations. It is also important to note that the levels of elevated CO<sub>2</sub> in many of the studies will  
30 not be experienced in the field for 30 or 40 years, but elevated levels of O<sub>3</sub> can occur in several areas  
31 of the U.S. Therefore, the CO<sub>2</sub> × O<sub>3</sub> interaction studies may be less policy relevant for current  
32 ambient conditions.

33 Another caveat concerns the interactions of O<sub>3</sub> and CO<sub>2</sub> with other climatic variables, such as  
34 temperature and precipitation. In light of the key role played by temperature in regulating  
35 physiological processes and modifying plant response to increased CO<sub>2</sub> levels (Long, 1991,  
36 [029710](#))(Morison and Lawlor, 1999, [094194](#)) and the knowledge that relatively modest increases in  
37 temperature may lead to dramatic consequences in terms of plant development (Lawlor, 1998,  
38 [029015](#)), it is important to consider that studying CO<sub>2</sub> and O<sub>3</sub> interactions alone may not create a  
39 complete understanding of effects on plants under future climate change.

## 9.6. Effects of Ozone on Ecosystems and Services

### 9.6.1. Ecosystem Scale, Function, and Structure

1 Information presented in this section was collected at multiple scales, ranging from the  
2 physiology of a given species to population, community, and ecosystem-level investigations. For this  
3 assessment, “ecosystem” is defined as a functional entity consisting of interacting groups of living  
4 organisms and their abiotic (chemical and physical) environment. Ecosystems cover a hierarchy of  
5 spatial scales and can comprise the entire globe, biomes at the continental scale, or small, well-  
6 circumscribed systems such as a small pond.

7 Ecosystems have both structure and function. Structure may refer to a variety of measurements  
8 including the species richness, abundance, community composition and biodiversity as well as  
9 landscape attributes. Competition among and within species and their tolerance to environmental  
10 stressors are key elements of survivorship. When environmental conditions are shifted, for example,  
11 by the presence of anthropogenic air pollution, these competitive relationships may change and  
12 tolerance to stress may be exceeded. “Function” refers to the suite of processes and interactions  
13 among the ecosystem components and their environment that involve nutrient and energy flow as  
14 well as other attributes including water dynamics and the flux of trace gases. Plant processes  
15 including photosynthesis, respiration, C allocation, nutrient uptake and evaporation, are directly  
16 related to functions of energy flow and C, nutrient and water cycling. The energy accumulated and  
17 stored by vegetation (via photosynthetic C capture) is available to other organisms. Energy moves  
18 from one organism to another through food webs, until it is ultimately released as heat. Nutrients and  
19 water can be recycled. Air pollution alters the function of ecosystems when elemental cycles or the  
20 energy flow are altered. This alteration can also be manifested in changes in the biotic composition  
21 of ecosystems.

22 There are at least three levels of ecosystem response to pollutants: (1) the individual organism  
23 and its environment; (2) the population and its environment; and (3) the biological community  
24 composed of many species and their environment (Billings, 1978, [034165](#)). Individual organisms  
25 within a population vary in their ability to withstand the stress of environmental change. The  
26 response of individual organisms within a population is based on their genetic constitution, stage of  
27 growth at time of exposure to stress, and the microhabitat in which they are growing (Levine and  
28 Pinto, 1998, [029599](#)). The stress range within which organisms can exist and function determines the  
29 ability of the population to survive. Those best able to cope with environmental stressors survive and  
30 reproduce. Competition among different species results in succession (community change over time)  
31 and, ultimately, sensitive species may be progressively replaced and communities shift to favor those  
32 species that may have the capability to tolerate stressors such as O<sub>3</sub> (Guderian, 1985,  
33 [019325](#))(Rapport and Whitford, 1999, [004595](#)). In the sections that follow, available information on  
34 individual, population and community response to O<sub>3</sub> will be discussed. Effects of O<sub>3</sub> on productivity  
35 and C sequestration, water cycling, below-ground processes, competition and biodiversity, and

1 insects and wildlife are considered below and in the context of ecosystem services where  
2 appropriate.

### 9.6.1.1. Ecosystem Services

3 Ecosystem structure and function may be translated into ecosystem services. Ecosystem  
4 services identify the varied and numerous ways that ecosystems are important to human welfare.  
5 Ecosystems provide many goods and services that are of vital importance for the functioning of the  
6 biosphere and provide the basis for the delivery of tangible benefits to human society. Hassan et al.  
7 (2005, [092759](#)) define these benefits to include supporting, provisioning, regulating, and cultural  
8 services:

- 9       ▪ Supporting services are necessary for the production of all other ecosystem services.  
10       Some examples include biomass production, production of atmospheric O<sub>2</sub>, soil  
11       formation and retention, nutrient cycling, water cycling, and provisioning of habitat.  
12       Biodiversity is a supporting service that is increasingly recognized to sustain many of the  
13       goods and services that humans enjoy from ecosystems. These provide a basis for three  
14       higher-level categories of services.
  
- 15       ▪ Provisioning services, such as products (Gitay et al., 2001, [092761](#)), i.e., food (including  
16       game, roots, seeds, nuts and other fruit, spices, fodder), fiber (including wood, textiles),  
17       and medicinal and cosmetic products (such as aromatic plants, pigments).
  
- 18       ▪ Regulating services that are of paramount importance for human society such as  
19       (1) C sequestration, (2) climate and water regulation, (3) protection from natural hazards  
20       such as floods, avalanches, or rock-fall, (4) water and air purification, and (5) disease and  
21       pest regulation.
  
- 22       ▪ Cultural services that satisfy human spiritual and aesthetic appreciation of ecosystems  
23       and their components.

### 9.6.1.2. Assessing Ozone Effects at Larger Spatial Scales

24 Ozone effects at large spatial scales start as effects on plants at smaller spatial scales. Ozone enters  
25 leaves through stomata, and has been shown to alter stomatal conductance and reduce the activity  
26 and concentration of Rubisco (Section 9.4.6). Those changes alter the rates of CO<sub>2</sub> uptake and water  
27 loss from leaves, and therefore the rates of photosynthesis and transpiration at the plant level  
28 (Section 9.5.2). Those O<sub>3</sub>-induced effects could translate from the plant level to the ecosystem level,  
29 and cause changes in ecosystem services, such as C storage, water production, nutrient cycling, and

1 community composition (Figure 9-1). Changes at the ecosystem level are difficult to evaluate  
2 directly due to the complexity and the large spatial and temporal scale of ecosystems. These  
3 assessments generally involve the extrapolation of laboratory or field results by ecological models or  
4 long-term field experiments as discussed below.

## 9.6.2. Productivity and Carbon Sequestration

5 During the previous NAAQS review, there were very few studies that investigated the effect of  
6 O<sub>3</sub> exposure on ecosystem productivity and C sequestration. Recent studies from long-term FACE  
7 experiments provide new evidence of the association of O<sub>3</sub> exposure and changes in productivity at  
8 the ecosystem level. In addition to experimental studies, several model studies also assessed the  
9 impact of O<sub>3</sub> exposure on productivity and C sequestration from stand to global scales. Three types  
10 of models are most often used to study the ecological consequences of O<sub>3</sub> exposure: (1) regression  
11 models such as dose-response function derived from the Nation Crop Loss Assessment Network  
12 (NCLAN) (Wang and Mauzerall, 2004, [179978](#))(Tong and Mauzerall, 2008, [621169](#)); (2) tree growth  
13 models such as TREGRO and ECOPHYS (Hogsett et al., 2008, [191229](#))(Martin et al., 2001,  
14 [043678](#)); and (3) process-based ecosystem models such as PnET, Dynamic Land Ecosystem Model  
15 (DLEM) and Terrestrial Ecosystem Model (TEM) (Ollinger et al., 2002, [180189](#))(Ren et al., 2007,  
16 [191366](#))(Felzer et al., 2009, [191460](#)). The experimental and model studies on ecosystem productivity  
17 and C sequestration, at the stand scale as well as regionally and globally, are reviewed in the  
18 following section.

### 9.6.2.1. Stand Scale

19 The above- and below-ground biomass and net primary production (NPP) were measured at  
20 the Aspen FACE site after 7-year O<sub>3</sub> exposure. Elevated O<sub>3</sub> caused 23, 13 and 14% reductions in  
21 total biomass relative to the control in the aspen, aspen–birch and aspen–maple communities,  
22 respectively (King et al., 2005, [191701](#)). At the Kranzberg Forest FACE experiment, O<sub>3</sub> reduced  
23 annual volume growth by 9.5 m<sup>3</sup>/ha in a mixed mature stand of Norway spruce and European beech  
24 (Pretzsch et al., 2010, [580435](#)). Ozone also altered C accumulation and turnover in soil, and the  
25 details of these studies are discussed in Section 9.6.4.

26 Changes in stand productivity under elevated O<sub>3</sub> were assessed by several model studies.  
27 TREGRO is a process-based, single tree growth model and has been widely used to simulate the  
28 effects of O<sub>3</sub> on the growth of several species in different regions in the U.S. Ozone acts within the  
29 model by reducing the maximum potential photosynthetic rate as a function of the cumulative uptake  
30 of O<sub>3</sub> (Weinstein et al., 1991, [043993](#))(Tingey et al., 2004, [042385](#)). Hogsett et al. (2008, [191229](#))  
31 used TREGRO to evaluate the effectiveness of various forms and levels of air quality standards for  
32 protecting tree growth in the San Bernardino Mountains of California. They found that O<sub>3</sub> exposures  
33 at the Crestline site resulted in a mean 20.9% biomass reduction from 1980 to 1985 and 10.3%  
34 biomass reduction from 1995 to 2000, compared to the “background” O<sub>3</sub> concentrations (O<sub>3</sub>

1 concentration in Crook County, Oregon). The level of vegetation protection projected was different  
2 depending on the air quality scenarios under consideration. Specifically, when air quality was  
3 simulated to just meet the California 8 h average maximum of 70 ppb and the maximum 3 months  
4 12-h SUM06 of 25 ppm-h, annual growth reductions were limited to 1% or less, while air quality  
5 that just met a previous NAAQS (the second highest 1-h max [125 ppb]) resulted in 6-7% annual  
6 reduction in growth, resulting in the least protection relative to background O<sub>3</sub> (Hogsett et al., 2008,  
7 [191229](#)).

8 Combining TREGRO with ZELIG, Weinstein et al. (2005, [179965](#)) simulated the effects of  
9 different O<sub>3</sub> levels ( 0.5, 1.5, 1.75, and 2 times ambient) on the growth and competitive interactions  
10 of white fir and ponderosa pine at three sites in California: Lassen National Park, Yosemite National  
11 Park, and Crestline. Their results suggested that O<sub>3</sub> had little impact on white fir, but greatly reduced  
12 the growth of ponderosa pine. If current O<sub>3</sub> concentrations continue over the next century, ambient  
13 O<sub>3</sub> exposure (SUM06 of 110 ppm-h) at Crestline was predicted to decrease individual tree C budget  
14 by 10% and decrease ponderosa pine abundance by 16%. Effects at Lassen National Park and  
15 Yosemite National Park sites were found to be smaller because of lower O<sub>3</sub> exposure levels  
16 (Weinstein et al., 2005, [179965](#)).

17 The effects of O<sub>3</sub> on stand productivity and dynamics were also studied by other tree growth or  
18 stand models, such as ECOPHYS, INTRAST and LINKAGES. ECOPHYS is a functional-structural  
19 tree growth model. The model used the linear relationship between the maximum capacity of  
20 carboxylation and O<sub>3</sub> dose to predict the relative effect of O<sub>3</sub> on leaf photosynthesis (Martin et al.,  
21 2001, [043678](#)). Simulations with ECOPHYS found that O<sub>3</sub> decreased stem dry matter production,  
22 stem diameter and leaf dry matter production, induced earlier leaf abscission, and inhibited root  
23 growth (Martin et al., 2001, [043678](#)). Simulation with INTRAST and LINKAGES showed similar  
24 adverse effects on stand growth. Linking INTRAST with LINKAGES, Hanson et al. (2005, [191461](#))  
25 found that a simulated increase O<sub>3</sub> concentration in 2100 (a mean 20-ppb increase over the current  
26 O<sub>3</sub> concentration) yields a 35% loss of net ecosystem C exchange (NEE) with respect to the current  
27 conditions (174 g C/m<sup>2</sup>/year).

### 9.6.2.2. Regional and Global Scales

28 Since the publication of the 2006 O<sub>3</sub> AQCD, there is additional evidence suggesting that O<sub>3</sub>  
29 exposure alters ecosystem productivity and biogeochemical cycling at the regional and continental-  
30 scale. Most of those studies were conducted by using process-based ecosystem models (Table 9-5)  
31 and are briefly reviewed in the following sections.

#### **Carbon Dynamics in Natural Ecosystems**

32 Results of Reich (1987, [019314](#)) and Tjoelker et al. (1995, [035394](#)) indicated that O<sub>3</sub> effects  
33 on photosynthesis can be determined as a function of O<sub>3</sub> uptake to internal leaf surface. Pooling data  
34 from Reich (1987, [019314](#)) and Tjoelker et al. (1995, [035394](#)), Ollinger et al. (1997, [040707](#))  
35 derived an equation to simulate the O<sub>3</sub> effects on photosynthesis by cumulative O<sub>3</sub> dose (AOT40)

1 and stomatal conductance. They incorporated this equation into the PnET-II model and studied the  
2 effect of O<sub>3</sub> on hardwood forest productivity of 64 hardwood sites in northeastern U.S. Their model  
3 indicated that O<sub>3</sub> caused a 3-16% reduction in NPP from 1987 to 1992 (Table 9-5). Ollinger et al.  
4 (2002, [180189](#)) assessed the interactive effects of O<sub>3</sub>, N deposition, elevated CO<sub>2</sub> and land use  
5 history on C dynamics by PnET-CN. Their results indicated that O<sub>3</sub> offset the increase in net  
6 C exchange caused by elevated CO<sub>2</sub> and N deposition by 13% (25.0 g C/m<sup>2</sup>/year) under agriculture  
7 site history, and 23% (33.6 g C/m<sup>2</sup>/year) under timber harvest site history. PnET-CN was also used to  
8 assess changes in C sequestration of U.S. Mid-Atlantic temperate forest. Pan et al. (2009, [596032](#))  
9 designed a factorial modeling experiment to separate the effects of changes in atmospheric  
10 composition, historical climatic variability and land-disturbances on the C cycle. They also found O<sub>3</sub>  
11 acted as a negative factor, partially offsetting the growth stimulation caused by elevated CO<sub>2</sub> and N  
12 deposition of U.S. Mid-Atlantic temperate forest. Ozone decreased NPP of most forest types by 7-  
13 8%. Among all the forest types, spruce-fir forest was most resistant to O<sub>3</sub> damage, and NPP  
14 decreased by only 1% (Pan et al., 2009, [596032](#)).

15 Felzer et al. (2004, [186927](#)) developed TEM 4.3 to simulate the effects of O<sub>3</sub> on plant growth.  
16 The effects of O<sub>3</sub> on NPP and C sequestration of deciduous trees, conifers and crops in the  
17 conterminous U.S. were estimated by TEM. The results indicated that O<sub>3</sub> reduced NPP and  
18 C sequestration in the U.S. (Table 9-5) and the largest decreases (over 13% in some locations) in  
19 NPP occurred in the Midwest agricultural lands during the mid-summer. TEM was also used to  
20 evaluate the magnitude of O<sub>3</sub> damage at a global scale (Table 9-5) (Felzer et al., 2005, [186928](#)).  
21 Simulations for the historical period (1860-1995) show that the largest reductions in NPP and net  
22 C exchange occurred in the mid western U.S., eastern Europe, and eastern China (Felzer et al., 2005,  
23 [186928](#)). DLEM was developed to simulate the detrimental effect of O<sub>3</sub> on ecosystems, and has been  
24 used to examine the O<sub>3</sub> damage on NPP and C sequestration in Great Smoky Mountains National  
25 Park (Zhang et al., 2007, [196983](#)), grassland ecosystems and terrestrial ecosystems in China (Ren et  
26 al., 2007, [581541](#))(Ren et al., 2007, [191366](#)). Results of those simulations are listed in Table 9-5.

27 Instead of using AOT40 as their O<sub>3</sub> exposure metric as PnET, TEM and DLEM did, Sitch et al.  
28 (2007, [093294](#)) incorporated a different O<sub>3</sub> metric named CUOt (cumulative stomatal uptake of O<sub>3</sub>),  
29 derived from Pleijel et al. (2004, [056608](#)), into the MOSES-TRIFFID coupled model. In the CUOt  
30 metric, the fractional reduction of plant production is dependent on O<sub>3</sub> uptake by stomata over a  
31 critical threshold for damage and this threshold level is different for different plant functional types.  
32 Consistent with previous studies, their model simulation indicated that O<sub>3</sub> reduced global gross  
33 primary production (GPP), C exchange rate and C sequestration (Table 9-5). The largest reductions  
34 in GPP and land-C storage were projected over North America, Europe, China and India. In the  
35 model, reduced ecosystem C uptake due to O<sub>3</sub> damage, results in additional CO<sub>2</sub> accumulation in the  
36 atmosphere and an indirect radiative forcing of climate change. Their simulations indicated that the  
37 indirect radiative forcing caused by O<sub>3</sub> (0.62-1.09 W/m<sup>2</sup>) could have even greater impact on global  
38 warming than the direct radiative forcing of O<sub>3</sub> (0.89 W/m<sup>2</sup>) (Sitch et al., 2007, [093294](#)).

## Crop Yield Loss

1 Two large scale field studies were conducted in the U.S. (NCLAN) and in Europe (European  
2 Open Top Chamber Programme, EOTCP) to assess the impact of O<sub>3</sub> on crop production. Ozone  
3 exposure-response regression models derived from the two programs have been widely used to  
4 estimate crop yield loss (Wang and Mauzerall, 2004, [179978](#))(Tong and Mauzerall, 2008,  
5 [621169](#))(Van Dingenen et al., 2009, [199765](#)). Those studies found that O<sub>3</sub> generally reduced crop  
6 yield and different crops showed different sensitivity to O<sub>3</sub> pollution (Table 9-5). Ozone was  
7 calculated to induce a possible 45-82 million metric tons loss for wheat globally. Production losses  
8 for rice, maize and soybean were on the order of 17-23 million metric tons globally (Van Dingenen  
9 et al., 2009, [199765](#)). The largest yield losses occur in high-production areas exposed to high O<sub>3</sub>  
10 concentrations, such the Midwest and the Mississippi Valley regions in the U.S., Europe, China and  
11 India (Van Dingenen et al., 2009, [199765](#))(Tong et al., 2007, [107431](#)).

**Table 9-5. The effects of ozone on primary production, C exchange, C sequestration and yield loss**

	Scale	Model	Index	Ozone Impacts	Reference
GPP	Global	MOSES-TRIFFID	CUOta	Decreased by 14-23% over the period 1901-2100	Sitch et al. (2007, <a href="#">093294</a> )
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, <a href="#">186928</a> )
	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, <a href="#">186928</a> )
	U.S.	TEM	AOT40	Reduced by 2.6–6.8% during the late 1980s-early 1990s.	Felzer et al. (2004, <a href="#">186927</a> )
	northeastern U.S.	PnET	AOT40	A reduction of 3-16% from 1987-1992	Ollinger et al. (1997, <a href="#">040707</a> )
	U.S. Mid-Atlantic	PnET	AOT40	Decreased NPP of most forest types by 7-8%	Pan et al. (2009, <a href="#">596032</a> )
	China	DLEM	AOT40	Reduced NPP of grassland in China by 8.5 Tg C from 1960s to 1990s	Ren et al. (2007, <a href="#">581541</a> )
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, <a href="#">186928</a> )
	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 <sub>3</sub> sensitivity models, respectively	Sitch et al. (2007, <a href="#">093294</a> )
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, <a href="#">093294</a> )
	U.S.	TEM	AOT40	Reduced C sequestration by 18–38 Tg C/yr from 1950 to 1995	Felzer et al. (2004, <a href="#">186927</a> )
	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. (2007, <a href="#">196983</a> )
	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. (2007, <a href="#">191366</a> )
Crop yield loss	Global	Dose–response function	M7b; M12c; 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, <a href="#">199765</a> )
	U.S.	Dose–response function	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, <a href="#">199765</a> )
	U.S.	Dose–response function	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, <a href="#">107431</a> )
	East Asia	Dose–response function	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, <a href="#">179978</a> )

<sup>a</sup>CUOt is defined as the cumulative stomatal uptake of O<sub>3</sub>, using a constant O<sub>3</sub>-uptake rate threshold of t nmol/m<sup>2</sup>/s.

<sup>b</sup>M7 is defined as 7-h mean O<sub>3</sub> concentration (ppb).

<sup>c</sup>M12 is defined as 12-h mean O<sub>3</sub> concentration (ppb).

<sup>d</sup>Pg equals 1 × 10<sup>15</sup> grams.

### 9.6.3. Water Cycling

1 Ozone has been shown to alter stomatal performance, which affects plant and stand  
2 transpiration and therefore hydrological cycling. However, there is not a clear consensus on stomatal  
3 response to O<sub>3</sub> exposure. A meta-analysis found that O<sub>3</sub> reduced stomatal conductance by 11%  
4 (Wittig et al., 2007, [191695](#)). Stomatal closure could help protect the plant from water loss. On the  
5 other hand, a number of studies suggested that O<sub>3</sub> exposure could impair stomatal function, which  
6 leads to greater stomatal apertures, delays stomatal closure at night and results in higher transpiration  
7 (Grulke et al., 2004, [042646](#))(McLaughlin et al., 2007, [090348](#))(McLaughlin et al., 2007,

1 [090347](#))(Mills et al., 2009, [191272](#))(Wilkinson and Davies, 2009, [199758](#))(Wilkinson and Davies,  
2 2010, [598245](#)). This O<sub>3</sub>-induced impairment of stomatal control may be more pronounced for plants  
3 growing under drought stress (McLaughlin et al., 2007, [090348](#))(McLaughlin et al., 2007,  
4 [090347](#))(Wilkinson and Davies, 2010, [598245](#)). The discrepancy regarding stomatal function has  
5 lead to further debate on the effects of O<sub>3</sub> on ecosystem water production.

6 Felzer et al. (2009, [191460](#)) used TEM-Hydro to assess the interactions of O<sub>3</sub>, climate,  
7 elevated CO<sub>2</sub> and N limitation on the hydrological cycle in the eastern U.S. They found that elevated  
8 CO<sub>2</sub> decreased evapotranspiration by 2-4% and increased runoff by 3-7%, as compared to the effects  
9 of climate alone. When O<sub>3</sub> damage and N limitation were included, evapotranspiration was reduced  
10 by an additional 4-7% and runoff was increased by an additional 6-11% (Felzer et al., 2009,  
11 [191460](#)). Based upon simulation with INTRAST and LINKAGES, Hanson et al. (2005, [191461](#))  
12 found that increasing O<sub>3</sub> concentration by 20 ppb above the current ambient level yields a modest  
13 3% reduction in water use. Those ecological models were generally built on the assumption that O<sub>3</sub>  
14 induces stomatal closure. Therefore, results of those models normally found that O<sub>3</sub> reduced water  
15 use.

16 In contrast to the model simulations (Hanson et al., 2005, [191461](#))(Felzer et al., 2009,  
17 [191460](#)), field studies conducted by McLaughlin et al. (2007, [090348](#))(2007, [090347](#)) indicated that  
18 O<sub>3</sub> increases water use in a mixed deciduous forest in eastern Tennessee. McLaughlin et al. (2007,  
19 [090348](#))(2007, [090347](#)) found that O<sub>3</sub>, with daily maximum levels ranging from 69.2 to 82.9 ppb,  
20 reduced stem growth by 30-50% in the high-O<sub>3</sub> year 2002. The decrease in growth rate was caused  
21 in part by amplification of diurnal cycles of water loss and recovery. Peak hourly O<sub>3</sub> exposure  
22 increased the rate of water loss through transpiration as indicated by the increased stem sap flow.  
23 The increased canopy conductance resulted in higher water uptake as reflected in the reduced soil  
24 moisture in the 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 O<sub>3</sub> exposure was reported to reduce late-  
26 season modeled streamflow in three forested watersheds in eastern Tennessee (McLaughlin et al.,  
27 2007, [090347](#)).

28 In addition to the impacts on stomatal performance, O<sub>3</sub>-induced physiological changes, such as  
29 reduced leaf area index and accelerated leaf senescence, could alter water use efficiency. At the  
30 Aspen FACE experiment, stand-level water use, as indicated by sap flux per unit ground area, was  
31 not significantly affected by elevated O<sub>3</sub> despite a 22% decrease in leaf area index and 20% decrease  
32 in basal area (Uddling et al., 2008, [191655](#)). Several factors could contribute to the lack of negative  
33 effect of elevated O<sub>3</sub> on stand water use. The maximum sap flux per unit total leaf area was  
34 substantially increased by elevated O<sub>3</sub>, suggesting that whole-plant hydraulic conductance per unit  
35 leaf area was increased (Uddling et al., 2009, [596219](#)). Other potential contributing factors included  
36 the higher proportion of sun leaves, and similar or even increased fine root biomass under elevated  
37 O<sub>3</sub> (Uddling et al., 2008, [191655](#)). Elevated O<sub>3</sub> could also affect evapotranspiration by altering tree  
38 crown interception of precipitation. Ozone has been shown to change branch architectural  
39 parameters, and the effects were species specific at the Aspen FACE experiment (Rhea et al., 2010,

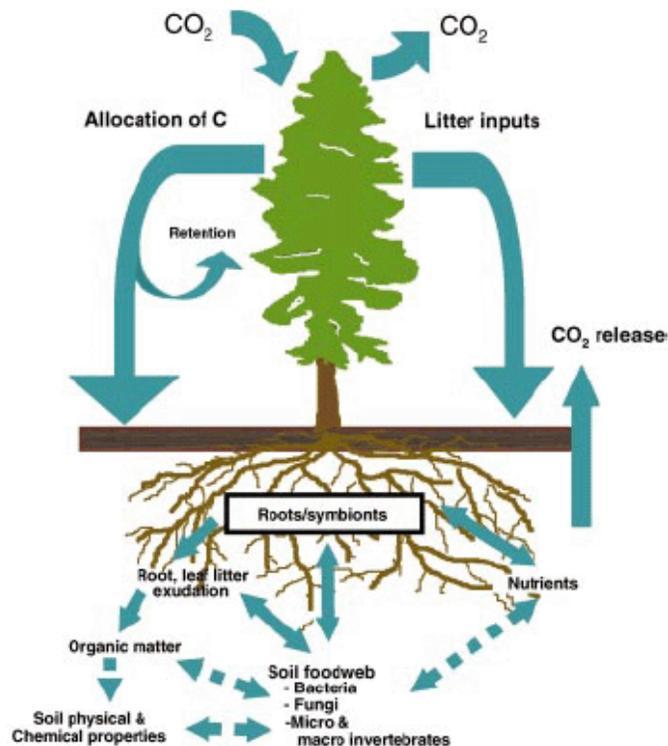
1 [647084](#)). The authors found that there was a significant correlation between canopy architecture  
2 parameters and stem flow for birch but not aspen.

#### 9.6.4. Below-Ground Processes

3 Above-ground and below-ground processes are tightly interconnected. Because roots and soil  
4 organisms are not exposed directly to O<sub>3</sub>, below-ground processes are affected by O<sub>3</sub> more through  
5 altering the quality and quantity of C supply from photosynthates and litterfall (Andersen, 2003,  
6 [041673](#)). Ozone can decrease leaf C uptake by altering stomatal function, reducing the activity and  
7 concentration of Rubisco, and accelerating leaf senescence (Section 9.4). Ozone can also increase  
8 the metabolic costs by stimulating the production of chemical compounds for defense and repair  
9 processes, and increasing the synthesis of antioxidants to neutralize free radicals (see Section 9.4),  
10 which increase the consumption of carbon for above-ground processes. Therefore, O<sub>3</sub> could  
11 significantly reduced the amount of C available for allocation to below-ground by decreasing  
12 C uptake but increasing C consumption of above-ground processes (Andersen, 2003, [041673](#)).

13 Since the 2006 O<sub>3</sub> AQCD, there is additional evidence for O<sub>3</sub> effects on below-ground  
14 processes. Ozone has been found to alter root growth, soil food web structure, decomposer activities,  
15 C turnover and nutrient flow (Figure 9-7). Ozone effects on root development and root biomass  
16 production (Section 9.5.2.1) and soil food web structure (Section 9.6.5.3) are reviewed in other  
17 sections. The focus in this section is on the response of litter input, decomposer activities, soil  
18 respiration, soil C formation and nutrient cycling.

## Carbon movement in plant and soil



Source: Used with permission from Andersen (2003, [041673](#))

**Figure 9-7.** Conceptual diagram showing where ozone disrupts C flow in a tree-soil system, including transfer between biotic and abiotic components below ground that influence soil physical and chemical properties. Arrows denote C flux pathways that are affected by ozone. Dashed lines indicate where the impact of ozone is suspected but unknown.

### 9.6.4.1. Litter Carbon Chemistry, Litter Nutrient and Their Ecosystem Budgets

Consistent with previous findings, recent studies show that, although the responses are often species specific, O<sub>3</sub> tends to alter litter chemistry (U.S. EPA, 2006, [088089](#)). Alterations in chemical parameters, such as changes in C chemistry and nutrient concentrations, were observed in both leaf and root litter (Table 9-6).

At the Aspen FACE site, several studies investigated litter chemistry changes (Chapman et al., 2005, [191345](#))(Liu et al., 2005, [187005](#))(Johnson and Pregitzer, 2007, [191287](#))(Parsons et al., 2008, [191853](#)). In both aspen and birch leaf litter, elevated O<sub>3</sub> increased the concentrations of soluble sugars, soluble phenolics and condensed tannins (Liu et al., 2005, [187005](#))(Parsons et al., 2008, [191853](#)). Compared to other treatments, aspen litter under elevated O<sub>3</sub> had the highest fiber concentration, with the lowest concentration associated with the birch litter under the same conditions (Parsons et al., 2008, [191853](#)). Chapman et al. (2005, [191345](#)) measured chemical changes in fine root litter and found that elevated O<sub>3</sub> decreased lignin concentration. The O<sub>3</sub>-induced

1 chemistry changes were also reported from other experimental sites. Results from an OTC study in  
 2 Finland suggested that elevated O<sub>3</sub> increased the concentration of acid-soluble lignin, but had no  
 3 significant impact on other chemicals such as total sugars, hemicelluloses, cellulose or total lignin in  
 4 the litter of silver birch (Kasurinen et al., 2006, [191269](#)). Results from the free air canopy O<sub>3</sub>  
 5 exposure experiment at Kranzberg Forest, showed that O<sub>3</sub> increased starch concentrations but had no  
 6 impact on cellulose and lignin in beech and spruce leaf litter (Aneja et al., 2007, [191472](#)). The effect  
 7 of O<sub>3</sub> on three antioxidants (ascorbate, glutathione and α-tocopherol) in fine roots of beech was also  
 8 assessed at Kranzberg Forest. The results indicated that O<sub>3</sub> had no significant effect on α-tocopherol  
 9 and ascorbate concentrations, but decreased glutathione concentrations in fine roots (Haberer et al.,  
 10 2008, [191334](#)). In addition to changing C chemistry, O<sub>3</sub> also altered nutrient concentrations in green  
 11 leaves and litter (Table 9-6).

12 The combined effects of O<sub>3</sub> on biomass productivity and chemistry changes could alter  
 13 C chemicals and nutrient contents at the canopy or ecosystem level. For example, although O<sub>3</sub> had  
 14 different impacts on their concentrations, annual fluxes of C chemicals (soluble sugar, soluble  
 15 phenolics, condensed tannins, lipid and hemicelluloses), macro nutrients (N, P, K and S) and micro  
 16 nutrients (Mg, B, Cu and Zn) to soil were all reduced due to lower litter biomass productivity at  
 17 Aspen FACE (Liu et al., 2005, [187005](#))(Liu et al., 2007, [093286](#)). At the Kranzberg Forest, N  
 18 content of spruce canopy in a mixed culture and Ca<sup>2+</sup> content of beech canopy in a monoculture  
 19 increased due to elevated O<sub>3</sub> increased leaf concentrations of those nutrients although leaf production  
 20 was not significantly altered by O<sub>3</sub> (Rodenkirchen et al., 2009, [191540](#)).

**Table 9-6. The effect of elevated ozone on leaf/litter nutrient concentrations**

Study Site	Species	Ozone Concentration	Response	Reference
Suonenjoki Research Station, Finland	Silver birch	Ambient: 10-60 ppb Elevated: 2xambient	Decreased the concentration of P, Mn, Zn and B in leaf litter	Kasurinen et al. (2006, <a href="#">191269</a> )
Aspen FACE	Aspen and birch	Ambient: 50-60 ppb Elevated: 1.5xambient	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 href="#">093286</a> )
Aspen FACE	Birch	Ambient: 50-60 ppb Elevated: 1.5xambient	Increase N concentration in birch litter	Parsons et al. (2008, <a href="#">191853</a> )
Kranzberg Forest, Germany	Beech and spruce	Ambient: 9-41 ppb Elevated: 2xambient	Increased N concentration in beech leaf, but not in spruce needle	Kozovits et al. (2005, <a href="#">191282</a> )
Kranzberg Forest, Germany	Beech and spruce	Ambient: 9-41 ppb Elevated: 2xambient	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, <a href="#">191540</a> )

#### 9.6.4.2. Decomposer Metabolism and Litter Decomposition

21 The above- and below-ground physiological changes caused by O<sub>3</sub> exposure cascade through  
 22 the ecosystem and affect soil food webs. In the 2006 O<sub>3</sub> AQCD, there were very few studies on the  
 23 effect of O<sub>3</sub> on the structure and function of soil food webs, except two studies conducted by Larson  
 24 et al. (2002, [053015](#)) and Phillips et al. (2002, [041768](#)). Since the last O<sub>3</sub> AQCD (U.S. EPA, 2006,

1 [088089](#)), new studies have provided more information on how O<sub>3</sub> affects the metabolism of soil  
2 microbes and soil fauna.

3 Chung et al.(2006, [191729](#)) found that the activity of the cellulose-degrading enzyme 1,4-β-  
4 glucosidase was reduced by 25% under elevated O<sub>3</sub> at AspenFACE. The decrease in cellulose-  
5 degrading enzymatic activity was associated with the lower cellulose availability under elevated O<sub>3</sub>  
6 (Chung et al., 2006, [191729](#)). The suppression of soil enzyme activities was also found in the  
7 rhizosphere of beech trees (*Fagus sylvatica*) in a lysimeter study in Germany (Esperschütz et al.,  
8 2009, [595669](#))(Pritsch et al., 2009, [626808](#)). Except for xylosidase, enzyme activities involved in  
9 plant cell wall degradation (cellobiohydrolase, beta-glucosidase and glucuronidase) were decreased  
10 in rhizosphere soil samples under elevated O<sub>3</sub> (2 × ambient level) (Pritsch et al., 2009, [626808](#)).  
11 Similarly, Chen et al. (2009, [191452](#)) found O<sub>3</sub> exposure, with a 3-month AOT40 of  
12 21.4-44.1 ppm-h, decreased the microbial metabolic capability in the rhizosphere and bulk soil of  
13 wheat, although the observed reduction in bulk soil was not significant.

14 Ozone-induced change in soil organisms' activities could affect litter decomposition rates.  
15 However, no general decomposition pattern has been identified. The responses varied among  
16 species, sites and exposure length. Parsons et al. (2008, [191853](#)) collected litter from aspen and birch  
17 seedlings at AspenFACE site, and conducted a 23-month field litter incubation starting in 1999. They  
18 found that elevated O<sub>3</sub> had different impacts on the decomposition of aspen and birch litter. Elevated  
19 O<sub>3</sub> was found to reduce aspen litter decomposition. However, O<sub>3</sub> accelerated birch litter  
20 decomposition under ambient CO<sub>2</sub>, but reduced it under elevated CO<sub>2</sub> (Parsons et al., 2008, [191853](#)).  
21 Liu et al. (2009, [191470](#)) conducted another litter decomposition study at Aspen FACE from 2003 to  
22 2006, when stand leaf area index (LAI) reached its maximum. During the 935-day field incubation,  
23 elevated O<sub>3</sub> was shown to reduce litter mass loss in the first year, but not in the second year. They  
24 suggested that higher initial tannin and phenolic concentrations under elevated O<sub>3</sub> reduced microbial  
25 activity in the first year (Liu et al., 2009, [191470](#)). In an OTC experiment, Kasurinen et al. (2006,  
26 [191269](#)) collected silver birch leaf litter from three consecutive growing seasons and conducted three  
27 separate litter-bag incubation experiments. Litter decomposition was not affected by O<sub>3</sub> exposure in  
28 the first two incubations, but a slower decomposition rate was found in the third incubation. Their  
29 principle component analysis indicated that the litter chemistry changes caused by O<sub>3</sub> (decreased  
30 Mn, P, B and increased C:N) might be partially responsible for the decreased mass loss of their third  
31 incubation.

### 9.6.4.3. Soil respiration and carbon formation

32 Ozone could reduce the availability of photosynthates for export to roots, and increase root  
33 mortality and turnover rates. Ozone has also been shown to reduce above-ground litter productivity  
34 and alter litter chemistry, which would affect the quality and quantity of the C supply to soil  
35 organisms (Section 9.6.6.1). The complex interactions among those changes make it difficult to  
36 predict the response of soil C cycling under elevated O<sub>3</sub>. The 2006 O<sub>3</sub> AQCD concluded that O<sub>3</sub> had  
37 no consistent impact on soil respiration (U.S. EPA, 2006, [088089](#)). Ozone could increase or decrease

1 soil respiration, depending on the approach and timing of the measurements. Ozone may also alter  
 2 soil C formation. However, very few experiments directly measured changes in soil organic matter  
 3 content under O<sub>3</sub> fumigation (U.S. EPA, 2006, [088089](#)). Recent studies on soil respiration and soil  
 4 C content also found mixed responses. Most importantly, new publications derived from long-term  
 5 fumigation experiments, such as the Aspen FACE experiment, suggest that ecosystem response to O<sub>3</sub>  
 6 exposure can change over time. Observations made during the late exposure years can be  
 7 inconsistent with those during the early years, highlighting the need for caution to assess O<sub>3</sub> effects  
 8 based on short-term studies (Table 9-7).

**Table 9-7. The temporal variation of ecosystem responses to ozone exposure at AspenFACE site**

Endpoint	The Time of the Measurement	Response	Reference
Litter decomposition	1999-2001	O <sub>3</sub> reduced aspen litter decomposition. However, O <sub>3</sub> accelerated birch litter decomposition under ambient CO <sub>2</sub> , but reduced it under elevated CO <sub>2</sub>	Parsons et al. (2008, <a href="#">191853</a> )
	2003-2006	O <sub>3</sub> reduced litter mass loss in the first year, but not in the second year.	Liu et al. (2009, <a href="#">191470</a> )
Fine root production	1999	O <sub>3</sub> had no significant impact on fine root biomass	King et al. (2001, <a href="#">041751</a> )
	2002, 2005	O <sub>3</sub> increased fine root biomass	Pregitzer et al. (2008, <a href="#">191677</a> )
Soil respiration	1998-1999	Soil respiration under +CO <sub>2</sub> +O <sub>3</sub> treatment was lower than that under +CO <sub>2</sub> treatment	King et al. (2001, <a href="#">041751</a> )
	2003-2007	Soil respiration under +CO <sub>2</sub> +O <sub>3</sub> treatment was 5-25% higher than under elevated CO <sub>2</sub> treatment.	Pregitzer et al. (2006, <a href="#">191676</a> ), Pregitzer et al. (2008, <a href="#">191677</a> )
Soil C formation	1998-2001	O <sub>3</sub> reduced the formation rates of total soil C by 51% and acid-insoluble soil C by 48%	Loya et al. (2003, <a href="#">074380</a> )
	2004-2008	No significant effect of O <sub>3</sub> on the new C formed under elevated CO <sub>2</sub>	Talhelm et al. (2009, <a href="#">596189</a> )

## Soil Respiration

9 Ozone has shown inconsistent impacts on soil respiration. A sun-lit controlled-environment  
 10 chamber study found that O<sub>3</sub> had no significant effects on soil respiration, fine root biomass or any  
 11 of the soil organisms in a reconstructed ponderosa pine/soil-litter system (Tingey et al., 2006,  
 12 [191341](#)). In an adult European beech/Norway spruce forest at Kranzberg Forest, the free air O<sub>3</sub>  
 13 fumigation (AOT40 of 10.2-117 ppm-h) increased soil respiration under both beech and spruce  
 14 during a humid year (Nikolova et al., 2010, [626810](#)). The increased soil respiration under beech has  
 15 been accompanied by the increase in fine root biomass and ectomycorrhizal fungi diversity and  
 16 turnover (Grebenc and Kraigher, 2007, [191265](#)). The stimulating effect on soil respiration  
 17 disappeared under spruce in a dry year, which was associated with a decrease in fine root production  
 18 in spruce under drought. This finding suggested that drought was a more dominant stress than O<sub>3</sub> for  
 19 spruce (Nikolova et al., 2010, [626810](#)). Andersen et al. (2010, [628559](#)) labeled the canopies of  
 20 European beech and Norway spruce with CO<sub>2</sub> depleted in <sup>13</sup>C at the same site. They did not observe  
 21 any significant changes in soil respiration for either species.

22 The nearly 10 year long studies at AspenFACE indicated that the response of soil respiration to  
 23 O<sub>3</sub> interacted with CO<sub>2</sub> exposure and varied temporally (Table 9-7) (King et al., 2001,  
 24 [041751](#))(Pregitzer et al., 2006, [191676](#))(Pregitzer et al., 2008, [191677](#)). Ozone treatment alone

1 generally had the lowest mean soil respiration rates, although those differences between control and  
2 elevated O<sub>3</sub> were usually not significant. However, soil respiration rates were different with O<sub>3</sub> alone  
3 and when acting in combination with elevated CO<sub>2</sub>. In the first five years (1998-2002), soil  
4 respiration under +CO<sub>2</sub>+O<sub>3</sub> treatment was similar to that under control and lower than that under  
5 +CO<sub>2</sub> treatment (King et al., 2001, [041751](#))(Pregitzer et al., 2006, [191676](#)). Since 2003, +CO<sub>2</sub>+O<sub>3</sub>  
6 treatment started to show the greatest impact on soil respiration. Compared to elevated CO<sub>2</sub>, soil  
7 respiration rate under +CO<sub>2</sub>+O<sub>3</sub> treatment was 15-25% higher from 2003-2004, and 5-10% higher  
8 from 2005-2007 (Pregitzer et al., 2006, [191676](#))(Pregitzer et al., 2008, [191677](#)). Soil respiration was  
9 highly correlated with the biomass of roots with diameters of <2 mm and <1 mm, across plant  
10 community and atmospheric treatments. The authors suggested that the increase in soil respiration  
11 rate may be due to +CO<sub>2</sub>+O<sub>3</sub> increased fine root (<1.0 mm) biomass production (Pregitzer et al.,  
12 2008, [191677](#)).

### Soil Carbon Formation

13 Ozone-induced reductions in plant growth can result in reduced C input to soil and therefore  
14 soil C content (Andersen, 2003, [041673](#)). The simulations of most ecosystem models support this  
15 prediction (Felzer et al., 2004, [186927](#))(Zhang et al., 2007, [196983](#))(Ren et al., 2007, [191366](#)).  
16 However, very few studies have directly measured soil C dynamics under elevated O<sub>3</sub>. After the first  
17 four years of fumigation (from 1998 to 2001) at the Aspen FACE site, Loya et al. (2003, [074380](#))  
18 found that forest stands exposed to both elevated O<sub>3</sub> and CO<sub>2</sub> accumulated 51% less total soil C, and  
19 48% less acid-insoluble soil C compared to stands exposed only to elevated CO<sub>2</sub>. Soil organic carbon  
20 (SOC) was continuously monitored at the Aspen FACE site, and the later data showed that the initial  
21 reduction in new C formation (soil C derived from plant litter since the start of the experiment) by  
22 O<sub>3</sub> under elevated CO<sub>2</sub> is only a temporary effect (Table 9-7) (Talhelm et al., 2009, [596189](#)). The  
23 amount of new soil C in the elevated CO<sub>2</sub> and the combined elevated CO<sub>2</sub> and O<sub>3</sub> treatments has  
24 converged since 2002. There was no significant effect of O<sub>3</sub> on the new C formed under elevated  
25 CO<sub>2</sub> over the last four years of the study (2004-2008). Talhelm et al. (2009, [596189](#)) suggested the  
26 observed reduction in the early years of the experiment might be driven by a suppression of  
27 C allocated to fine root biomass. During the early exposure years, O<sub>3</sub> had no significant impact on  
28 fine root production (King et al., 2001, [041751](#)). However, the effect of O<sub>3</sub> on fine root biomass was  
29 observed later in the experiment. Ozone increased fine root production and the highest fine root  
30 biomass was observed under the combined elevated CO<sub>2</sub> and O<sub>3</sub> treatment in the late exposure years  
31 (Table 9-7) (Pregitzer et al., 2006, [191676](#)). This increase in fine root production was due to changes  
32 in community composition, such as better survival of O<sub>3</sub>-tolerant aspen genotype, birch and maple,  
33 rather than changes in C allocation at the individual tree level (Pregitzer et al., 2008, [191677](#))(Zak et  
34 al., 2007, [191239](#)).

#### 9.6.4.4. Nutrient cycling

1 Nutrient cycling is important for sustaining ecosystem production. Ozone can affect nutrient  
2 cycling by changing nutrient release from litter and uptake by plants. Nitrogen is the limiting  
3 nutrient for most ecosystems, and several studies examined N dynamics under elevated O<sub>3</sub>. Holmes  
4 et al. (2006, [191372](#)) found that elevated O<sub>3</sub> decreased gross N mineralization at the Aspen FACE  
5 site, indicating that O<sub>3</sub> may reduce N availability. However, other N cycling processes, such as NH<sub>4</sub><sup>+</sup>  
6 immobilization, gross nitrification, microbial biomass N and soil organic N, were not affected by  
7 elevated O<sub>3</sub> (Holmes et al., 2006, [191372](#)). Similarly, Kanerva et al. (2006, [191747](#)) found total N,  
8 NO<sub>3</sub><sup>-</sup>, microbial biomass N, potential nitrification and denitrification in their meadow mesocosms  
9 were not affected by elevated O<sub>3</sub> (40-50 ppb). Ozone also showed small impact on other micro and  
10 macro nutrients. Liu et al. (2007, [093286](#)) assessed N, P, K, S, Ca, Mg, Mn, B, Zn and Cu release  
11 dynamics at Aspen FACE, and they found that O<sub>3</sub> had no effects on most nutrients, except to  
12 decrease N and Ca release from litter.

13 Using the SImple NItrogen Cycle model (SINIC), Hong et al. (2006, [186989](#)) evaluated the  
14 impacts of O<sub>3</sub> exposure on soil N dynamics and streamflow nitrate flux. The detrimental effect of O<sub>3</sub>  
15 on plant growth was found to reduce plant uptake of N and therefore increase nitrate leaching. Their  
16 model simulation indicated that ambient O<sub>3</sub> exposure increased the mean annual stream flow nitrate  
17 export by 12% (0.042 g N/m<sup>2</sup>/year) at the Hubbard Brook Experimental Watershed from 1964-1994  
18 (Hong et al., 2006, [186989](#)).

#### 9.6.4.5. Dissolved Organic Carbon and Biogenic Trace Gases Emission

19 The O<sub>3</sub>-induced changes in plant growth, C and N fluxes to soil and microbial metabolism can  
20 alter other biogeochemical cycling processes, such as soil dissolved organic carbon (DOC) turnover  
21 and trace gases emission.

22 Jones et al. (2009, [199881](#)) collected fen cores from two peatlands in North Wales, UK and  
23 exposed them to one of four levels of O<sub>3</sub> (AOT40 of 0, 3.69, 5.87 and 13.80 ppm-h for 41 days).  
24 They found the concentration of porewater DOC in fen cores was significantly decreased by  
25 increased O<sub>3</sub> exposure. A reduction of the low molecular weight fraction of DOC was concurrent  
26 with the observed decrease in DOC concentration. Their results suggested that O<sub>3</sub> damage to  
27 overlying vegetation may decrease utilizable C flux to soil. Microbes, therefore, have to use labile C  
28 in the soil to maintain their metabolism, which, the authors hypothesized, leads to a decreased DOC  
29 concentration with a shift of the DOC composition to more aromatic, higher molecular weight  
30 organic compounds.

31 Several studies since the 2006 O<sub>3</sub> AQCD have examined the impacts of O<sub>3</sub> on nitrous oxide  
32 (N<sub>2</sub>O) and methane (CH<sub>4</sub>) emission. Kanerva et al. (2007, [191405](#)) measured the fluxes of N<sub>2</sub>O and  
33 CH<sub>4</sub> in meadow mesocosms, which were exposed to elevated CO<sub>2</sub> and O<sub>3</sub> in OTCs in south-western  
34 Finland. They found that the daily N<sub>2</sub>O fluxes were decreased in the NF+O<sub>3</sub> (non-filtered air +  
35 elevated O<sub>3</sub>, 40-50 ppb) after three seasons of exposure. Elevated O<sub>3</sub> alone or combined with CO<sub>2</sub>

1 did not have any significant effect on the daily fluxes of CH<sub>4</sub> (Kanerva et al., 2007, [191405](#)). In  
2 another study conducted in central Finland, the 4 year open air O<sub>3</sub> fumigation (AOT40 of 20.8-  
3 35.5 ppm-h for growing season) also did not affect the rate of potential CH<sub>4</sub> production, but it  
4 slightly increased potential CH<sub>4</sub> oxidation by 15% in the peatland microcosms (Morsky et al., 2008,  
5 [191507](#)). However, O<sub>3</sub> has no overall effects on CH<sub>4</sub> emissions, which is the net result of the  
6 potential CH<sub>4</sub> production and oxidation (Morsky et al., 2008, [191507](#)).

### 9.6.5. Competition and biodiversity

7 The effects of O<sub>3</sub> on species competition (AX9.3.3.4) and community composition (AX9.6.4)  
8 were summarized in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)). Plant species differ in their  
9 sensitivity to O<sub>3</sub>. Fast growing plants with high stomatal conductance and high specific leaf area  
10 (SLA) were more likely to be sensitive to O<sub>3</sub> exposure. Further, different genotypes of a given  
11 species also vary in their sensitivity. This differential sensitivity could change the competitive  
12 interactions that lead to loss in O<sub>3</sub> sensitive species or genotypes. A shift in community composition  
13 in forest and grassland ecosystems noted in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) has  
14 continued to be observed from experimental and gradient studies. Additionally, research since the  
15 last review has shown that O<sub>3</sub> can alter community composition and diversity of soil microbial  
16 communities.

#### 9.6.5.1. Forest

17 In the San Bernardino Mountains in southern California, O<sub>3</sub> pollution caused a significant  
18 decline in ponderosa pine (*Pinus ponderosa*) and Jeffrey pine (*Pinus jeffreyi*) (U.S. EPA, 2006,  
19 [088089](#)). Pine trees in the young mature age class group exhibited higher mortality rates compared  
20 with mature trees at a site with severe O<sub>3</sub> visible foliar injury. The vulnerability of young mature  
21 pines was most likely caused by the fact that trees in this age class were emerging into the canopy,  
22 where higher O<sub>3</sub> concentrations were encountered (McBride and Laven, 1999, [053050](#)). Because of  
23 the loss of O<sub>3</sub>-sensitive pines, mixed forests of ponderosa pine, Jeffrey Pine and white fir (*Abies*  
24 *concolor*) shifted to predominantly white fir (Miller, 1973, [039165](#)). Ozone may have indirectly  
25 caused the decline in understory diversity in coniferous forests in the San Bernardino Mountains  
26 through an increase in pine litterfall. This increase in litterfall from O<sub>3</sub> exposure results in an  
27 understory layer that may prohibit the establishment of native herbs, but not exotic annual *Galium*  
28 *aparine* (Allen et al., 2007, [196876](#)).

29 Ozone damage to conifer forests has also been observed in several other regions. In the Valley  
30 of Mexico, a widespread mortality of sacred fir (*Abies religiosa*) was observed in the heavily  
31 polluted area of the Desierto de los Leones National Park in the early 1980s (de Lourdes de Bauer  
32 and Hernandez-Tejeda, 2007, [196891](#))(Fenn et al., 2002, [626806](#)). Ozone damage was widely  
33 believed to be an important causal factor in the dramatic decline of sacred fir. In alpine regions of  
34 southern France and the Carpathians Mountains, O<sub>3</sub> was also considered as the major cause of the

1 observed decline in cembran pine (*Pinus cembra*)(Wieser et al., 2006, [191391](#)). However, for those  
2 pollution gradient studies, several possible factors, such as drought, insect outbreak and forest  
3 management, may also contribute to the mortality of trees (de Lourdes de Bauer and Hernandez-  
4 Tejada, 2007, [196891](#))(Wieser et al., 2006, [191391](#)).

5 New evidence from long-term free O<sub>3</sub> fumigation experiments provided additional support for  
6 the potential impacts of O<sub>3</sub> on species competition and community composition changes in forest  
7 ecosystems. At the Aspen FACE site, community composition at both the genetic and species levels  
8 was altered after seven years of fumigation with O<sub>3</sub> (Kubiske et al., 2007, [191336](#)). In the pure aspen  
9 community, O<sub>3</sub> fumigation reduced growth and increased mortality of sensitive clone 259, while the  
10 O<sub>3</sub> tolerant clone 8L emerged as the dominant clone. Growth of clone 8L was even greater under  
11 elevated O<sub>3</sub> compared to controls, probably due to O<sub>3</sub> alleviated competitive pressure on clone 8L by  
12 reducing growth of other clones. In the mixed aspen-birch and aspen-maple communities, O<sub>3</sub>  
13 reduced the competitive capacity of aspen compared to birch and maple (Kubiske et al., 2007,  
14 [191336](#)). In a phytotron study, O<sub>3</sub> fumigation reduced growth of beech but not spruce in mixed  
15 culture, suggesting a higher susceptibility of beech to O<sub>3</sub> under interspecific competition (Kozovits  
16 et al., 2005, [191282](#)).

#### 9.6.5.2. Grassland and Agricultural Land

17 The response of managed pasture, often cultivated as a mixture of grasses and clover, to O<sub>3</sub>  
18 pollution has been studied for many years. The tendency for O<sub>3</sub>-exposure to shift the biomass of  
19 grass-legume mixtures in favor of grass species, reported in the previous O<sub>3</sub> AQCD (U.S. EPA, 2006,  
20 [088089](#)) has been generally confirmed by recent studies. In a mesocosm study, *Trifolium repens* and  
21 *Lolium perenne* mixtures were exposed to an episodic rural O<sub>3</sub> regime within solardomes for  
22 12 weeks. *T. repens* showed significant changes in biomass but not *L. perenne*, and the proportion of  
23 *T. repens* decreased in O<sub>3</sub>-exposed mixtures compared to the control (Hayes et al., 2009, [191360](#)).  
24 After 5-year O<sub>3</sub> fumigation (AOT40 of 13.3-59.5 ppm-h) at the Le Mouret FACE experiment,  
25 Switzerland, legumes in fumigated plots declined from their initial over-representation (128%) to a  
26 mere 59% in control plots(Volk et al., 2006, [191434](#)). However, Stampfli and Fuhrer (2010, [102180](#))  
27 re-analyzed the species and soil data and suggested that Volk et al. (2006, [191434](#)) overestimated the  
28 O<sub>3</sub> effect. Stampfli and Fuhrer (2010, [102180](#)) found that the difference in the species dynamics  
29 between control and O<sub>3</sub> treatment was more caused by heterogeneous initial conditions than O<sub>3</sub>  
30 exposure. Several studies also suggested the mature/species-rich ecosystems were more resilient to  
31 O<sub>3</sub> exposure. At another FACE experiment, located at Alp Flix, Switzerland, O<sub>3</sub> fumigation (AOT40  
32 of 15.2-64.9 ppm-h) showed no significant impact on community composition of this species-rich  
33 pasture (Bassin et al., 2007, [191534](#)). Pflieger et al. (2010, [644281](#)) collected seed bank soil from an  
34 agricultural field and examined how the plant community responded over several generations to  
35 elevated O<sub>3</sub> exposures. Sixty plant species from 22 families emerged in the chambers over their  
36 four year study. Overall, they found that O<sub>3</sub> appeared to have small impacts on seed germination and  
37 only a minor effect on species richness of pioneer plant communities.

1 Several review papers have discussed the physiological and ecological characteristics of O<sub>3</sub>-  
2 sensitive herbaceous plants. Hayes et al. (2007, [196911](#)) assessed species traits associated with O<sub>3</sub>  
3 sensitivity by the changes in biomass caused by O<sub>3</sub> exposure. Plants of the therophyte (e.g., annual)  
4 life form were particularly sensitive to O<sub>3</sub>. Species with higher mature leaf N concentration tended to  
5 be more sensitive than those with lower leaf N concentration. Plants growing under high oxidative  
6 stress environments, such as high light or high saline, were more sensitive to O<sub>3</sub>. Using the same  
7 dataset from Hayes et al. (2007, [196911](#)), Mills et al. (2007, [196934](#)) identified the O<sub>3</sub> sensitive  
8 communities. They found that the largest number of these O<sub>3</sub> sensitive communities were associated  
9 with grassland ecosystems. Among grassland ecosystems, alpine grassland, sub-alpine grassland,  
10 woodland fringe, and dry grassland were identified as the most sensitive communities.

### 9.6.5.3. Microbes

11 Several methods have been used to study microbial composition changes associated with  
12 elevated O<sub>3</sub>. Phospholipid fatty acid (PLFA) analysis is widely used to determine whether O<sub>3</sub> elicits  
13 an overall effect on microbial community composition. However, since PLFA markers cover a broad  
14 range of different fungi, resolution of this method may be not fine enough to detect small changes in  
15 the composition of fungal communities. Methods, such as microscopic analyses and polymerase  
16 chain reaction–denaturing gradient gel electrophoresis (PCR–DGGE), have better resolution to  
17 specifically analyze the fungal community composition. The resolution differences among those  
18 methods needs to be considered when assessing the O<sub>3</sub> impact on microbial community composition.

19 Kanerva et al. (2008, [191264](#)) found that elevated O<sub>3</sub> (40-50 ppb) decreased total, bacterial,  
20 actinobacterial and fungal PLFA biomass values as well as fungal:bacterial PLFA biomass ratio in  
21 their meadow mesocosms in south-western Finland. The relative proportions of individual PLFAs  
22 between the control and elevated O<sub>3</sub> treatments were significantly different, suggesting that O<sub>3</sub>  
23 modified the structure of the microbial community. Morsky et al. (2008, [191507](#)) exposed boreal  
24 peatland microcosms to elevated O<sub>3</sub>, with growing season AOT40 of 20.8-35.3 ppm-h, in an open-air  
25 O<sub>3</sub> exposure field in Central Finland. They also found that microbial composition was altered after  
26 three growing seasons with O<sub>3</sub> fumigation, as measured by PLFA. Ozone tended to increase the  
27 presence of Gram-positive bacteria and the biomass of fungi in the peatland microcosms. Ozone also  
28 resulted in higher microbial biomass, which co-occurred with the increases in concentrations of  
29 organic acids and leaf density of sedges (Morsky et al., 2008, [191507](#)). In a lysimeter study in  
30 Germany, O<sub>3</sub> was found to alter the PLFA profiles in the upper 0-20 cm rhizosphere soil of European  
31 beech. Elevated O<sub>3</sub> reduced bacterial abundance but had no detectable effect on fungal abundance  
32 (Pritsch et al., 2009, [626808](#)). Using microscopic analyses, Kasurinen et al. (2005, [191245](#)) found  
33 that elevated O<sub>3</sub>, with 5 or 6 months of AOT40 of 20.6-30.9 ppb-h, decreased the proportions of  
34 black and liver-brown mycorrhizas and increased that of light brown/orange mycorrhizas. In an  
35 herbaceous plant study, SSCP (single-strand conformation polymorphism) profiles indicated that O<sub>3</sub>  
36 stress (about 75 ppb) had a very small effect on the structural diversity of the bacterial community in  
37 rhizospheres (Dohrmann and Tebbe, 2005, [191320](#)). At the Aspen FACE site, O<sub>3</sub> had no significant

1 effect on fungal relative abundance, as indicated by PLFA profile. However, elevated O<sub>3</sub> altered  
2 fungal community composition, according to the identification of 39 fungal taxonomic units from  
3 soil using polymerase chain reaction–denaturing gradient gel electrophoresis (PCR-DGGE) (Chung  
4 et al., 2006, [191729](#)). Ozone was found to change microbial community composition in an  
5 agricultural system. Chen et al. (2010, [644257](#)) found elevated O<sub>3</sub> (100-150 ppb) had significant  
6 effects on soil microbial composition expressed as PLFA percentage in a rice paddy in China.

## 9.6.6. Insects and Wildlife

### 9.6.6.1. Insects

7 Insects may respond indirectly to changes to plants (i.e., increased reactive oxygen species,  
8 altered phytochemistry, altered nutrient content) that occur under elevated O<sub>3</sub> conditions, or O<sub>3</sub> can  
9 have a direct effect on insect performance (Menendez et al., 2009, [191430](#)). Effects of O<sub>3</sub> on insects  
10 occur at the species level (i.e., growth, survival, reproduction, development, feeding behavior) and at  
11 the population and community-level (i.e., population growth rate, community composition). In  
12 general, effects of O<sub>3</sub> on insects are highly context- and species-specific (Bidart-Bouzat and Imeh-  
13 Nathaniel, 2008, [191431](#); Lindroth, 2010, [596479](#)). Furthermore, plant responses to O<sub>3</sub> exposure and  
14 herbivore attack have been demonstrated to share signaling pathways, complicating characterization  
15 of these stressors (Lindroth, 2010, [596479](#); Menendez et al., 2009, [191430](#); Menendez et al., 2010,  
16 [384046](#))

#### Species-Level Responses

17 In considering insect growth, survival and reproduction in elevated O<sub>3</sub> conditions, several  
18 studies have indicated an effect while others have found no correlation. The performance of five  
19 herbivore species (three moths and two weevils) was assessed in an OTC experiment at 2 × ambient  
20 concentration (Peltonen et al., 2010, [596482](#)). Growth of larvae of the Autumnal moth, *Epirrita*  
21 *autumna*, was significantly decreased in the O<sub>3</sub> treatment while no effects were observed in the other  
22 species. In an aphid oviposition preference study using birch buds grown in a three year OTC  
23 experiment, O<sub>3</sub> had neither a stimulatory or deterring effect on egg-laying (Peltonen et al., 2006,  
24 [196946](#)). Furthermore, changes in birch bud phenolic compounds associated with the doubled  
25 ambient concentrations of O<sub>3</sub> did not correlate with changes in aphid oviposition (Peltonen et al.,  
26 2006, [196946](#)). Reproduction in *Popillia japonica*, that were fed soybeans and grown under elevated  
27 O<sub>3</sub>, appeared to be unaffected (O'Neill et al., 2008, [195653](#)). In a meta-analysis of effects of elevated  
28 O<sub>3</sub> on 22 species of trees and 10 species of insects, the rates of survival, reproduction and food  
29 consumption were typically unaffected while development times were reduced and pupal masses  
30 were increased (Valkama et al., 2007, [191348](#)).

31 At the Aspen FACE site insect performance under elevated (50-60 ppb) O<sub>3</sub> conditions  
32 (approximately 1.5 × background ambient levels of 30-40 ppb O<sub>3</sub>) have been considered for several

1 species. Cumulative fecundity of aphids (*Cepegilletta betulaefoliae*), that were reared on O<sub>3</sub>-  
2 exposed paper birch (*Betula papyrifera*) trees, was lower than aphids from control plots (Awmack et  
3 al., 2004, [052926](#)). No effects on growth, development, adult weight, embryo number and birth  
4 weight of newborn nymphs were observed. In a study conducted using three aspen genotypes,  
5 performance of the aspen beetle (*Chrysomela crochi*) decreased across all parameters measured  
6 (development time, adult mass and survivorship) under elevated O<sub>3</sub> (Vigue and Lindroth, 2010,  
7 [644185](#)). There was an increase in the development time of male and female aspen beetle larvae  
8 although the percentages varied across genotypes. Decreased beetle adult mass and survivorship was  
9 observed across all genotypes under elevated O<sub>3</sub> conditions. Another study from the Aspen FACE  
10 site, did not find any significant effects of elevated O<sub>3</sub> on performance (longevity, fecundity,  
11 abundance) of the invasive weevil (*Polydrusus sericeus*) (Hillstrom et al., 2010, [644679](#)).

12 Since the 2006 O<sub>3</sub> AQCD, several studies have considered the effect of elevated O<sub>3</sub> on feeding  
13 behavior of insects. In a feeding preference study, the common leaf weevil (*Phyllobius pyri*)  
14 consumed significantly more leaf discs from one aspen clone when compared to a second clone  
15 under ambient air conditions (Freiwald et al., 2008, [196903](#)). In a moderately elevated O<sub>3</sub>  
16 environment (1.5 × ambient), this preference for a certain aspen clone was less evident, however,  
17 leaves from O<sub>3</sub>-exposed trees were significantly preferred to leaves grown under ambient conditions.  
18 Other plant-herbivore interactions have shown no effects of elevated O<sub>3</sub> on feeding. Feeding  
19 behavior of Japanese beetles (*P. japonica*) appeared to be unchanged when beetles were fed soybean  
20 leaves grown under elevated O<sub>3</sub> conditions (O'Neill et al., 2008, [195653](#)). At the Aspen FACE site,  
21 feeding by the invasive weevil (*Polydrusus sericeus*), as measured by leaf area consumption, was not  
22 significantly different between foliage that was grown under elevated O<sub>3</sub> versus ambient conditions  
23 (Hillstrom et al., 2010, [644679](#)).

### **Population-Level and Community-Level Responses**

24 Recent data on insects provide evidence of population-level and community-level responses to  
25 O<sub>3</sub>. Elevated levels of O<sub>3</sub> can affect plant phytochemistry and nutrient content which in turn can alter  
26 population density and structure of the associated herbivorous insect communities and impact  
27 ecosystem processes (Lindroth, 2010, [596479](#)). In a long-term study of elevated O<sub>3</sub> on herbivore  
28 performance at the Aspen FACE site, individual performance and population-level effects of the  
29 aphid *C. betulaefoliae* were assessed. Elevated O<sub>3</sub> levels had a strong positive effect on the  
30 population growth rates of the aphids; although effects were not detected by measuring growth,  
31 development, adult weight, embryo number or birth weight of newborn nymphs (Awmack et al.,  
32 2004, [052926](#)). Conversely, a lower rate of population growth was observed in aphids previously  
33 exposed to O<sub>3</sub> in an OTC (Menendez et al., 2010, [384046](#)). No direct effects of O<sub>3</sub> were observed;  
34 however, nymphs born from adults exposed to and feeding on O<sub>3</sub> exposed plants were less capable of  
35 infesting new plants when compared to nymphs in the control plots (Menendez et al., 2010, [384046](#)).  
36 Elevated O<sub>3</sub> reduced arthropod abundance by 17% at Aspen FACE, largely as a result of the negative  
37 effects on parasitoids, although phloem-feeding insects may benefit (Hillstrom and Lindroth, 2008,

1 [191367](#)). Herbivore communities effected by O<sub>3</sub> and N were sampled along an air pollution gradient  
2 in the Los Angeles basin (Jones and Paine, 2006, [191301](#)). Abundance, diversity, and richness of  
3 herbivores were not affected. However, a shift in community structure, from phloem-feeding to  
4 chewing dominated communities, was observed along the gradient. No consistent effect of elevated  
5 O<sub>3</sub> on herbivory or insect population size was detected at SoyFACE (Dermody et al., 2008, [191850](#)).

6 Evidence of modification of insect populations and communities in response to elevated O<sub>3</sub>  
7 includes genotypic and phenotypic changes. In a study conducted at the Aspen FACE site, elevated  
8 O<sub>3</sub> altered the genotype frequencies of the pea aphid (*Acyrtosiphon pisum*) grown on red clover  
9 (*Trifolium pratense*) over multiple generations (Mondor et al., 2005, [191217](#)). Aphid color was used  
10 to distinguish between the two genotypes. Ozone increased the genotypic frequencies of  
11 pink-morph:green-morph aphids from 2:1 to 9:1, and depressed wing-induction responses more  
12 strongly in the pink than the green genotype (Mondor et al., 2005, [191217](#)). Growth and  
13 development of individual green and pink aphids reared as a single genotype or mixed genotypes  
14 were unaffected by elevated O<sub>3</sub> (Mondor et al., 2010, [644271](#)). Furthermore, growth of pea aphid  
15 populations is not readily predictable using individual growth rates.

## 9.6.6.2. Wildlife

### Herpatofauna

16 Since the 2006 O<sub>3</sub> AQCD, direct effects of O<sub>3</sub> exposure including physiological changes and  
17 alterations of ecologically important behaviors such as feeding and thermoregulation have been  
18 observed in wildlife. These studies have been conducted in limited laboratory exposures, and the  
19 levels of O<sub>3</sub> treatment (e.g. 0.2-0.8 ppm) were often unrealistically higher than the ambient levels.  
20 Amphibians may be especially vulnerable to airborne oxidants due to the significant gas exchange  
21 that occurs across the skin (Andrews et al., 2008, [645771](#))(Dohm et al., 2008, [604584](#)). Exposure to  
22 0.2 ppm to 0.8 ppm O<sub>3</sub> for 4 h resulted in a decrease of oxygen consumption and depressed lung  
23 ventilation in the California tree frog *Pseudacris cadaverina* (Mautz and Dohm, 2004, [644188](#)).  
24 Following a single 4-h exposure to O<sub>3</sub>, reduced pulmonary macrophage phagocytosis was observed  
25 at 1 and 24 hours postexposure in the marine toad (*Bufo marinus*) indicating an effect on immune  
26 system function (Dohm et al., 2005, [180452](#)). There was no difference in macrophage function at  
27 48 hours postexposure in exposed and control individuals.

28 Behavioral effects of O<sub>3</sub> observed in amphibians include responses to minimize the surface  
29 area of the body exposed to the air and a decrease in feeding rates (Dohm et al., 2008, [604584](#);  
30 Mautz and Dohm, 2004, [644188](#)). The adoption of a low-profile “water conservation posture” during  
31 O<sub>3</sub> exposure was observed in experiments with the California tree frog (Mautz and Dohm, 2004,  
32 [644188](#)). Toads, *Bufo marinus*, exposed to 0.06 μL/L O<sub>3</sub> for 4 hours ate significantly fewer  
33 mealworms at 1 hour and 48 hours postexposure than control toads (Dohm et al., 2008, [604584](#)). In  
34 the same study, escape/exploratory behavior as measured by total distance moved was not adversely  
35 affected in the O<sub>3</sub>-exposed individuals as compared to the controls (Dohm et al., 2008, [604584](#)).

1 Water balance and thermal preference in herpatofauna are altered with elevated O<sub>3</sub>. Toads  
2 exposed to 0.8 ppm O<sub>3</sub> for 4 hours exhibited behavioral hypothermia when preferred body  
3 temperatures were measured at 1, 24 and 48 hours postexposure (Dohm et al., 2001, [017086](#)).  
4 Ozone-exposed individuals lost almost 5g more body mass on average than controls due to  
5 evaporative water loss. At 24 hours after exposure, the individuals that had lost significant body  
6 mass had lower preferred body temperatures(Dohm et al., 2001, [017086](#)). Behavioral hypothermia  
7 was also observed in reptiles following 4-h exposures to 0.6 ppm O<sub>3</sub>. Exposure of the Western Fence  
8 Lizard (*Sceloporus occidentalis*) at 25°C induced behavioral hypothermia that recovered to control  
9 temperatures by 24 hours (Mautz and Dohm, 2004, [644188](#)). The behavioral hypothermic response  
10 persisted in lizards exposed to O<sub>3</sub> at 35°C at 24 hours postexposure resulting in a mean body  
11 temperature 3.3°C over controls.

### Soil Fauna Communities

12 Ozone has also been shown to alter soil fauna communities (Kasurinen et al., 2007, [199826](#);  
13 Loranger et al., 2004, [072712](#); Meehan et al., 2010, [644184](#)). Abundance of Acari (mites and ticks)  
14 decreased by 47% under elevated O<sub>3</sub> at AspenFACE site, probably due to the higher secondary  
15 metabolites and lower N concentrations in litter and foliage under elevated O<sub>3</sub> (Loranger et al., 2004,  
16 [072712](#)). In another study from the AspenFACE site, leaf litter collected from aspen grown under  
17 elevated O<sub>3</sub> conditions were higher in fiber and lignin concentrations than trees grown under ambient  
18 conditions. These chemical characteristics of the leaves were associated with an increased springtail  
19 population growth following 10 weeks in a laboratory microcosm (Meehan et al., 2010, [644184](#)).  
20 Consumption rates of earthworms fed on leaf litter for 6 weeks from trees grown under elevated O<sub>3</sub>  
21 conditions and ambient air did not vary significantly between treatments (Meehan et al., 2010,  
22 [644184](#)). In another study on juvenile earthworms *Lumbricus terrestris*, individual growth was  
23 reduced when worms were fed high-O<sub>3</sub> birch litter from trees exposed for three years to elevated O<sub>3</sub>  
24 in an OTC system (Kasurinen et al., 2007, [199826](#)). In the same study no significant growth or  
25 mortality effects were observed in isopods.

#### 9.6.6.3. Indirect Effects on Wildlife

26 In addition to the direct effects of O<sub>3</sub> exposure on physiological and behavioral endpoints  
27 observed in the laboratory, there are indirect effects to wildlife. These effects include changes in  
28 biomass and nutritive quality of O<sub>3</sub>-exposed plants (reviewed in Section 9.5) that are consumed by  
29 wildlife. Reduced digestibility of O<sub>3</sub>-exposed plants may alter dietary intake and foraging strategies  
30 in herbivores. In a study using native highbush blackberry (*Rubus argutus*) relative feed value of the  
31 plants decreased in bushes exposed to double ambient concentrations of O<sub>3</sub> (Ditchkoff et al., 2009,  
32 [192230](#)). Indirect effects of elevated O<sub>3</sub> on wildlife include changes in chemical signaling important  
33 in ecological 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 against herbivory;  
3 and (3) predator-prey interactions (McFrederick et al., 2009, [191329](#); Pinto et al., 2007, [196949](#);  
4 Pinto et al., 2007, [196950](#); Pinto et al., 2010, [596490](#); Yuan et al., 2009, [199779](#)). Each signal  
5 released by emitters has an atmospheric lifetime and a unique chemical signature comprised of  
6 different ratios of individual hydrocarbons that is susceptible to atmospheric oxidants such as O<sub>3</sub>  
7 (Wright et al., 2005, [626463](#); Yuan et al., 2009, [199779](#)). Under elevated O<sub>3</sub> conditions, these  
8 olfactory cues may travel shorter distances before losing their specificity (McFrederick et al., 2008,  
9 [196931](#); McFrederick et al., 2009, [191329](#)). Additional non-phytogenic VOC-mediated  
10 interrelationships with the potential to be modified by O<sub>3</sub> include territorial marking, pheromones for  
11 attraction of mates and various social interactions including scent trails, nestmate recognition and  
12 signals involved in aggregation behaviors (McFrederick et al., 2009, [191329](#)). In general, effects of  
13 O<sub>3</sub> on scent-mediated ecological interactions are highly context- and species-specific (Bidart-Bouzat  
14 and Imeh-Nathaniel, 2008, [191431](#); Lindroth, 2010, [596479](#)).

## Pollination and Seed Dispersal

15 Phytogenic VOC's attract pollinators and seed dispersers to flowers and fruits (Dudareva et al.,  
16 2006, [626458](#); Theis and Raguso, 2005, [626461](#)). These floral scent trails in plant-insect interactions  
17 may be destroyed or transformed by O<sub>3</sub> (McFrederick et al., 2008, [196931](#)). Using a Lagrangian  
18 model, the rate of destruction of phytogenic VOC's was estimated in air parcels at increasing  
19 distance from a source in response to increased regional levels of O<sub>3</sub>, hydroxyl and nitrate radicals  
20 (McFrederick et al., 2008, [196931](#)). Based on the model, the ability of pollinators to locate highly  
21 reactive VOCs from emitting flowers may have decreased from kilometers during pre-industrial  
22 times to <200 m at current ambient conditions (McFrederick et al., 2008, [196931](#)). Scents that travel  
23 shorter distances (0-10 m) are less susceptible to air pollutants, while highly reactive scents that  
24 travel longer distances (10 to 100's of meters), are at a higher risk for degradation (McFrederick et  
25 al., 2009, [191329](#)). For example, male euglossine bees can detect bait stations from a distance of at  
26 least one kilometer (Dobson, 1994, [626466](#)). The alcohols, ketones and aldehydes comprising sex  
27 pheromones in moths could be especially vulnerable to degradation by O<sub>3</sub>, since some males travel  
28 >100 m to find mates (Carde and Haynes, 2004, [626467](#)).

## Defense Against Herbivory

29 Ozone can alter the chemical signature of VOCs emitted by plants and these VOCs are  
30 subsequently detected by herbivores (Blande et al., 2010, [643928](#); Cannon, 1990, [626460](#); Iriti and  
31 Faoro, 2009, [199313](#); Jackson et al., 1999, [026877](#); Pinto et al., 2007, [196949](#); Vuorinen et al., 2004,  
32 [626462](#)). These modifications can make the plant either more attractive or repellant to phytophagous  
33 insects (Pinto et al., 2010, [596490](#)). For example, under elevated O<sub>3</sub>, the host plant preference by  
34 forest tent caterpillars increased for birch compared to aspen (Agrell et al., 2005, [074324](#)). Ozone-

1 induced emissions from red spruce needles were found to repel spruce budworm larvae (Cannon,  
2 1990, [626460](#)). Transcriptional profiles of field grown soybean (*Glycine max*) grown in elevated O<sub>3</sub>  
3 conditions were altered due to herbivory by Japanese beetles. The herbivory resulted in a higher  
4 number of transcripts in the leaves of O<sub>3</sub>-exposed plants and up-regulation of antioxidant metabolism  
5 associated with plant defense (Casteel et al., 2008, [191696](#)).

6 Ozone may modify signals involved in plant-to-plant interactions and plant defense against  
7 pathogens (Blande et al., 2010, [643928](#); McFrederick et al., 2009, [191329](#); Pinto et al., 2010,  
8 [596490](#); Yuan et al., 2009, [199779](#)). In a recent study with lima beans, 80 ppb O<sub>3</sub> degraded several  
9 herbivore-induced VOC's, reducing the distance over which plant-to-plant signaling occurred  
10 (Blande et al., 2010, [643928](#)).

### **Predator-Prey Interactions**

11 Elevated O<sub>3</sub> conditions are associated with disruption of pheromone-mediated interactions at  
12 higher trophic levels (e.g., predators and parasitoids of herbivores). In a study from the Aspen FACE  
13 site, predator escape behaviors of the aphid (*Chatophorus stevensis*) were enhanced on O<sub>3</sub>-fumigated  
14 aspen trees although the mechanism of this response remains unknown (Mondor et al., 2004,  
15 [074334](#)). The predatory mite *Phytoseiulus persimilis* can distinguish between the VOC signature of  
16 ozonated lima bean plants and ozonated plants simultaneously damaged by *T. urticae* (Vuorinen et  
17 al., 2004, [626462](#)) however, other tritrophic interactions have shown no effect (Pinto et al., 2007,  
18 [196950](#)).

19 There are few studies that consider host location behaviors of parasites under elevated O<sub>3</sub>. In  
20 closed chambers fumigated with O<sub>3</sub>, the searching efficiency and proportion of the host larval fruit  
21 flies parasitized by *Asobara tabida*, declined when compared to filtered air controls (Gate et al.,  
22 1995, [026655](#)). The host location behavior and rate of parasitism of the wasp (*Coesia plutellae*) on  
23 *Plutella xylostella*-infested potted cabbage plants was tested under ambient and doubled O<sub>3</sub>  
24 conditions in an open-air fumigation system (Pinto et al., 2008, [616554](#)). The number of wasps  
25 found in the field and the percentages of parasitized larvae were not significantly different from  
26 controls under elevated O<sub>3</sub>.

27 Elevated O<sub>3</sub> has the potential to perturb specialized food-web communication in transgenic  
28 crops. In insect-resistant oilseed rape *Brassica napus* grown under 100 ppb O<sub>3</sub> in a growth chamber,  
29 reduced feeding damage by *Putella xylostella* led to decreased attraction of the endoparasitoid  
30 (*Costesia vestalis*) (Himanen et al., 2009, [191338](#)). Under chronic O<sub>3</sub>-exposure, the insect resistance  
31 trait BT cry1Ac in transgenic *B. napus* was higher than the control (Himanen et al., 2009, [191369](#)).  
32 There was a negative relative growth rate of the Bt target herbivore, *P. xylostella*, in all O<sub>3</sub>  
33 treatments.

## 9.7. Effects-Based Air Quality Exposure Indices and Dose Modeling

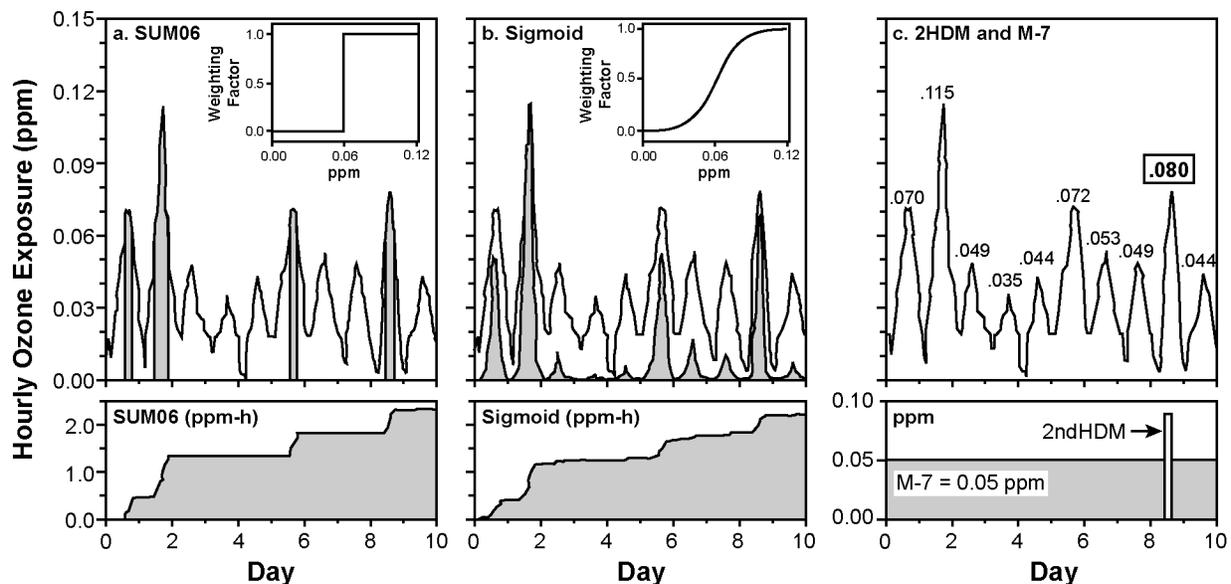
### 9.7.1. Introduction

1 Exposure indices are metrics that quantify exposure as it relates to measured plant damage  
2 (i.e., reduced growth). They are summary measures of monitored ambient O<sub>3</sub> concentrations over  
3 time, intended to provide a consistent metric for reviewing and comparing exposure-response effects  
4 obtained from various studies. Such indices may also provide a basis for developing a biologically-  
5 relevant air quality standard for protecting vegetation and ecosystems. Effects on plant growth and/or  
6 yield have been a major focus of the characterization of O<sub>3</sub> impacts on plants for purposes of the air  
7 quality standard setting process (U.S. EPA, 1986, [017607](#))(U.S. EPA, 1996, [039046](#))(U.S. EPA,  
8 2007, [090207](#)). The quantitative characterization of the relationship of O<sub>3</sub> and plant responses has  
9 been referred to as “dose-response” and “exposure-response” alternatively. The distinction is in how  
10 the pollutant concentration is expressed: “dose” is the pollutant concentration absorbed by the leaf  
11 over some time period, and is very difficult to measure directly, whereas “exposure” is the ambient  
12 air concentration measured near the plant over some time period, and summarized for that period  
13 using an index. Exposure indices have been most useful in considering the form of secondary O<sub>3</sub>  
14 NAAQS standard, in large part because they only require ambient air quality data rather than more  
15 complex indirect calculations of dose to the plant. The attributes of exposure indices that most  
16 require consideration are the weighting of O<sub>3</sub> concentrations, and the daily and seasonal time-periods  
17 that are most relevant to plant damage. Several different types of exposure indices are discussed in  
18 Section 9.7.2.

19 Theoretically, a measure of plant O<sub>3</sub> uptake or dose from ambient air (either rate of uptake or  
20 cumulative seasonal uptake) might be a more ideal predictor of O<sub>3</sub> damage to plants than an  
21 exposure index and may be more useful in improving risk assessment. An uptake measure would  
22 have to integrate all those environmental factors that influence stomatal conductance, including but  
23 not limited to temperature, humidity, and soil water status (Section 9.7.4). Even when integrating  
24 those environmental factors, a direct measure of the internal leaf concentration of O<sub>3</sub>, however, is  
25 technically difficult. Therefore, uptake values are generally obtained with simulation models that  
26 require knowledge of species- and site-specific values for the variables mentioned. In addition, it has  
27 also been recognized that O<sub>3</sub> detoxification processes and the temporal dynamics of detoxification  
28 must be taken into account in dose modeling (Heath et al., 2009, [196783](#)) (Section 9.7.4). Because of  
29 this, research has focused historically on predictors of O<sub>3</sub> damage to plants based only on exposure  
30 as a summary measure of monitored ambient pollutant concentration over some integral of time,  
31 rather than dose (Lee et al., 1988, [042136](#))(Lefohn and Benedict, 1982, [039395](#))(O’Gara, 1922,  
32 [015018](#))(U.S. EPA, 1986, [017607](#))(U.S. EPA, 1992, [042599](#))(U.S. EPA, 1996, [080828](#)).

## 9.7.2. Description of Exposure Indices Available in the Literature

1           Mathematical approaches for summarizing ambient air quality information in biologically  
2 meaningful forms for O<sub>3</sub> vegetation effects assessment purposes have been explored for more than  
3 80 years (O'Gara, 1922, [015018](#))(U.S. EPA, 1996, [080827](#)). In the context of broad-scale national  
4 NAAQS standards that protect for "known or anticipated" effects on many plant species in a variety  
5 of habitats, exposure indices provide a numerical summary of very large numbers of ambient  
6 observations of concentration over extended periods. Like any summary statistic, exposure indices  
7 retain information on some characteristics of the original observations, at the exclusion of others. It  
8 is expected that indices that incorporate the characteristics that are most relevant to plant response  
9 will lead to more reliable protection. Several indices have attempted to incorporate some of the  
10 biological, environmental, and exposure factors (directly or indirectly) that influence the magnitude  
11 of the biological response and contribute to observed variability (Hogsett et al., 1988, [042128](#)). In  
12 the 1996 O<sub>3</sub> AQCD (U.S. EPA, 1996, [080828](#)), the exposure indices were arranged into five  
13 categories; (1) One event, (2) Mean, (3) Cumulative, (4) Concentration weighted, and (5)  
14 Multicomponent, and were discussed in detail (Lee et al., 1989, [042137](#)). Figure 9-8 illustrates how  
15 several of the indices weight concentration and accumulate exposure.  
16



Source: Used with permission from Air and Waste Management Association, Tingey et al. (1991, [042623](#))

**Figure 9-8. Diagrammatic representation of several exposure indices, illustrating how they weight concentration and accumulate exposure. (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 to 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.**

2 Various components of the exposure-response relationship, including concentration, time of  
 3 day, respite time, frequency of peak occurrence, plant phenology, predisposition, etc., were weighted  
 4 with various functions and evaluated on their ability in ordering the regression of exposure versus  
 5 growth or yield response (Lee et al., 1989, [042137](#)). The statistical evaluations for each of these  
 6 indices were completed using growth or yield response data from many earlier exposure studies  
 7 (e.g., NCLAN). This retrospective approach was necessary because there were no studies  
 8 specifically designed to test the goodness of fit of the various indices. The goodness of fit of a set of  
 9 linear and nonlinear models for exposure-response was ranked as various proposed indices were  
 10 used in turn to quantify exposure. This approach provided evidence for the best indices.

1 Most of the early retrospective studies reporting regression approaches used data from the  
2 NCLAN program or data from Corvallis, Oregon or California (Lee et al., 1987, [042135](#))(Lee et al.,  
3 1988, [042136](#))(Lefohn et al., 1988, [042138](#))(Musselman et al., 1988, [042144](#))(U.S. EPA, 1992,  
4 [042599](#))(U.S. EPA, 1986, [017607](#)). These studies were previously reviewed by the EPA (U.S. EPA,  
5 1992, [042599](#))(U.S. EPA, 1996, [080828](#)) and were in general agreement that the best fit of the data  
6 were cumulative concentration-weighted exposure indices. Lee et al. (1987, [042135](#)) suggested that  
7 exposure indices that included all the 24-h data performed better than those that used only 7 hours of  
8 data; this was consistent with the conclusions of Heagle et al. (1987, [042124](#)) that plants receiving  
9 exposures for an additional 5 h/day showed 10% greater yield loss than those exposed for 7 h/day. In  
10 an earlier analysis using the National Crop Loss Assessment Network (NCLAN) data, Lee et al.  
11 (1988, [042138](#)) found the “best” exposure index was a phenologically weighted cumulative index,  
12 with sigmoid weighting on concentration and a gamma weighting function as a surrogate for plant  
13 growth stage. This index provided the best statistical fit when used in the models under  
14 consideration, but it required data on species and site conditions, making specification of weighting  
15 functions difficult for general use. The next best fits were the several indices which only cumulated  
16 and weighted higher concentrations (e.g., W126, SUM06, SUM08, and AOT40). Amongst this group  
17 no index lead to consistently better fits across all studies and species (Heagle et al., 1994,  
18 [042656](#))(Lefohn et al., 1988, [042138](#))(Musselman et al., 1988, [042144](#)).

19 Other factors, including predisposition time (Hogsett et al., 1988, [042128](#))(McCool et al.,  
20 1988, [041877](#)) and crop development stage (Heagle et al., 1991, [042530](#))(Tingey et al., 2002,  
21 [040896](#)) contributed to variation in the biological response and suggested the need for weighting O<sub>3</sub>  
22 concentrations to account for predisposition time and phenology. However, the roles of  
23 predisposition and phenology in plant response vary considerably with species and environmental  
24 conditions; therefore, specification of a weighting function for general use in characterizing plant  
25 exposure was not possible.

26 European scientists took a similar approach in developing indices describing growth and yield  
27 loss in crops and tree seedlings, using OTCs with modified ambient exposures, but many fewer  
28 species and study locations were employed in the European studies. There is evidence from some  
29 European studies that a lower (Pleijel et al., 1997, [043747](#)) or higher (Finnan et al., 1996,  
30 [042545](#))(Finnan et al., 1997, [083315](#)) cutoff value in indices with a threshold may provide a better  
31 statistical fit to the experimental data. Finnan et al. (1997, [083315](#)) used seven exposure studies of  
32 spring wheat to confirm that cumulative exposure indices emphasizing higher O<sub>3</sub> concentrations  
33 were best related to plant response and that cumulative exposure indices using weighting functions,  
34 including cutoff concentrations, allometric and sigmoidal, provided a better fit and that the ranking  
35 of these indices differed depending on the exposure-response model used. Weighting those  
36 concentrations associated with sunshine hours in an attempt to incorporate an element of plant  
37 uptake did not improve the index performance (Finnan et al., 1997, [083315](#)). A more recent study  
38 using data from several European studies of Norway spruce, analyzed the relationship between  
39 relative biomass accumulation and several cumulative, weighted indices, including the AOT40 and

1 the SUM06 (Skarby et al., 2004, [080375](#)). All the indices performed relatively well in regressing  
2 biomass and exposure index, with the AOT20 and AOT30 doing slightly better than others ( $r^2 =$   
3 0.46-0.47). In another comparative study of four independent data sets of potato yield and different  
4 cumulative uptake indices with different cutoff values, a similarly narrow range of  $r^2$  was observed  
5 ( $r^2 = 0.3-0.4$ ) (Pleijel et al., 2004, [036662](#)).

6 In both the U.S. and Europe, the adequacy of these numerical summaries of exposure in  
7 relating biomass and yield changes have, for the most part, all been evaluated using data from  
8 studies not necessarily designed to compare one index to another (Lefohn et al., 1988, [042138](#))(Lee  
9 et al., 1989, [042137](#))(Skarby et al., 2004, [080375](#)). Very few studies in the U.S. have addressed this  
10 issue since the 2006 O<sub>3</sub> AQCD. McLaughlin et al. (2007, [090348](#)) reported that the cumulative  
11 exposure index of AOT60 related well to reductions in growth rates at forest sites in the southern  
12 Appalachian Mountains. However, the authors did not report an analysis to compare multiple  
13 indices. Overall, given the available data from previous O<sub>3</sub> AQCDs and the few recent studies, the  
14 cumulative, concentration-weighted indices perform better than the peak or mean indices. It is still  
15 not possible, however, to distinguish the differences in performance among the cumulative,  
16 concentration-weighted indices.

17 The main conclusions from the 1996 and 2006 O<sub>3</sub> AQCDs (U.S. EPA, 1996,  
18 [080828](#))(U.S. EPA, 2006, [088089](#)) regarding an index based on ambient exposure are still valid. No  
19 information has come forth since the 2006 O<sub>3</sub> AQCD to alter those conclusions significantly. These  
20 key conclusions can be restated as follows:

- 21       ▪ O<sub>3</sub> effects in plants are cumulative;
- 22       ▪ higher O<sub>3</sub> concentrations appear to be more important than lower concentrations in  
23       eliciting a response;
- 24       ▪ plant sensitivity to O<sub>3</sub> varies with time of day and plant development stage; and
- 25       ▪ exposure indices that accumulate the O<sub>3</sub> hourly concentrations and preferentially weight  
26       the higher concentrations have better statistical fits to growth/yield response than do the  
27       mean and peak indices.

28 Following the 2006 criteria review process (U.S. EPA, 2006, [088089](#)), the EPA proposed an  
29 alternative form of the secondary NAAQS for O<sub>3</sub> using a cumulative, concentration-weighted  
30 exposure index to protect vegetation from damage (72 FR 37818 (2007, [684055](#)), 75 FR 2938 (2010,  
31 [684211](#)), p. 3003). The EPA considered two specific concentration-weighted indices: the cutoff  
32 concentration weighted SUM06 and the sigmoid-weighted W126 exposure index (U.S. EPA, 2007,  
33 [090207](#)). These two indices performed equally well in predicting the exposure-response relationships  
34 observed in the crop and tree seedlings studies (Lee et al., 1989, [042137](#)). At a workshop convened

1 to consider the science supporting these indices (Heck and Cowling, 1997, [084484](#)) the participants  
2 agreed that these cumulative concentration-weighted indices being considered were equally capable  
3 of predicting plant response. A short-term daily 8-h avg was also proposed in the review that ended  
4 in 2008 (73 FR 16436, (2008, [684051](#))), but at the time there were no scientific studies supporting  
5 the utility of this index for vegetation. Below are the definitions of the three index forms considered  
6 in the previous staff paper review (U.S. EPA, 2007, [090207](#)):

- 7       ▪ **8-h average form:** 4th-highest daily max 8-h avg over the O<sub>3</sub> season.
  
- 8       ▪ **SUM06:** Sum of all hourly O<sub>3</sub> concentrations greater than or equal to 0.06 ppm observed  
9       during a specified daily and seasonal time window (Figure 9-8a).
  
- 10       ▪ **W126:** Sigmoidally weighted sum of all hourly O<sub>3</sub> concentrations observed during a  
11       specified daily and seasonal time window (Similar to Figure 9-8b). The sigmoidal  
12       weighting of hourly O<sub>3</sub> concentration is given in the equation below, where C is the  
13       hourly O<sub>3</sub> concentration in ppm:

$$w_c = \frac{1}{1 + 4403e^{-126C}}$$

Equation 9-1

14 The SUM06 and W126 indices have a variety of relevant time windows that may be applied and are  
15 discussed in Section 9.7.3.

16 Other exposure indices are discussed in the literature and are currently used outside the U.S. In  
17 Europe, the cutoff concentration-weighted index AOT40 was selected in developing exposure-  
18 response relationships based on OTC studies of a limited number of crops and trees (Grunhage and  
19 Jager, 2003, [052972](#)). The United Nations Economic Commission for Europe (United Nations  
20 Economic Commission for Europe UNECE, 1988, [055354](#)) adopted the critical levels approach for  
21 assessment of O<sub>3</sub> risk to vegetation across Europe. As used by the UNECE, the critical levels are not  
22 like the air quality regulatory standards used in the U.S., but rather planning targets for reductions in  
23 pollutant emissions to protect ecological resources. Critical levels for O<sub>3</sub> are intended to prevent  
24 long-term deleterious effects on the most sensitive plant species under the most sensitive  
25 environmental conditions, but not intended to quantify O<sub>3</sub> effects. A critical level was defined as “the  
26 concentration of pollutant in the atmosphere above which direct adverse effects on receptors, such as  
27 plants, ecosystems, or materials may occur according to present knowledge” (United Nations  
28 Economic Commission for Europe UNECE, 1988, [055354](#)). The nature of the “adverse effects” was  
29 not specified in the original definition, which provided for different levels for different types of  
30 harmful effect (e.g., visible injury or loss of crop yield). There are also different critical levels for  
31 crops, forests, and semi-natural vegetation. The caveat, “according to present knowledge” is

1 important because critical levels are not rigid; they are revised periodically as new scientific  
2 information becomes available. For example, the original critical level for O<sub>3</sub> specified  
3 concentrations for three averaging times, but further research and debate led to the current critical  
4 level being stated as the cumulative exposure (concentration × hours) over a cutoff concentration of  
5 40 ppb (AOT40) (Fuhrer et al., 1997, [030380](#)).

6 In Europe, a decision was made to work towards a flux-based approach for the critical levels  
7 (“Level II”), with the goal of modeling O<sub>3</sub> flux-effect relationships for three vegetation types: crops,  
8 forests, and semi-natural vegetation (Grunhage and Jager, 2003, [052972](#)). Progress has been made in  
9 modeling flux (see section AX9.4.5; U.S. EPA, 2006, [088089](#)) and the Mapping Manual is being  
10 revised (Ashmore et al., 2004, [056623](#))(Ashmore MEMberson et al., 2004, [056624](#))(Grennfelt, 2004,  
11 [056625](#))(Karlsson et al., 2003, [055331](#)). The revisions may include a flux-based approach for three  
12 crops: wheat, potatoes, and cotton. However, because of a lack of flux-response data, a cumulative,  
13 cutoff concentration-based (AOT<sub>x</sub>) exposure index will remain in use for the near future for most  
14 crops and for forests and semi-natural herbaceous vegetation (Ashmore et al., 2004, [056623](#)).

### 9.7.3. Important Components of Exposure Indices

15 The efficacy of exposure indices in predicting biological responses requires that researchers  
16 identify a relationship between measured growth and/or yield effects and important components of  
17 exposure indices. In the previous O<sub>3</sub> AQCDs it was established that higher hourly concentrations  
18 have greater effects on vegetation than lower concentrations (U.S. EPA, 1996, [080828](#))(U.S. EPA,  
19 2006, [088089](#)). Further, it was determined that the diurnal and seasonal duration of exposure is  
20 important for plant response. Weighting of hourly concentrations and the diurnal and seasonal time  
21 window of exposure are the most important variables in a cumulative exposure index and will be  
22 discussed below. However, these variables must be taken in the context of plant phenology, diurnal  
23 conductance rates, plant canopy structure, and detoxification mechanisms of vegetation as well as  
24 the climate and meteorology, all of which are determinants of plant response. These more specific  
25 factors will be discussed in the uptake and dose modeling section (Section 9.7.4).

#### 9.7.3.1. Role of Concentration

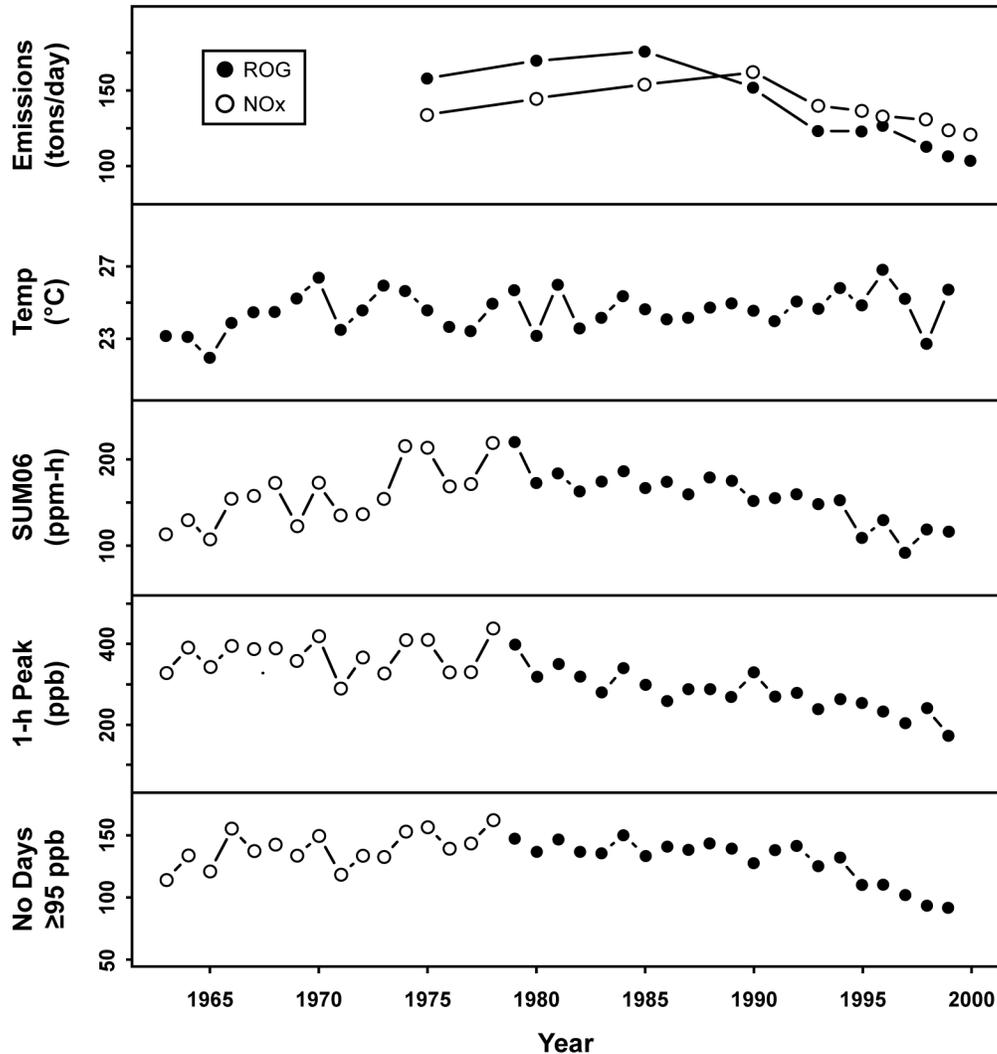
26 The significant role of higher O<sub>3</sub> concentrations was established based on several experimental  
27 studies (U.S. EPA, 1996, [080828](#)). Several studies (Nussbaum et al., 1995, [030141](#))(Oksanen and  
28 Holopainen, 2001, [019538](#))(Yun and Laurence, 1999, [044165](#)) have added support for the important  
29 role that peak concentrations, as well as the pattern of occurrence, plays in plant response to O<sub>3</sub>.  
30 Oksanen and Holopainen (2001, [019538](#)) found that the peak concentrations and the shape of the O<sub>3</sub>  
31 exposure (i.e., duration of the event) were important determinants of foliar injury in European white  
32 birch saplings, but growth reductions were found to be more related to total cumulative exposure.  
33 Based on air quality data from 10 U.S. cities, three 4-week exposure treatments having the same  
34 SUM06 value were constructed by Yun and Laurence (1999, [044165](#)). The authors used different

1 exposure regimes to explore effects of treatments with variable versus uniform peak occurrence  
2 during the exposure period. The authors reported that the variable peak exposures were important in  
3 causing injury, and that the different exposure treatments, although having the same SUM06,  
4 resulted in very different patterns of foliar injury. Nussbaum et al. (1995, [030141](#)) also found peak  
5 concentrations and the pattern of occurrence to be critical in determining the measured response. The  
6 authors recommended that to describe the effect on total forage yield, peak concentrations  
7 >0.11 ppm must be emphasized by using an AOT with higher threshold concentrations.

8 A greater role for higher concentrations affecting plant growth might be inferred based on air  
9 quality analyses for the southern California area (Lee et al., 2003, [053031](#))(Tingey et al., 2004,  
10 [042385](#)). In the late 1960s and 1970s, extremely high O<sub>3</sub> concentrations had impacted the San  
11 Bernardino National Forest. However, over the past 20+ years, significant reductions in O<sub>3</sub> exposure  
12 have occurred (Davidson, 1993, [043366](#))(Lee et al., 2003, [053031](#))(Lefohn and Shadwick, 2000,  
13 [040483](#))(Bytnerowicz et al., 2008, [196881](#)). An illustration of this improvement in air quality is  
14 shown by the 37-year history of O<sub>3</sub> air quality at the Crestline site in the San Bernardino Mountains  
15 (Figure 9-9) (Lee et al., 2003, [053031](#)). Ozone exposure increased from 1963 to 1979 concurrent  
16 with increased population and vehicular miles, followed by a decline to the present mirroring  
17 decreases in precursor emissions. The pattern in exposure was evident in various exposure indices  
18 including the cumulative concentration weighted (SUM06), as well as maximum peak event (1 h  
19 peak), and the number of days having hourly averaged O<sub>3</sub> concentrations greater than or equal to  
20 95 ppb. The number of days having hourly averaged O<sub>3</sub> concentrations greater than or equal to  
21 95 ppb declined significantly from 163 days in 1978 to 103 days in 1997. The changes in ambient O<sub>3</sub>  
22 air quality for the Crestline site were reflected in the changes in frequency and magnitude of the peak  
23 hourly concentration and the duration of exposure (Figure 9-9). Considering the role of exposure  
24 patterns in determining response, the seasonal and diurnal patterns in hourly O<sub>3</sub> concentration did not  
25 vary appreciably from year to year over the 37-year period (Lee et al., 2003, [053031](#)).

26 The inference for a role of higher concentrations comes both from results of measures of tree  
27 conditions on established plots and from results of model simulations. Across a broad area of the San  
28 Bernardino National Forest, the Forest Pest Management (FPM) method of injury assessment  
29 indicated an improvement in crown condition from 1974 to 1988; and the area of improvement in  
30 injury assessment is coincident with an improvement in O<sub>3</sub> air quality (Miller and Rechel, 1999,  
31 [040702](#)). A more recent analysis of forest changes in the San Bernardino National Forest using an  
32 expanded network of monitoring sites has verified significant changes in growth, mortality rates,  
33 basal area, and species composition throughout the area since 1974 (Arbaugh et al., 2003, [052925](#)).  
34 A model simulation of ponderosa pine growth over the 40-year period in the San Bernardino  
35 National Forest showed a significant impact of O<sub>3</sub> exposure on tree growth and indicates improved  
36 growth with improving O<sub>3</sub> air quality. This area has also experienced elevated N deposition and  
37 based on a number of environmental indicators, it appears that this area is experiencing N saturation  
38 (Fenn et al., 1996, [083540](#)). To account for this potential interaction, the model simulations were  
39 conducted under conditions of unlimited soil N. The actual interactions are not known. The

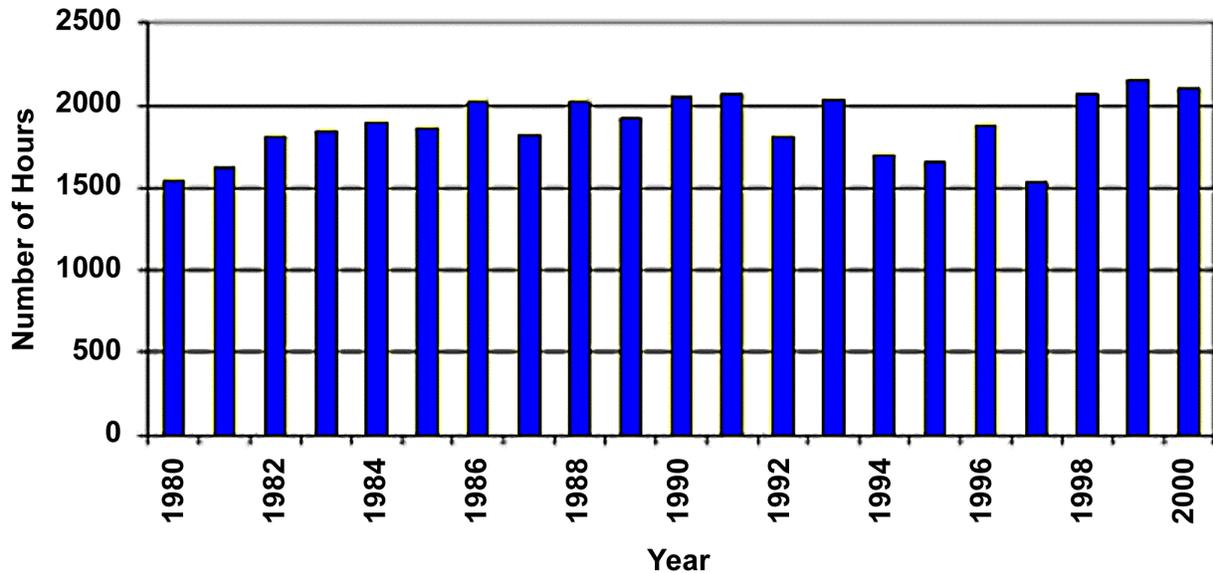
1 improvement in growth over the years was assigned to improved O<sub>3</sub> air quality, but no distinction  
2 was made regarding the relative role of mid-range and higher hourly concentrations, only that  
3 improved growth tracked decreasing SUM06, maximum peak concentration, and number of days of  
4 hourly O<sub>3</sub> >95 ppb (Tingey et al., 2004, [042385](#)). A summary of air quality data from 1980 to 2000  
5 for the San Bernardino National Forest area of the number of “mid-range” hourly concentrations  
6 indicated no dramatic changes over this 20-year period, ranging from about 1,500 to 2,000 hours per  
7 year (Figure 9-10). There was a slow increase in the number of mid-range concentrations from 1980  
8 to 1986, which corresponds to the period after implementation of the air quality standard. Another  
9 sharper increase was observed in the late 1990s. This pattern of occurrence of mid-range hourly  
10 concentrations suggests a lesser role for these concentration ranges compared to the higher values in  
11 either of the ground-level tree injury observations of the model simulation of growth over the  
12 40-year period.



Source: Used with permission from Elsevier Science Ltd., (Lee et al., 2003, [053031](#)).

**Figure 9-9. Trends in May to September 12-h SUM06, peak 1-h 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<sub>x</sub>) for San Bernardino County. Annual ROG and NO<sub>x</sub> emissions data for San Bernardino County were obtained from Alexis et al. (2001, [079886](#)) and the California Air Resource Board's emission inventory available at <http://www.arb.ca.gov/aqd/aqdp.htm> (Cal EPA, 2009, [677487](#)).**

**Crestline, San Bernardino, CA**  
**Number of Hours 50 - 89 ppb**  
**060710005**



**Figure 9-10.** 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.

### 9.7.3.2. Diurnal and Seasonal Exposure

#### Diurnal Exposure

1 The diurnal patterns of maximal leaf/needle conductance and occurrence of higher ambient  
2 concentrations can help determine which hours during the day over a season should be cumulated.  
3 Stomatal conductance is species and phenology dependent and is linked to both diurnal and seasonal  
4 meteorological activity as well as to soil/site conditions (e.g., soil moisture). Daily patterns of  
5 leaf/needle conductance are often highest in midmorning, whereas higher ambient O<sub>3</sub> concentrations  
6 generally occurred in early to late afternoon when stomata were often partially closed and  
7 conductances were lower. Total O<sub>3</sub> flux depends on atmospheric and boundary layer resistances, both  
8 of which exhibit variability throughout the day. Experimental studies with tree species demonstrated  
9 the decoupling of ambient O<sub>3</sub> exposure, peak occurrence, and gas exchange, particularly in areas of  
10 drought (Panek, 2004, [079202](#)). Several studies have suggested that ponderosa pine trees in the  
11 southern and northern Sierra Nevada Mountains may not be as susceptible to high O<sub>3</sub> concentrations  
12 as to lower concentrations, due to reduced needle conductance and O<sub>3</sub> uptake during the period when  
13 the highest concentrations occur (Arbaugh et al., 1998, [040297](#))(Bauer et al., 2000, [040315](#))(Panek et  
14 al., 2002, [040712](#))(Panek and Goldstein, 2001, [030190](#)). Panek et al. (2002, [040712](#)) compared direct  
15 O<sub>3</sub> flux measurements into a canopy of ponderosa pine and demonstrated a lack of correlation of  
16 daily patterns of conductance and O<sub>3</sub> occurrence, especially in the late season drought period; the

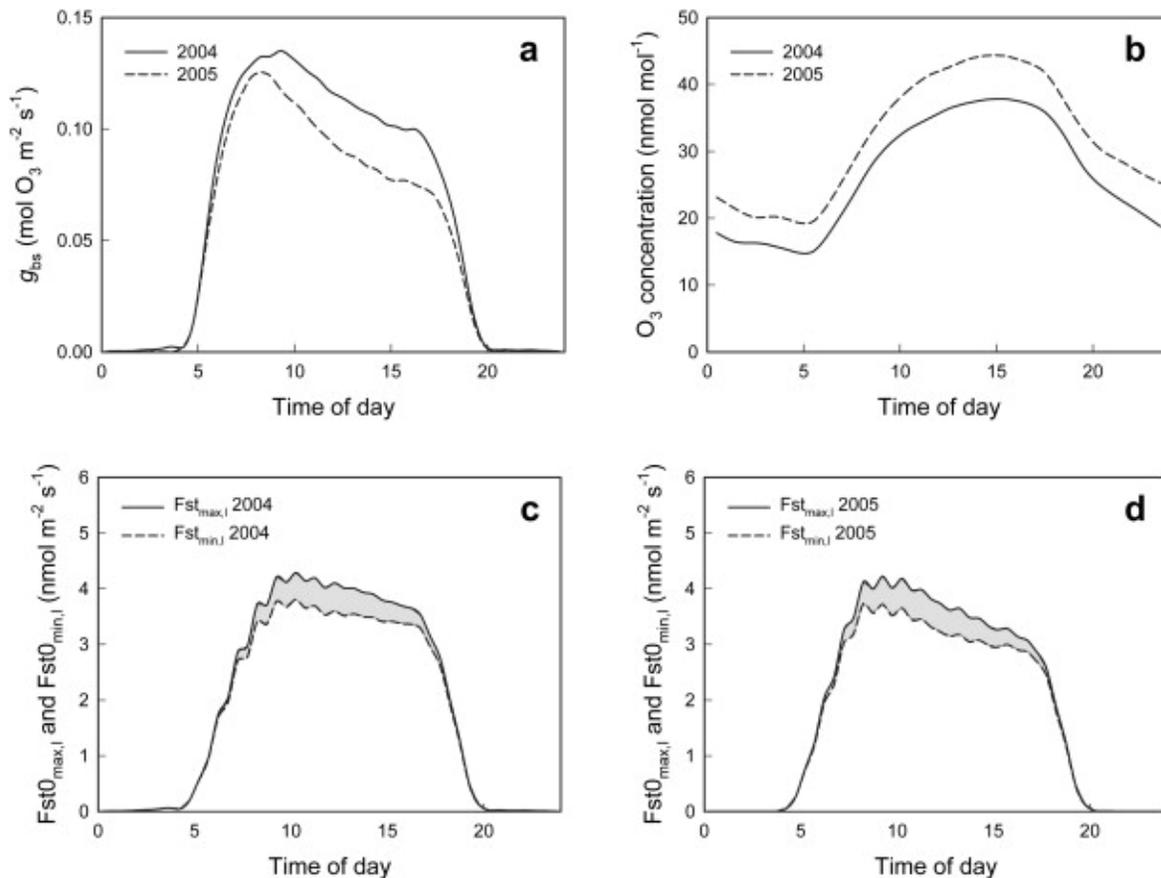
1 authors concluded that a consideration of climate or season was essential, especially considering the  
2 role of soil moisture and conductance/uptake. In contrast, Grulke et al. (2002, [035283](#)) reported high  
3 conductance when O<sub>3</sub> concentrations were high in the same species, but under different growing site  
4 conditions. The decoupling of conductance and higher ambient O<sub>3</sub> concentration would hold true for  
5 more mesic environments as well as xeric landscapes. The longer-term biological responses reported  
6 by Miller and Rechel (1999, [040702](#)) for ponderosa pine in the same region, and the general  
7 reduction in recent years in ambient O<sub>3</sub> concentrations, suggest that stomatal conductance alone may  
8 not be a sufficient indicator of potential vegetation injury or damage. Another consideration for the  
9 effect of O<sub>3</sub> uptake is the diurnal pattern of detoxification capacity of the plant. The detoxification  
10 capacity may not follow the same pattern as stomatal conductance (Heath et al., 2009, [196783](#)).

11 A 12-h (8:00 a.m. to 8:00 p.m.) daylight period for a W126 cumulating exposure was proposed  
12 in 2007 (72 FR 37818, (2007, [684055](#))) and 2010 (75 FR 2938, (2010, [684211](#)), p. 3003) following  
13 the release of the 2006 O<sub>3</sub> AQCD, based primarily on evidence that the conditions for uptake of O<sub>3</sub>  
14 into the plant occur mainly during the daytime hours. In general, plants have the highest stomatal  
15 conductance during the daytime and in many areas atmospheric turbulent mixing is greatest during  
16 the day as well (U.S. EPA, 2006, [088089](#))(Uddling et al., 2010, [387073](#)). However, notable  
17 exceptions to maximum daytime conductance are cacti and other plants with crassulacean acid  
18 metabolism (CAM photosynthesis) which only open their stomata at night. This section will focus on  
19 plants with C<sub>3</sub> and C<sub>4</sub> photosynthesis, which generally have maximum stomatal conductance during  
20 the daytime.

21 Recent reviews of the literature reported that a large number of species had varying degrees of  
22 nocturnal stomatal conductance (Caird et al., 2007, [199337](#))(Dawson et al., 2007,  
23 [670381](#))(Musselman and Minnick, 2000, [011612](#)). This night-time conductance can also be  
24 enhanced by O<sub>3</sub> damage during the day that could result in loss of stomatal control, and less  
25 complete closure of stomata, than under low O<sub>3</sub> conditions (Grulke et al., 2007, [199376](#)). In general,  
26 the rate of stomatal conductance at night is much lower than during the day (Caird et al., 2007,  
27 [199337](#)). Atmospheric turbulence at night is also often low, which results in stable boundary layers  
28 and unfavorable conditions for O<sub>3</sub> uptake into vegetation (Finkelstein et al., 2000, [024029](#)).  
29 Nevertheless, nocturnal turbulence does intermittently occur and may result in nonnegligible O<sub>3</sub> flux  
30 into the plants. In addition, plants might be more susceptible to O<sub>3</sub> exposure at night than during the  
31 daytime, because of potentially lower plant defenses (Musselman and Minnick, 2000,  
32 [011612](#))(Musselman et al., 2006, [121678](#))(Loreto and Fares, 2007, [180259](#))(Heath et al., 2009,  
33 [196783](#)). For significant nocturnal stomatal flux and O<sub>3</sub> effects to occur, specific conditions must  
34 exist. A susceptible plant with nocturnal stomatal conductance and low defense must be growing in  
35 an area with relatively high night-time O<sub>3</sub> concentrations and appreciable nocturnal atmospheric  
36 turbulence. It is unclear how many areas there are in the U.S. where these conditions occur. It may  
37 be possible that these conditions exist in mountainous areas of southern California, front-range of  
38 Colorado (Turnipseed et al., 2009, [588752](#)) and the Great Smoky Mountains of North Carolina and

1 Tennessee. More information is needed in these locations to assess the local O<sub>3</sub> patterns,  
2 micrometeorology and responses of potentially vulnerable plant species.

3 Several field studies have attempted to quantify night-time O<sub>3</sub> uptake with a variety of  
4 methods. However, many of these studies have not linked the night-time flux to measured effects on  
5 plants. Grulke et al. (2004, [042646](#)) showed that the stomatal conductance at night for ponderosa  
6 pine in the San Bernardino National Forest (CA) ranged from one tenth to one fourth that of  
7 maximum daytime stomatal conductance. In June, at a high-elevation site, it was calculated that 11%  
8 of the total daily O<sub>3</sub> uptake of pole-sized trees occurred at night. In late summer, however, O<sub>3</sub> uptake  
9 at night was negligible. However, this study did not consider the turbulent conditions at night.  
10 Finklestein et al. (2000, [024029](#)) investigated O<sub>3</sub> deposition velocity to forest canopies at three  
11 different sites. The authors found the total flux (stomatal and non-stomatal) to the canopy to be very  
12 low during night-time hours as compared to day-time hours. However, the authors did note that  
13 higher nocturnal deposition velocities at conifer sites may be due to some degree of stomatal opening  
14 at night (Finkelstein et al., 2000, [024029](#)). Work by Mereu et al. (2009, [102168](#)) in Italy on  
15 mediterranean species indicated that nocturnal uptake was from 10 to 18% of total daily uptake  
16 during a weak drought and up to 24% as the drought became more pronounced. The proportion of  
17 night-time uptake was greater during the drought due to decreases in daytime stomatal conductance  
18 (Mereu et al., 2009, [102168](#)). In a recent study at the AspenFACE site in Wisconsin, calculated leaf-  
19 level stomatal O<sub>3</sub> flux was near zero from the night-time hours of 8:00 p.m. to 5:00 a.m. (Uddling et  
20 al., 2010, [387073](#)). This was likely due to low horizontal wind speed (>1 m/s) and low O<sub>3</sub>  
21 concentrations (<25 ppb) during those same night-time hours (Figure 9-11).



Source: Used with permission from Elsevier Ltd., Uddling et al. (2010, [387073](#)).

**Figure 9-11. Mean diurnal.**

**(a) conductance through boundary layer and stomata ( $g_{bs}$ ), (b) Ozone concentration, and leaf-level stomatal ozone flux without flux cut-off threshold ( $\text{Fst0}_i$ ) in control plots from mid-June through August in (c) 2004 and (d) 2005 in the Aspen FACE experiment. Subscripts “max” and “min” refer to stomatal fluxes calculated neglecting and accounting for potential non-stomatal ozone flux, respectively.**

1 A few studies have tested the biological effects of night-time  $\text{O}_3$  exposure on vegetation in  
 2 controlled chambers. Biomass of ponderosa pine seedlings was significantly reduced when seedlings  
 3 were exposed to either daytime or nighttime episodic profiles (Lee and Hogsett, 1999, [040451](#)).  
 4 However, the biomass reductions were much greater with daytime peak concentrations than with  
 5 nighttime peak concentrations. Similarly, birch cuttings grown in field chambers that were exposed  
 6 to  $\text{O}_3$  at night only, daytime only, and 24 hours showed similar reductions in biomass in night only  
 7 and day only treatments. Birch seedling showed greater reductions in growth in 24-h exposures than  
 8 those exposed to  $\text{O}_3$  at night or day only (Matyssek et al., 1995, [040700](#)). Field mustard (*Brassica*  
 9 *rapa*) plants exposed to  $\text{O}_3$  during the day or night showed little significant difference in the amounts  
 10 of injury or reduced growth response to  $\text{O}_3$  treatment, although the stomatal conductance was  
 11 70-80% lower at night (Winner et al., 1989, [043403](#)). These studies show that effects can be seen

1 with night-time exposures to O<sub>3</sub> but if atmospheric conditions are stable at night, it is uncertain how  
2 these exposures may affect plants and trees with complex canopies in the field.

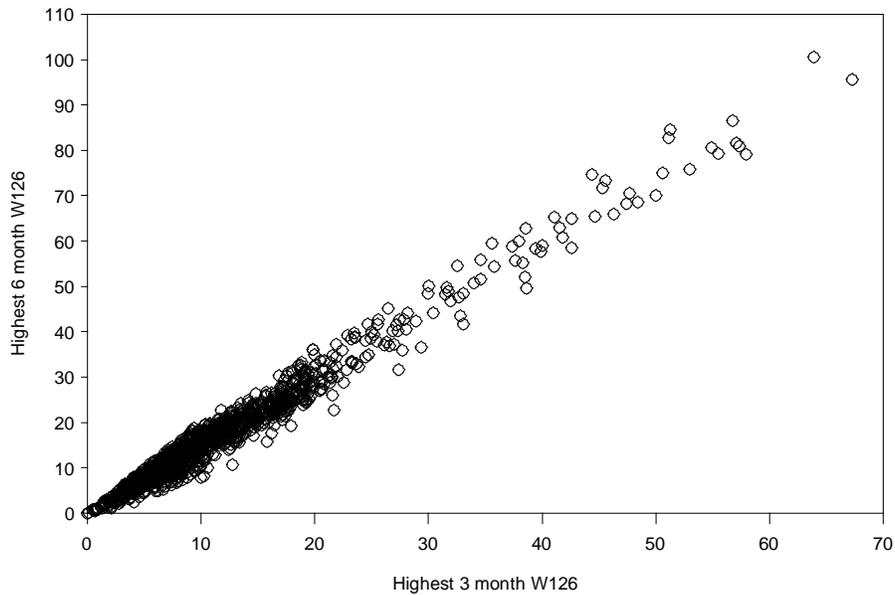
### Seasonal Exposure

3 Vegetation across the U.S. has widely varying periods of physiological activity during the year  
4 due to variability in climate and phenology. In order for a particular plant to be vulnerable to O<sub>3</sub>  
5 pollution, it must have foliage and be physiologically active. Annual crops are typically grown for  
6 periods of two to three months. In contrast, perennial species may be photosynthetically active  
7 longer (up to 12 months each year for some species) depending on the species and where it is grown.  
8 In general, the period of maximum physiological activity and thus, potential O<sub>3</sub> uptake for vegetation  
9 coincides with some or all of the intra-annual period defined as the O<sub>3</sub> season, which varies on a  
10 state-by-state basis (Figure 3-18). This is because the high temperature and high light conditions that  
11 typically promote the formation of tropospheric O<sub>3</sub> also promote physiological activity in vegetation.  
12 There are very limited exceptions to this pattern where O<sub>3</sub> can form in the winter in areas in the  
13 western U.S. with intense natural gas exploration (Pinto, 2009, [187038](#)), but this is typically when  
14 plants are dormant and there is little chance of O<sub>3</sub> uptake. The selection of any single window of  
15 time for a national standard to consider hourly O<sub>3</sub> concentrations represents a compromise, given the  
16 significant variability in growth patterns and lengths of growing season among the wide range of  
17 vegetation species that may experience adverse effects associated with O<sub>3</sub> exposure.

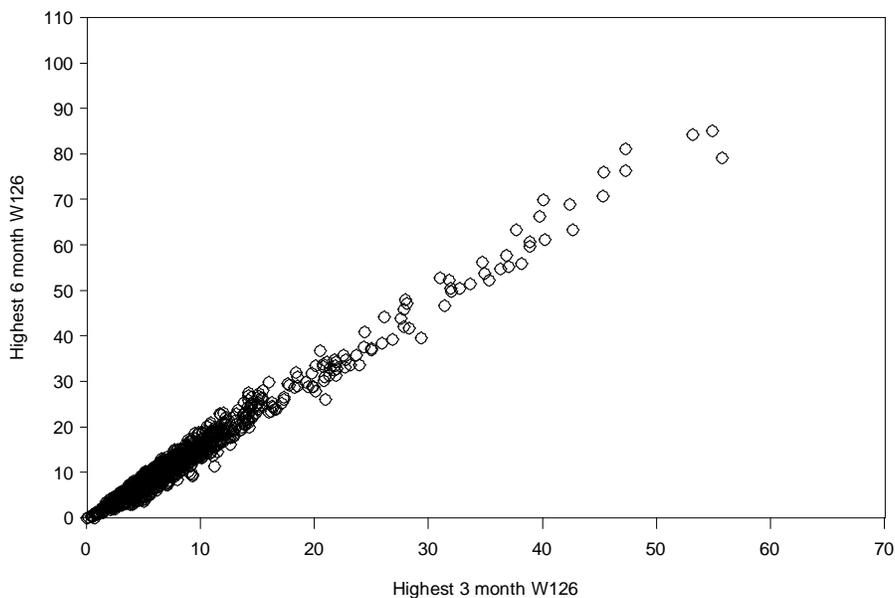
18 Various intra-annual averaging and accumulation time periods have been considered for the  
19 protection of vegetation. The 2010 proposal for secondary O<sub>3</sub> standard (75 FR 2938, (2010, [684211](#)),  
20 p. 3003) proposed to use the maximum consecutive 3-month period within the O<sub>3</sub> season. The U.S.  
21 Forest Service and federal land managers have used a 24-h W126 accumulated for 6 months from  
22 April through September (see FLAG report; Federal land managers' air quality related values  
23 workgroup (FLAG) phase I report, 2000, [088923](#)). However, some monitors in the U.S. are  
24 operational for as little as four months and would not have enough data for a 6-month seasonal  
25 window. The exposure period in the vast majority of O<sub>3</sub> exposure studies conducted in the U.S. has  
26 been much shorter than 6 months. Most of the crop studies done through NCLAN had exposures less  
27 than three months with an average of 77 days. Open-top chamber studies of tree seedlings, compiled  
28 by the EPA, had an average exposure of just over three months or 99 days. In more recent FACE  
29 experiments, SoyFACE exposed soybeans for an average of approximately 120 days per year and the  
30 Aspen FACE experiment exposed trees to an average of approximately 145 days per year of elevated  
31 O<sub>3</sub>, which included the entire growing season at those particular sites. Despite the possibility that  
32 plants may be exposed to ambient O<sub>3</sub> longer than 3 months in some locations, there is a lack of  
33 exposure experiments conducted for longer than 3 months.

34 In an analysis of the 3- and 6-month maximum W126 values calculated for over 1,200 AQS  
35 (Air Quality System) and CASTNET (Clean Air Status and Trend Network) EPA monitoring sites for  
36 the years 2008-2009, it was found that these 2 accumulation periods resulted in highly correlated  
37 metrics (Figure 9-12). The two cumulation periods were centered on the yearly maximum for each

1 monitoring site, and it is possible that this correlation would be weaker if the two periods were not  
2 temporally aligned. In the U.S., W126 cumulated over 3 months, and W126 cumulated over 6  
3 months are proxies of one another, as long as the period in which daily W126 is accumulated  
4 corresponds to the seasonal maximum. Therefore, it is expected that either statistic will predict  
5 vegetation response equally well. In other words, the strength of the correlation between maximum  
6 3-month W126 and maximum 6-month W126 is such that there is no material difference in their  
7 predictive value for vegetation response.



**A**



**B**

**Figure 9-12. Maximum 3-month, 12-h W126 plotted against maximum 6-month, 12-h W126. 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).**

#### 9.7.4. Ozone Uptake/Dose Modeling for Vegetation

- 1 Another approach for improving risk assessment of vegetation response to ambient O<sub>3</sub> is based
- 2 on estimating the O<sub>3</sub> concentration from the atmosphere that enters the leaf (i.e., flux or deposition).

1 Interest has been increasing in recent years, particularly in Europe, in using mathematically tractable  
2 flux models for O<sub>3</sub> assessments at the regional, national, and European scale (Matyssek et al., 2008,  
3 [191262](#))(Paoletti and Manning, 2007, [180174](#))(Emberson et al., 2000, [040350](#))(Emberson et al.,  
4 2000, [042537](#))(ICP M&M, 2004, [677471](#)). Some researchers have claimed that using flux models  
5 can be used to better predict vegetation responses to O<sub>3</sub> than exposure-based approaches (Matyssek  
6 et al., 2008, [191262](#)). However, other research has suggested that flux models do not predict  
7 vegetation responses to O<sub>3</sub> better than exposure-based models, such as AOT40 (Gonzalez-Fernandez  
8 et al., 2010, [381357](#)). While some efforts have been made in the U.S. to calculate O<sub>3</sub> flux into leaves  
9 and canopies (Grantz et al., 1997, [026664](#))(Grantz et al., 1995, [026659](#))(Grulke et al., 2004,  
10 [042646](#))(Turnipseed et al., 2009, [588752](#))(Uddling et al., 2009, [596219](#))(Bergweiler et al., 2008,  
11 [191656](#))(Hogg et al., 2007, [199349](#)), little information has been published relating these fluxes to  
12 effects on vegetation. The lack of flux data in the U.S. and the lack of understanding of  
13 detoxification processes have made this technique less viable for vulnerability and risk assessments  
14 in the U.S.

15 Flux calculations are data intensive and must be carefully implemented. Reducing  
16 uncertainties in flux estimates for areas with diverse surface or terrain conditions to within  $\pm 50\%$   
17 requires “very careful application of dry deposition models, some model development, and support  
18 by experimental observations” (Wesely and Hicks, 2000, [025018](#)). As an example, the annual  
19 average deposition velocity of O<sub>3</sub> among three nearby sites in similar vegetation was found to vary  
20 by  $\pm 10\%$ , presumably due to terrain (Brook et al., 1997, [041857](#)). Moreover, the authors stated that  
21 the actual variation was even greater, because stomatal uptake was unrealistically assumed to be the  
22 same among all sites, and flux is strongly influenced by stomatal conductance (Brook et al., 1997,  
23 [041857](#)). This uptake-based approach to quantify the vegetation impact of O<sub>3</sub> requires inclusion of  
24 those factors that control the diurnal and seasonal O<sub>3</sub> flux to vegetation (e.g., climate patterns,  
25 species and/or vegetation-type factors and site-specific factors). The models have to distinguish  
26 between stomatal and non-stomatal components of O<sub>3</sub> deposition to adequately estimate actual  
27 concentration reaching the target tissue of a plant to elicit a response (Uddling et al., 2009, [596219](#)).  
28 Determining this O<sub>3</sub> uptake via canopy and stomatal conductance by necessity relies on models to  
29 predict flux and ultimately the “effective” flux (Grunhage et al., 2004, [056621](#))(Massman et al.,  
30 2000, [011616](#))(Massman, 2004, [055350](#)). “Effective flux” has been defined as the balance between  
31 O<sub>3</sub> flux and detoxification processes (Dammgen et al., 1993, [055312](#))(Grunhage and Haenel, 1997,  
32 [040392](#))(Musselman and Massman, 1999, [040706](#))(Heath et al., 2009, [196783](#)). The time-integrated  
33 “effective flux” is termed “effective dose.” The uptake mechanisms and the resistances in this  
34 process, including stomatal conductance and biochemical defense mechanisms, are discussed below.  
35 The flux-based index is the goal for the “Level II” critical level for assessment of O<sub>3</sub> risk to  
36 vegetation and ecosystems across Europe (Ashmore MEmberson et al., 2004, [056624](#)).

### 9.7.4.1. Canopy Structure

1 A factor important in both O<sub>3</sub> exposure and uptake is how canopy structure affects O<sub>3</sub>  
2 concentration in and under forest canopies. There have been several investigations of O<sub>3</sub>  
3 concentrations under tree canopies (Enders, 1992, [040355](#))(Fontan et al., 1992,  
4 [040370](#))(Fredericksen et al., 1995, [038898](#))(Joss and Graber, 1996, [040408](#))(Kolb et al., 1997,  
5 [052597](#))(Lorenzini and Nali, 1995, [040691](#))(Neufeld et al., 1992, [038971](#))(Samuelson and Kelly,  
6 1997, [040832](#)). In general, they indicated a reduction in O<sub>3</sub> of ~20 to 40% in the area below the  
7 canopy but above the shrub/herb layers. An essential component in the determination of the AOT40  
8 as a critical level was the height at which the O<sub>3</sub> concentration was measured. The measurement  
9 heights are related to the O<sub>3</sub> concentration measured at the top of the canopy, i.e., upper surface  
10 boundary of the (quasi-) laminar layer (Grunhage and Jager, 2003, [052972](#)). This location is  
11 presumably more closely related to stomatal uptake. Weighting the O<sub>3</sub> concentration at this location  
12 takes into account stomatal opening and, if weighted with the Jarvis-Steward factors for radiation,  
13 temperature, and soil moisture, the “toxicologically” effective AOT40 is obtained (Grunhage and  
14 Jager, 2003, [052972](#)). A question exists however as to whether this “canopy” O<sub>3</sub> concentration is  
15 clearly connected to stomatal O<sub>3</sub> uptake. During site conditions that limit stomatal conductance (e.g.,  
16 low soil moisture, high VPD), high concentrations of O<sub>3</sub> can occur at the top of the canopy with  
17 minimal risk.

### 9.7.4.2. Site and Climate Factors

18 Soil moisture is a critical factor in controlling O<sub>3</sub> uptake through its effect on plant water status  
19 and stomatal conductance. In an attempt to relate uptake, soil moisture, and ambient air quality to  
20 identify areas of potential risk, available O<sub>3</sub> monitoring data for 1983 to 1990 were used along with  
21 literature-based seedling exposure-response data from regions within the southern Appalachian  
22 Mountains that might have experienced O<sub>3</sub> exposures sufficient to inhibit growth (Lefohn et al.,  
23 1997, [082871](#)). In a small number of areas within the region, O<sub>3</sub> exposures and soil moisture  
24 availability were sufficient to possibly cause growth reductions in some O<sub>3</sub> sensitive species (e.g.,  
25 black cherry). The conclusions were limited, however, because of the uncertainty in interpolating O<sub>3</sub>  
26 exposures in many of the areas and because the hydrologic index used might not reflect actual water  
27 stress.

### 9.7.4.3. Plant Defense Mechanism – Detoxification

28 The non-stomatal component of plant defenses are the most difficult to quantify, but some  
29 studies are available (Barnes et al., 2002, [040313](#))(Chen et al., 1998, [040317](#))(Massman and Grantz,  
30 1995, [040698](#))(Plochl et al., 2000, [040802](#))(Heath et al., 2009, [196783](#)). Massman et al. (2000,  
31 [011616](#)) developed a conceptual model of a dose-based index to determine how plant injury response  
32 to O<sub>3</sub> relates to the traditional exposure-based parameters. The index used time-varying-weighted  
33 fluxes to account for the fact that flux was not necessarily correlated with plant injury or damage.

1 The model applied only to plant foliar injury and suggested that application of flux-based models for  
2 determining plant damage (yield or biomass) would require a better understanding and quantification  
3 of the relationship between injury and damage.

## 9.8. Ozone Exposure-Plant Response Relationships

### 9.8.1. Introduction

4 The adequate characterization of the effects of O<sub>3</sub> on plants for the purpose of setting air  
5 quality standards is contingent not only on the choice of the index used (i.e. SUM06, W126) to  
6 summarize O<sub>3</sub> concentrations (Section 9.7), but also on quantifying the response of the plant  
7 variables of interest at specific values of the selected index. The many factors that determine the  
8 response of plants to O<sub>3</sub> exposure have been discussed in previous sections. They include species,  
9 genotype and other genetic characteristics (Section 9.4), biochemical and physiological status  
10 (Section 9.4), previous and current exposure to other stressors (Section 9.5), and characteristics of  
11 the exposure itself (Section 9.7). Establishing a secondary air quality standard requires the capability  
12 to generalize those observations, in order to obtain predictions that are reliable enough under a broad  
13 variety of scenarios, taking into account these factors. This section reviews results that have related  
14 specific quantitative observations of O<sub>3</sub> exposure with quantitative observations of plant responses,  
15 and the predictions of responses that have been derived from those observations through empirical  
16 models.

17 For four decades, exposure to O<sub>3</sub> at ambient concentrations found in many areas of the U.S.  
18 has been known to cause detrimental effects in plants (U.S. EPA, 2006, [088089](#))(U.S. EPA, 1996,  
19 [080827](#))(U.S. EPA, 1984, [029711](#))(U.S. EPA, 1978, [040586](#)). Results published after the 2006 O<sub>3</sub>  
20 AQCD continue to support this finding, and the following sections deal with the quantitative  
21 characterizations of the relationship, and what new insights may have appeared since 2006.  
22 Detrimental effects on plants include visible injury, decreases in the rate of photosynthesis, reduced  
23 growth, and reduced yield of marketable plant parts. Most published exposure-response data have  
24 been reported O<sub>3</sub> 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 O<sub>3</sub> for the purpose of  
26 setting secondary air quality standards. In order to support quantitative modeling of exposure-  
27 response relationships, data should preferably include more than three levels of exposure, and some  
28 control of potential confounding or interacting factors should be present in order to model the  
29 relationship with sufficient accuracy. Letting potential confounders, such as other stressors, vary  
30 freely when generating O<sub>3</sub> exposure-response data might improve the ‘realism’ of the data, but it also  
31 greatly increases the amount of data necessary to extract a clear quantitative description of the  
32 relationship. Conversely however, experimental settings should not be so exhaustively restrictive as  
33 to make generalization outside of them problematic. During the last four decades, many of the  
34 studies of the effects of O<sub>3</sub> on growth and yield of plants have not included enough levels of O<sub>3</sub> to

1 parameterize more than the simplest linear model. The majority of these studies have only contrasted  
2 two levels, ambient and elevated, or sometimes three by adding carbon filtration in OTC studies,  
3 with little or no consideration of quantitatively relating specific values of exposure to specific values  
4 of growth or yield. This is not to say that studies that did not include more than two or three levels of  
5 O<sub>3</sub> exposure, or studies that were conducted in uncontrolled environments, do not provide exposure-  
6 response information that is highly relevant to reviewing air quality standards. In fact, they can be  
7 essential in verifying the agreement between predictions obtained through the empirical models  
8 derived from experiments such as NCLAN, and observations. The consensus of model predictions  
9 and observations from a variety of studies conducted in other locations, at other times, and using  
10 different exposure methods, greatly increases confidence in the reliability of both. Furthermore, if  
11 they are considered in the aggregate, studies with few levels of exposure or high unaccounted  
12 variability can provide additional independent estimates of decrements in plant growth and yield, at  
13 least within a few broad categories of exposure.

14 Extensive exposure-response information on a wide variety of plant species has been produced  
15 by two long-term projects that were designed with the explicit aim of obtaining quantitative  
16 characterizations of the response of such an assortment of crop plants and tree seedlings to O<sub>3</sub> under  
17 North American conditions: the NCLAN project for crops, and the EPA National Health and  
18 Environmental Effects Research Laboratory, Western Ecology Division tree seedling project  
19 (NHEERL/WED). The NCLAN project was initiated by the EPA in 1980 primarily to improve  
20 estimates of yield loss under field conditions and to estimate the magnitude of crop losses caused by  
21 O<sub>3</sub> throughout the U.S. (Heck et al., 1982, [039525](#))(Heck et al., 1991, [042621](#)). The cultural  
22 conditions used in the NCLAN studies approximated typical agronomic practices, and the primary  
23 objectives were: (1) to define relationships between yields of major agricultural crops and O<sub>3</sub>  
24 exposure as required to provide data necessary for economic assessments and development of O<sub>3</sub>  
25 NAAQS; (2) to assess the national economic consequences resulting from O<sub>3</sub> exposure of major  
26 agricultural crops; and (3) to advance understanding of cause-and-effect relationships that determine  
27 crop responses to pollutant exposures.

28 NCLAN experiments yielded 54 exposure-response curves for 12 crop species, some of which  
29 were represented by multiple cultivars at several of 6 locations throughout the U.S. The  
30 NHEERL/WED project was initiated by EPA in 1988 with the same objectives for tree species, and  
31 yielded 49 exposure-responses curves for multiple genotypes of 11 tree species grown for up to three  
32 years in Oregon, Michigan, and the Great Smoky Mountain National Park. Both projects used OTCs  
33 to expose plants to three to five levels of O<sub>3</sub>. Eight of the 54 crop datasets were from plants grown  
34 under a combination of O<sub>3</sub> exposure and experimental drought conditions. Figure 9-13 through 9-16  
35 summarize some of the NCLAN and NHEERL/WED results.

36 It should be noted that data from FACE experiments might also be used for modeling  
37 exposure-response. They only use two levels of O<sub>3</sub> (ambient concentration at the site and a multiple  
38 of it), but given that the value of both levels of exposure changes every year, and that they are  
39 typically run for many consecutive years, aggregating data over time produces twice as many levels

1 of O<sub>3</sub> as there are years. As described in Section 9.3.4, FACE experiments seek to impose fewer  
2 constraints on the growth environment than OTCs. As a consequence, FACE studies have to contend  
3 with larger variability, especially year-to-year variability, but the difference in experimental  
4 conditions between the two methodologies makes comparisons between their results especially  
5 useful.

6 Growth and yield of at least one crop (soybean) has been investigated in yearly experiments  
7 since 2001 at a FACE facility in Illinois (Morgan et al., 2006, [079186](#))(University of Illinois, 2010,  
8 [670286](#)), however almost all analyses of SoyFACE published so far have been based on subsets of  
9 one or two years, and have only contrasted ambient versus elevated O<sub>3</sub> as categorical variables. They  
10 have not modeled the response of growth and yield to O<sub>3</sub> exposure continuously over the range of  
11 exposure values that have occurred over time. The only exception is a study by Betzelberger et al.  
12 (2010, [644183](#)), who used a linear regression model on data pooled over 2 years. Likewise, trees of  
13 three species (trembling aspen, paper birch, and sugar maple) were grown between 1998 and 2009 in  
14 a FACE experiment located in Rhinelander, Wisconsin (Dickson et al., 2000, [628220](#))(Pregitzer et  
15 al., 2008, [191677](#)). The Aspen FACE experiment has provided extensive data on responses of trees  
16 beyond the seedling stage under long-term exposure, and also on ecosystem-level responses (Section  
17 9.6), but the only attempt to use those data in a continuous model of the response of tree growth to  
18 O<sub>3</sub> exposure (Percy et al., 2007, [093287](#)) suffered severe methodological problems, some of which  
19 are discussed in Section 9.8.3. Finally, one experiment was able to exploit a naturally occurring  
20 gradient of O<sub>3</sub> concentrations to fit a linear regression model to the growth of cottonwood (Gregg et  
21 al., 2003, [046996](#); Gregg et al., 2006, [186961](#)). Factors such as genotype, soil type and soil moisture  
22 were under experimental control, and the authors were able to partition out the effects of potential  
23 confounders such as temperature, atmospheric N deposition, and ambient CO<sub>2</sub>.

24 A serious difficulty in assessing results of exposure-response research is the multiplicity of O<sub>3</sub>  
25 metrics that have been used in reporting. As described in Section 9.7, metrics that entail either  
26 weighting or thresholding of hourly values cannot be converted into one another, or into unweighted  
27 metrics such as hourly average. When using weighted or thresholded metrics, which include W126,  
28 AOTx or SUMx metrics; O<sub>3</sub> exposure at every exposure-response data point must be computed  
29 separately for each metric, starting with the hourly data. Comparisons of exposure-response models  
30 can only be made between studies that used the same metric, and the value of exposure at which a  
31 given plant response is expected on one scale of exposure cannot be exactly converted to another  
32 scale. Determining the exposure value at which an effect would be observed in a different metric can  
33 only be accomplished by first computing the experimental exposures in this metric from the hourly  
34 data, then estimating (fitting) model coefficients again. This problem is irremediable, although useful  
35 comparisons might be made using categorical exposures such as ‘current ambient exposure’ or ‘2050  
36 projected exposure’, which can serve as a common reference for quantitative values expressed in  
37 various metrics. Studies that contained growth or yield exposure-response data at few levels of  
38 exposure, and/or using metrics other than W126 are summarized in Tables 9-16 and 9-17.

39

## 9.8.2. 1996 and 2006 Ozone AQCDs Estimates Of Crop Yield Loss And Tree Seedling Biomass Loss

1 The 1996 and 2006 O<sub>3</sub> AQCDs relied extensively on analyses of NCLAN and NHEERL/WED  
2 by Lee et al. (1987, [042135](#); 1988, [042136](#); 1989, [042137](#); 1994, [043268](#)), Hogsett et al. (1997,  
3 [040402](#)), Lee and Hogsett (1999, [040451](#)), Heck et al. (1984, [039380](#)), Rawlings and Cure (1985,  
4 [039419](#)), Lesser et al. (1990, [043015](#)), and Gumpertz and Rawlings (1992, [043259](#)). Those analyses  
5 concluded that a three-parameter Weibull model –

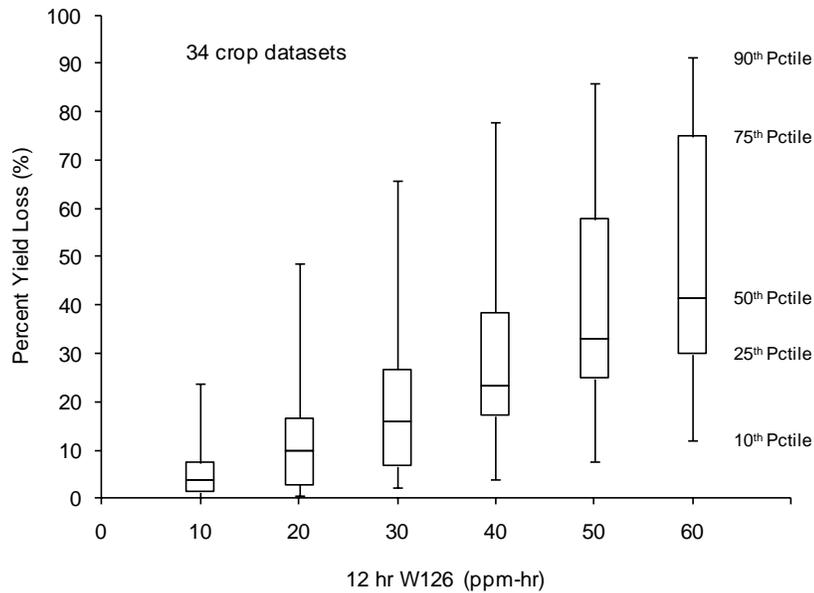
$$6 \quad Y = \alpha e^{-\left(\frac{W126}{\eta}\right)^\beta}$$

Equation 9-2□

6 is the most appropriate model for the response of absolute yield and growth to O<sub>3</sub> exposure, because  
7 of the interpretability of its parameters, its flexibility (given the small number of parameters), and its  
8 tractability for estimation. In addition, removing the intercept  $\alpha$  results in a model of relative yield  
9 (yield relative to [yield at exposure=0]) without any further reparameterization. Formulating the  
10 model in terms of relative yield or relative yield loss (yield loss=[1 – relative yield]) is essential in  
11 comparing exposure-response across species, genotypes, or experiments for which absolute values of  
12 the response may vary greatly. In the 1996 and 2006 O<sub>3</sub> AQCDs, the two-parameter model of relative  
13 yield was used in deriving common models for multiple species, multiple genotypes within species,  
14 and multiple locations.

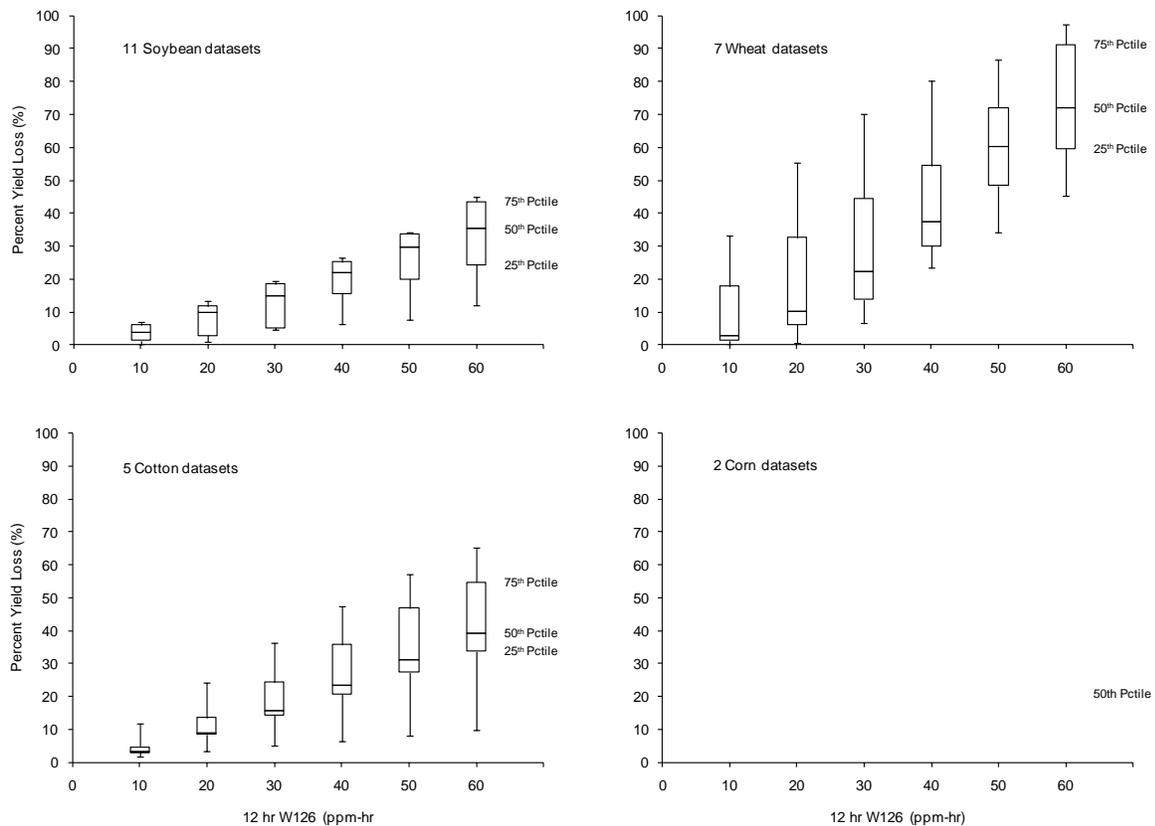
15 Given the disparate species, genotypes, and locations that were included in the NCLAN and  
16 NHEERL/WED projects, and in the absence of plausible distributional assumptions with respect to  
17 those variables, a three step process using robust methods was used to obtain parameter estimates  
18 that could be generalized. The models that were derived for each species or group of species were  
19 referred to as median composite functions. In the first step, the three parameters of the Weibull  
20 model were estimated (fitted) for absolute yield or biomass data from each NCLAN and  
21 NHEERL/WED experiment (54 crop datasets and 49 tree seedling datasets), using nonlinear  
22 regression. When data were only available for three levels of exposure because of experimental  
23 problems, the shape parameter  $\beta$  was constrained to 1, reducing the model to an exponential decay  
24 model. In the second step,  $\alpha$  was dropped, and predicted values of relative yield or biomass were  
25 then computed for 12-hr W126 exposures between 0 and 60 ppm-h. At each of these W126 exposure  
26 values, the 25th, 50th, and 75th percentiles of the response were identified among the predicted  
27 curves of relative response. For example, for the 34 NCLAN studies of 12 crop species grown under  
28 non-droughted conditions for a complete cropping cycle (Figure 9-13), the 3 quartiles of the  
29 response were identified at every integer value of W126 between 0 and 60. The third step fitted a  
30 two-parameter Weibull model to those percentiles, yielding the median composite function for the  
31 relative yield or biomass response to O<sub>3</sub> exposure for each grouping of interest (e.g., all crops, all  
32 trees, all datasets for one species), as well as composite functions for the other quartiles. In the 1996  
33 and 2006 O<sub>3</sub> AQCDs, this modeling of crop yield loss and tree seedling biomass loss was conducted

1 using the SUM06 metric for exposure. This section updates those results by using the 12-hr W126 as  
 2 proposed in 2007 (72 FR 37818 (2007, [684055](#))) and 2010 (75 FR 2938 (2010, [684211](#)), p. 3003).  
 3 Figures 9-13 through 9-16 present quantiles of predicted relative yield or biomass loss at seven  
 4 values of the 12-h W126 for some representative groupings of NCLAN and NHEERL/WED results.  
 5 Tables 9-8 through 9-10 give the 90-day 12-h W126 O<sub>3</sub> exposure values at which 10 and 20% yield  
 6 or biomass losses are predicted in 50 and 75% of crop or tree species using the composite functions.



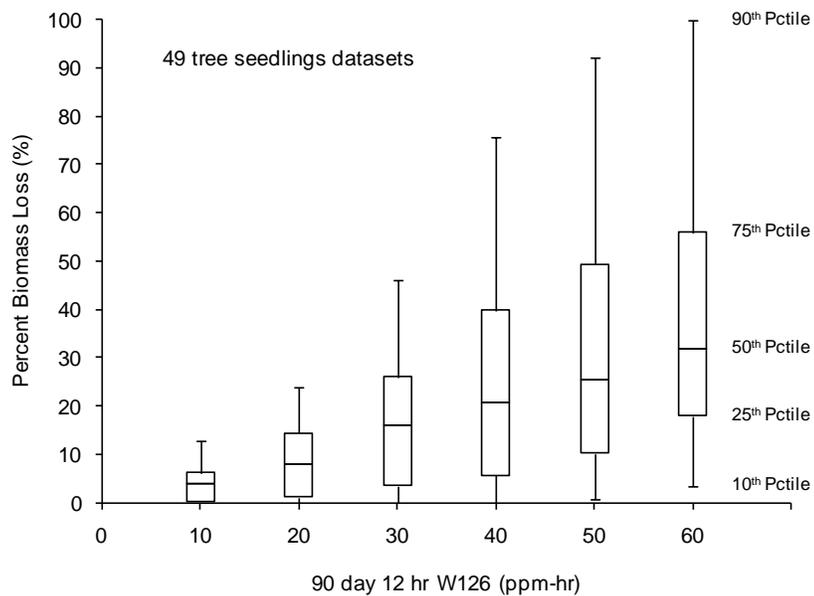
Source of Weibull parameters: Lee and Hogsett (1996, [670278](#)).

**Figure 9-13. Quantiles of predicted relative yield loss for 34 NCLAN crop experiments. 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.**



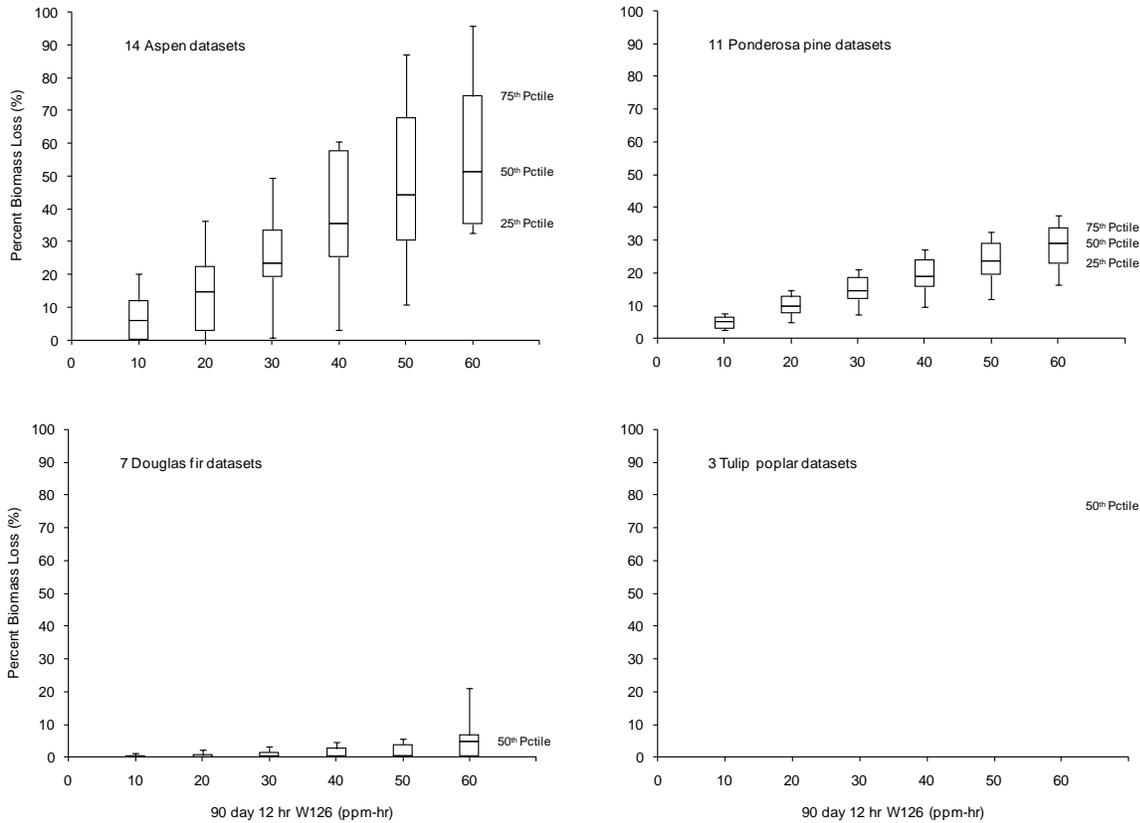
Source of Weibull parameters: Lee and Hogsett (1996, [670278](#)).

**Figure 9-14. Quantiles of predicted relative yield loss for 4 crop species in NCLAN experiments. □**  
**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, [670278](#)).

**Figure 9-15. Quantiles of predicted relative biomass loss for 49 tree species in NHEERL/WED experiments. 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, [670278](#)).

**Figure 9-16. Quantiles of predicted relative biomass loss for 4 tree species in NHEERL/WED experiments. 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.**

**Table 9-8. Ozone exposures at which 10 and 20% yield loss is predicted for 50 and 75% of crop species, based 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**

	90-day 12-h W126 for 10% yield loss (ppm-h)	90-day 12-h W126 for 20% yield loss (ppm-h)
<b>Model for the 50th Percentile of 34 curves</b>		
Relative yield= $\exp(-(W126/104.82)^{1.424})$	22	37
<b>Model for the 75th Percentile of 34 curves</b>		
Relative yield= $\exp(-(W126/78.12)^{1.415})$	16	27

Source of parameters for the 34 curves: Lee and Hogsett (1996, [670278](#))

**Table 9-9. Ozone exposures at which 10 and 20% yield loss is predicted for 50 and 75% of crop species under 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**

		90 day 12-h W126 for 10% yield loss (ppm-h)	90 day 12-h W126 for 20% yield loss (ppm-h)
<b>Model for the 50th Percentile of 2x8 curves</b>			
Watered	Relative yield= $\exp(-(W126/132.86)^{1.170})$	19	37
Droughted	Relative yield= $\exp(-(W126/179.84)^{1.713})$	48	75
<b>Model for the 75th Percentile of 2x8 curves</b>			
Watered	Relative yield= $\exp(-(W126/90.43)^{1.310})$	16	29
Droughted	Relative yield= $\exp(-(W126/105.16)^{1.833})$	31	46

Source of parameters for the 16 curves: Lee and Hogsett (1996, [670278](#))

**Table 9-10. Ozone exposures at which 10 and 20% biomass loss is predicted for 50 and 75 % of tree species, based 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**

	90 day 12 h W126 for 10% yield loss (ppm-h)	90 day 12 h W126 for 20% yield loss (ppm-h)
<b>Model for the 50th Percentile of 49 curves</b>		
Relative yield= $\exp(-(W126/131.57)^{1.242})$	21	39
<b>Model for the 75th Percentile of 49 curves</b>		
Relative yield= $\exp(-(W126/65.49)^{1.500})$	15	24

Source of parameters for the 49 curves: Lee and Hogsett (1996, [670278](#))

### 9.8.3. 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 have  
 2 been published that could provide a basis for estimates of exposure-response that can be compared to  
 3 those of the 1996 and 2006 O<sub>3</sub> AQCDs. Most experiments, regardless of exposure methodology,  
 4 include only two levels of exposure. In addition, very few studies have included measurements of  
 5 exposure using the W126 metric, or the hourly O<sub>3</sub> concentration data that would allow computing  
 6 exposure using the W126. Two FACE projects, however, were conducted over multiple years, and by  
 7 adding to the number of exposure levels over time, may support independent model estimation and  
 8 prediction using the same model and the same robust process as summarized in Section 9.8.2.  
 9 Hourly O<sub>3</sub> data were available from both FACE projects.

10 The SoyFACE project is situated near Champaign, IL, and comprises 32 octagonal rings (20m-  
 11 diameter), 4 of which in a given year are exposed to ambient conditions, and 4 of which are exposed  
 12 to elevated O<sub>3</sub> as a fixed proportion of the instantaneous ambient concentration (Betzelberger et al.,  
 13 2010, [644183](#); Morgan et al., 2004, [072764](#); Morgan et al., 2006, [079186](#))(University of Illinois,  
 14 2010, [670286](#)). Since 2002, yield data have been collected for up to 8 genotypes of soybean grown  
 15 in subplots within each ring. The Aspen FACE project is situated in Rhinelander, WI, and comprises  
 16 12 rings (30m-diameter), 3 of which are exposed to ambient conditions, and 3 of which are exposed  
 17 to O<sub>3</sub> as a fixed proportion of the instantaneous ambient concentration (Dickson et al., 2000, [628220](#);  
 18 Karnosky et al., 2005, [095556](#); Pregitzer et al., 2008, [191677](#)). In the summer of 1997, half the area  
 19 of each ring was planted with small (five to seven leaf sized) clonally propagated plants of five  
 20 genotypes of trembling aspen, which were left to grow in those environments until 2009. Biomass  
 21 data are currently available for the years 1997-2005 (King et al., 2005, [191701](#)). Ozone exposure in  
 22 these two FACE projects can be viewed as a categorical variable with two levels: ambient, and  
 23 elevated. However, this overlooks the facts that yearly ambient and elevated exposure both vary with  
 24 every year, and that the proportionality between them also changes. This change has two sources:

1 first, the dispensing of O<sub>3</sub> into the elevated exposure rings varies from the proportionality set point to  
2 some extent, and for SoyFACE, the set point changed between years. Second, the proportionality  
3 does not propagate predictably from the hourly data to the yearly value when using thresholded or  
4 concentration-weighted cumulative metrics (such as AOT40, SUM06 or W126). Hourly average  
5 elevated exposures that are, for example, 1.5 times ambient do not result in AOT40, SUM06 or  
6 W126 values that are some constant multiple of the ambient values of those indices. The greater the  
7 fraction of elevated hourly values that are above the threshold or heavily weighted, compared to the  
8 fraction of hourly ambient values that are, the greater the difference between ambient and elevated  
9 yearly exposure, as measured using weighted cumulative indices. When elevated exposure is a  
10 multiple of ambient hourly intervals, the number of hours for which elevated exposure meets the  
11 threshold for inclusion can vary widely, even though the hourly mean for the year retains the  
12 proportionality. As a consequence, the number of exposure levels in multi-year experiments is twice  
13 the number of years. In the case of SoyFACE for the period between 2002 and 2008, ambient  
14 exposure in the highest year was approximately equal to elevated exposure in the lowest year, with  
15 14 levels of O<sub>3</sub> exposure evenly distributed from lowest to highest. The particular conditions of the  
16 Aspen FACE experiment resulted in 12 exposure levels between 1998 and 2003, but they were not as  
17 evenly distributed between minimum and maximum over the 6-year period.

18 There are necessary differences in the modeling of exposure-response in annual plants such as  
19 soybean, and in perennial plants such as aspen trees, when exposure takes place over multiple years.  
20 In annual plants, responses recorded at the end of the life cycle, i.e., yearly, are analyzed in  
21 relationship to that year's exposure. Yield of soybeans is affected by exposure during the year the  
22 crop was growing, and a new crop is planted every year. Thus an exposure-response relationship can  
23 be modeled from yearly responses matched to yearly exposures, with those exposure-response data  
24 points having been generated in separate years. For perennial organisms, which are not harvested  
25 yearly and continue to grow from year to year, such pairing of exposure and response cannot be done  
26 without accounting for time. Not only does the size of the organism at the beginning of each year of  
27 exposure increase, but size is also dependent on the exposure from previous years. Therefore the  
28 relationship of response and exposure must be analyzed either one year at a time, or by standardizing  
29 the response as a yearly increment relative to size at the beginning of each year. Furthermore, the  
30 relevant measurement of exposure is cumulative, or cumulative yearly average exposure, starting in  
31 the year exposure was initiated, up to the end of the year of interest. When analyzing the growth of  
32 trees over several years, it would be evidently incorrect to pair the exposure level in every discrete  
33 year with absolute size of the trees that year, and posit a direct relationship between them. In the  
34 Aspen FACE experiment, for example, one could not establish an exposure-response relationship by  
35 matching 12 yearly exposures and 12 yearly tree sizes, as if size did not also depend on time. This is  
36 the basis of the 2007 study of Aspen FACE data by Percy et al. (2007, [093287](#)), and that study was  
37 therefore not informative.

### 9.8.3.1. Comparison of NCLAN-Based Prediction and SoyFACE Data.

1 For this ISA, EPA conducted a comparison between yield as predicted by the composite  
2 function three-step process (Section 9.8.2) using NCLAN data for soybean yield as observed in  
3 SoyFACE. The median composite function for relative yield was derived for the 11 NCLAN soybean  
4 Weibull functions for non-droughted studies, and several comparisons between prediction and  
5 SoyFACE observations were conducted as follows.

6 For the years 2007 and 2008, SoyFACE yield data were available for 7 and 6 genotypes,  
7 respectively. The EPA used those data to compare the change in relative yield observed in a given  
8 year between ambient O<sub>3</sub> and elevated O<sub>3</sub> in SoyFACE, versus the change in relative yield predicted  
9 by the NCLAN-based median composite function between those same two values of O<sub>3</sub> exposure.  
10 The two parameter median composite function for relative yield of soybean was used to predict yield  
11 response at the two observed values of exposure in each year, and the change between yield under  
12 ambient and elevated was compared to the change observed in SoyFACE for the relevant year (Table  
13 9-11). This approach results in a direct comparison of predicted versus observed change in yield.  
14 Because the value of relative response between any two values of O<sub>3</sub> exposure is independent of the  
15 intercept  $\alpha$ , this comparison does not require prediction of the absolute values of the responses.

16 Since comparisons of absolute values might be of interest, the predictive functions were also  
17 scaled to the observed data, using two distinct methods. In the first method, the intercept  $\alpha$  was  
18 calculated algebraically by entering the observed W126 value at ambient exposure and the  
19 corresponding value of the response into the three parameter model with the shape and scale  
20 parameters ( $\beta$  and  $\eta$ ) set to their value for the NCLAN predictive model. This method provides a  
21 comparison between the response observed under elevated exposure, and the response that would  
22 have been predicted with only the knowledge of what the response was under ambient exposure  
23 (Table 9-12; Method 1). In the second method, the intercept for the NCLAN predictive model was  
24 estimated by regression using both ambient and elevated data. This method gives a comparison of  
25 prediction and observation that takes all the observed information into account to provide the best  
26 possible estimate of the intercept, and thus the best possible scaling (Table 9-12, Method 2 and  
27 Figure 9-17). It should be noted that the similarity to each other of the predictions obtained by these  
28 two scaling methods is a reflection of the accuracy of the predictions: the distance between the  
29 predictions from the two methods increases as the distance between prediction and observation  
30 increases.

31 For the comparison of NCLAN and SoyFACE, this validation was possible for 2007 and 2008,  
32 where data for 7 and 6 soybean genotypes, respectively, were available. The median composite  
33 function for relative yield was derived for the 11 NCLAN soybean Weibull functions for  
34 nondroughted studies, and the values of median yield under ambient exposure at SoyFACE in 2007  
35 and 2008 were used to obtain an estimate of the intercept  $\alpha$  for the NCLAN median function in each  
36 of the two years

37 Table 9-11 presents the results of ambient/elevated relative yield comparisons between the  
38 NCLAN-derived predictions and SoyFACE observations. Table 9-12 presents the results of

1 comparisons between NCLAN-derived predictions and SoyFACE observations of yield, using two  
 2 methods for scaling the predictive function. Figure 9-17 presents yield observed in two years in  
 3 SoyFACE, and predicted by the median composite function derived from NCLAN data using the  
 4 second scaling method as described, with the intercept estimated using 14 observations in 2007, and  
 5 12 in 2008.

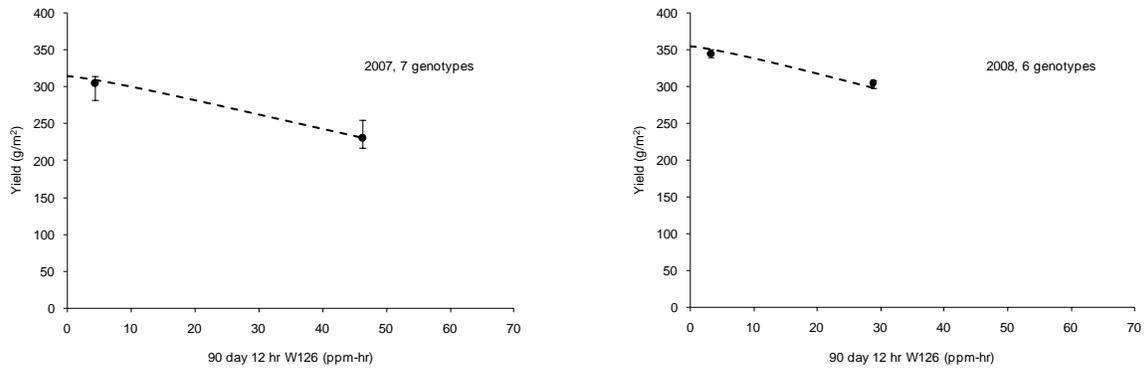
6 Finally, data were also available for one additional genotype from 2003 to 2007. By  
 7 aggregating data for each genotype over the years (5 years for one genotype, 2 years for the 6  
 8 others), a composite function for the 25th, 50th, and 75th percentiles was then developed for  
 9 SoyFACE, and compared to the corresponding NCLAN-based function. NCLAN functions were  
 10 obtained using 12-hr W126 standardized to 90 days. SoyFACE 12-hr W126 was cumulated over the  
 11 highest 90 days of the growing season.  
 12

**Table 9-11. Comparison between relative yield observed in the SoyFACE experiment, and relative yield predicted at the same values of ozone by the median composite function for NCLAN (two-parameter relative yield model)**

Year	90-day 12-h W126 (ppm-h)		Yield, Elevated Relative to Ambient	
	Ambient	Elevated	Observed in SoyFACE	Predicted by NCLAN
2007	4.39	46.23	0.76	0.75
2008	3.23	28.79	0.88	0.85

**Table 9-12. Comparison between yield observed in the SoyFACE experiment and yield predicted at the same values of ozone by the median composite function for NCLAN (three-parameter absolute yield model), using two scaling methods to calculate the intercept**

Year	90-day 12-h W126 (ppm-h)						
	Ambient	Elevated	Yield observed in SoyFACE ambient (g/m <sup>2</sup> )	Yield observed in SoyFACE elevated (g/m <sup>2</sup> )	Yield predicted by NCLAN in elevated, Method 1 (g/m <sup>2</sup> )	Yield predicted by NCLAN in ambient, Method 2 (g/m <sup>2</sup> )	Yield predicted by NCLAN in elevated, Method 2 (g/m <sup>2</sup> )
2007	4.39	46.23	305.2	230.6	227.6	309.2	230.6
2008	3.23	28.79	344.8	304.4	293.5	350.3	298.2

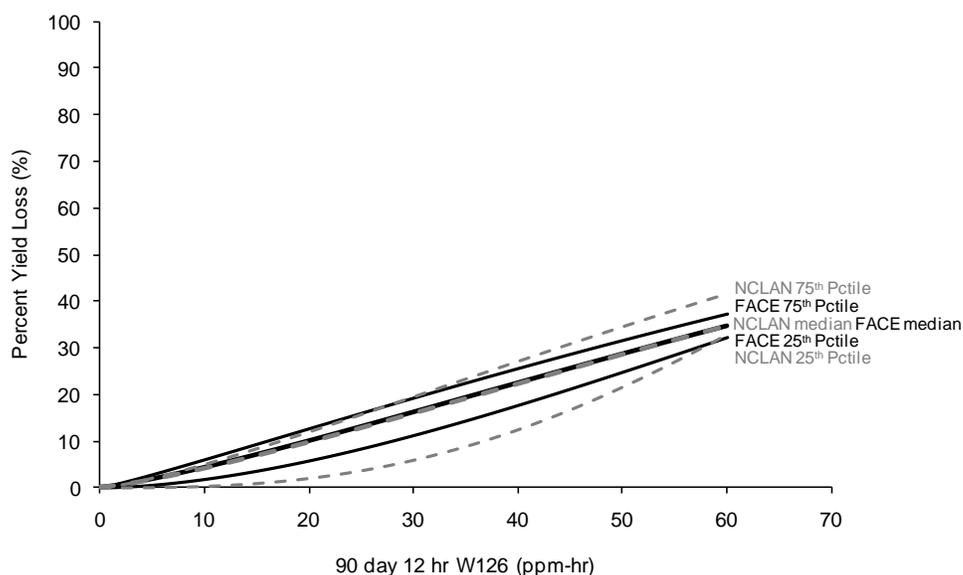


Source of data: Betzelberger et al. (2010, [644183](#));Morgan et al. (2006, [079186](#)); Lee and Hogsett (1996, [670278](#)).

Note: Black dots are median of 7 or 6 soybean genotypes in SoyFACE (2007, 2008); bars are IQR for genotypes; dashed line is median composite model for 11 studies in NCLAN.

**Figure 9-17. 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 by pooling one genotype from 2003 to 2007, and six genotypes in 2007  
 3 and 2008. NCLAN functions were obtained using 12-h W126 standardized to 90 days. SoyFACE  
 4 12-h W126 was cumulated over the highest 90 days of the growing season. The correlation between  
 5 W126 cumulated for the entire season in SoyFACE and W126 for the highest 90 days was greater  
 6 than 0.99 in all years. The same process was used for SoyFACE: first, the three parameter Weibull  
 7 model described in Section 9.8.2 was estimated using nonlinear regression on exposure-yield data  
 8 for each genotype separately, over the years for which data were available, totaling seven curves.  
 9 The 25th, 50th, and 75th percentiles of the predicted values for the two parameter relative yield  
 10 curves were then identified at every integer of W126 between 0 and 60, and a two-parameter Weibull  
 11 model estimated by regression for the three quartiles. The comparison between these composite  
 12 functions for the quartiles of relative yield loss in SoyFACE and the corresponding composite  
 13 functions for NCLAN is presented in Figure 9-18.



Source of data: Betzelberger et al. (2010, [644183](#));Morgan et al. (2006, [079186](#)); Lee and Hogsett (1996, [670278](#)).

**Figure 9-18. 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 Tables 9-11 and 9-12, and in Figure 9-17, the agreement between predictions based  
 2 on NCLAN data and SoyFACE observations was notably close in single-year comparisons. Together  
 3 with the very high agreement between median composite models for NCLAN and SoyFACE, it  
 4 provides very strong mutual confirmation of those two projects' results with respect to the response  
 5 of yield of soybeans to O<sub>3</sub> exposure. It is readily apparent from these results that the methodology  
 6 described in Section 9.8.2 for obtaining predictions of yield or yield loss from NCLAN data is  
 7 strongly validated by SoyFACE results. As described in Section 9.3, the exposure technologies used  
 8 in the two projects were in sharp contrast, specifically with respect to the balance each achieved  
 9 between control of potential interacting factors or confounders, and fidelity to real world conditions.  
 10 The comparisons that EPA conducted therefore demonstrate that the methodology used in developing  
 11 the composite functions is resistant to the influence of nuisance variables, and that predictions are  
 12 reliable. They may also suggest that the aspects in which the two exposure technologies differ have  
 13 less influence on exposure-response than initially supposed.

### 9.8.3.2. Comparison of NHEERL/WED-Based Prediction of Tree Biomass Response and Aspen FACE Data

14 EPA also conducted two comparisons between prediction of above-ground biomass loss based  
 15 on NHEERL/WED results and observations from Aspen FACE. The median composite function was  
 16 developed from NHEERL/WED data for 11 studies that used wild-type seedlings of aspen as well as

1 four clonally propagated genotypes. All plants were grown in OTCs for one growing season before  
 2 being destructively harvested. Aspen FACE data were from clonally propagated trees of five  
 3 genotypes grown from 1998 to 2003, with above-ground biomass calculated using allometric  
 4 equations derived from data for trees harvested destructively in 2000 and 2002 (King et al., 2005,  
 5 [191701](#)).

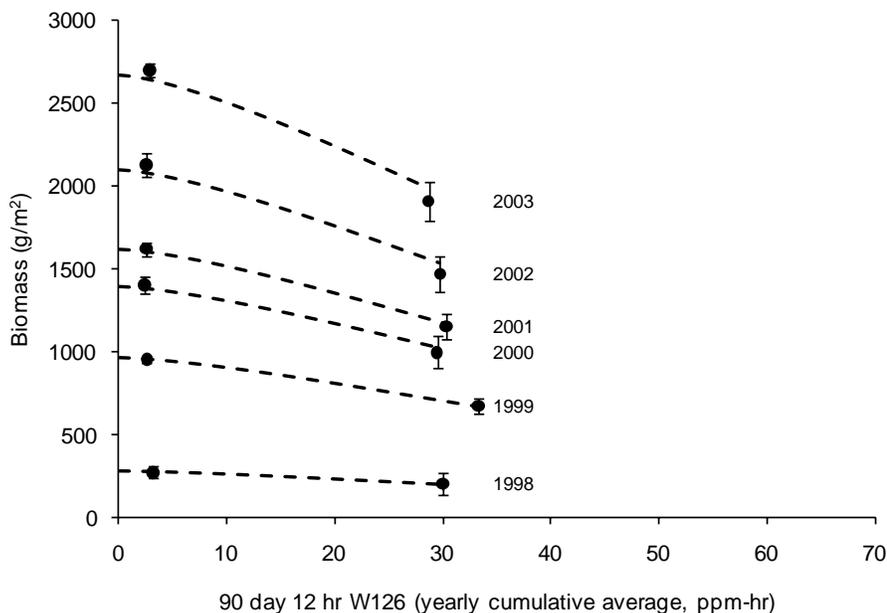
6 The two parameter median composite function for relative biomass was used to predict  
 7 biomass response under the observed elevated exposure, relative to its value under observed ambient  
 8 exposure. EPA first tested the accuracy of the prediction of biomass at elevated exposure relative to  
 9 biomass at ambient exposure, for each separate year of Aspen FACE. Comparisons between  
 10 observed and predicted biomass values were then conducted for each year by scaling the predictive  
 11 function to yearly Aspen FACE data using the two scaling methods described in Section 9.8.3.1.  
 12 Yearly 90 day 12-hour W126 values for Aspen FACE were computed as the cumulative average  
 13 from the year of planting up to the year of interest. A comparison of composite functions between  
 14 NHEERL/WED and Aspen FACE, similar to the one performed for NCLAN and SoyFACE, was not  
 15 possible: as discussed in the introduction to Section 9.8, the pairing of 12 exposure values from  
 16 separate years and 12 values of biomass cannot be the basis for a model of exposure-response,  
 17 because the trees continued growing for the six-year period of exposure. Table 9-13 presents the  
 18 results of ambient/elevated relative biomass comparisons between the NHEERL/WED-derived  
 19 predictions and Aspen FACE observations. Table 9-14 presents the results of comparisons between  
 20 NHEERL/WED-derived predictions and Aspen FACE observations of biomass, using two methods  
 21 for scaling the predictive function. Figure 9-19 presents biomass observed in six years at Aspen  
 22 FACE, and predicted by the median composite function derived from NHEERL/WED data using the  
 23 second scaling method as described, with the intercept estimated using 2 observations in each year.

**Table 9-13. Comparison between above-ground biomass observed under elevated ozone in Aspen FACE experiment in 6 year, relative to above-ground biomass observed under ambient ozone and relative above-ground biomass above-ground biomass at the same values of ozone predicted by the median composite function for NHEERL/WED (two-parameter relative biomass model)**

Year	90-day 12-h W126 (ppm-h) Cumulative Average		Above-Ground Biomass, Elevated Relative To Ambient	
	Ambient	Elevated	Observed in Aspen FACE	Predicted by NHEERL/WED
1998	3.19	30.08	0.75	0.74
1999	2.61	33.85	0.70	0.70
2000	2.43	30.16	0.71	0.74
2001	2.55	31.00	0.71	0.73
2002	2.51	30.27	0.69	0.74
2003	2.86	29.12	0.71	0.75

**Table 9-14. 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 (three-parameter absolute biomass model), using 2 scaling methods to calculate the intercept**

Year	90 day 12-h W126 (ppm-h) Cumulative Average		Biomass Observed in Aspen FACE (g/m <sup>2</sup> )		Biomass Predicted by NHEERL/WED, Method 1 (g/m <sup>2</sup> )	Biomass Predicted by NHEERL/WED, Method 2 (g/m <sup>2</sup> )	
	Ambient	Elevated	Ambient	Elevated	Elevated	Ambient	Elevated
1998	3.19	30.08	274.7	204.9	202.3	276.0	203.2
1999	2.61	33.85	955.3	673.3	665.9	958.7	668.3
2000	2.43	30.16	1400.3	998.6	1036.0	1382.4	1022.8
2001	2.55	31.00	1620.7	1154.9	1183.7	1607.0	1173.7
2002	2.51	30.27	2125.9	1468.41	1566.7	2079.0	1532.1
2003	2.86	29.12	2695.2	1907.8	2022.5	2640.1	1981.2



Source of data: King et al. (2005, [191701](#)), Lee and Hogsett (1996, [670278](#)).

Note: Black dots are aspen biomass/m<sup>2</sup> 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.

**Figure 9-19. 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.**

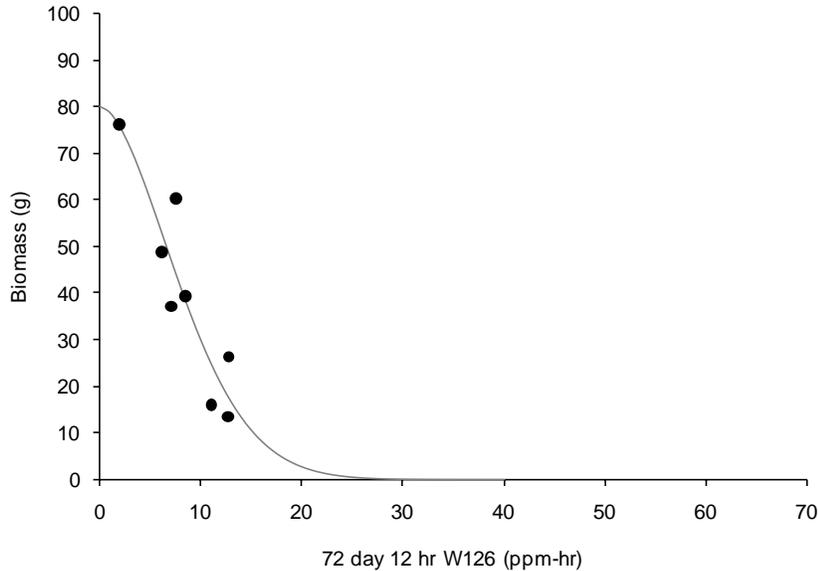
1 As in the comparisons between NCLAN and SoyFACE, the agreement between predictions  
2 based on NHEERL/WED data and Aspen FACE observations was exceptionally close. The results of  
3 the two projects strongly reinforce each other with respect to the response of aspen biomass to O<sub>3</sub>  
4 exposure. The methodology used for obtaining the median composite function is shown to be  
5 capable of deriving a predictive model despite potential confounders, and despite the added  
6 measurement error that is expected from calculating biomass using allometric equations. In addition,  
7 the function based on one year of growth was shown to be applicable to subsequent years.

8 The results of experiments that used different exposure methodologies, different genotypes,  
9 locations, and durations converged to the same values of response to O<sub>3</sub> exposure for each of two  
10 very dissimilar plant species, and predictions based on the earlier experiments were validated by the  
11 data from current ones. However, in these comparisons, the process used in establishing predictive  
12 functions involved aggregating data over variables such as time, locations, and genotypes, and the  
13 use of a robust statistic (quartiles) for that aggregation. The validating data, from SoyFACE and  
14 Aspen FACE, were in turn aggregated over the same variables. The accuracy of predictions is not  
15 expected to be conserved for individual values of those variables over which aggregation occurred.  
16 For example, the predicted values for soybean, based on data for five genotypes, are not expected to  
17 be valid for each genotype separately. As shown in the validation, however, aggregation that  
18 occurred over different values of the same variable did not affect accuracy: composite functions  
19 based on one set of genotypes were predictive for another set, as long as medians were used for both  
20 sets. A study of cottonwood (*Populus deltoides*) conducted using a naturally occurring gradient of O<sub>3</sub>  
21 exposure (Gregg et al., 2003, [046996](#); Gregg et al., 2006, [186961](#)) may provide an illustration of the  
22 response of an individual species whose response is far from the median response for an aggregation  
23 of species.

### 9.8.3.3. Exposure-Response in a Gradient Study

24 Gregg et al. (2003, [046996](#)) grew saplings of one clonally propagated genotype of cottonwood  
25 (*Populus deltoides*) in seven locations within New York City and in the surrounding region between  
26 July and September in 1992, 1993 and 1994, and harvested them 72 days after planting. Owing to  
27 regional gradients of atmospheric O<sub>3</sub> concentration, the experiment yielded eight levels of exposure  
28 (Figure 9-20), and the authors were able to rule out environmental variables other than O<sub>3</sub> to account  
29 for the large differences in biomass observed after one season of growth. The deficit in growth  
30 increased substantially faster with increasing O<sub>3</sub> exposure than has been observed in aspen, another  
31 species of the same genus (*Populus tremuloides*, Section 9.8.3.2). Using a three parameter Weibull  
32 model (Figure 9-20), the biomass of cottonwood at a W126 exposure of 15 ppm-h, relative to  
33 biomass at 5 ppm-h, is estimated to be 0.18 (18% of growth at 5 ppm-h). The relative biomass of  
34 trembling aspen within the same 5-15 ppm-h range of exposure is estimated to be 0.92, using the  
35 median composite model for aspen whose very close agreement with Aspen FACE data was shown  
36 in Section 9.8.3.2. Using a median composite function for all deciduous trees in the NHEERL/WED  
37 project (6 species in 21 studies) also gives predictions that are very distant from the cottonwood

1 response observed in this experiment. For all deciduous tree species in NHEERL/WED, biomass at a  
2 W126 exposure of 15 ppm-h, relative to biomass at 5 ppm-h, was estimated to be 0.87.



Source: Modified with permission from Nature Publishing Group, Gregg et al. (2003, [046996](#)).

**Figure 9-20. Above-ground biomass for one genotype of cottonwood grown in seven locations for one season in 3 years. Line represents the three-parameter Weibull model.**

3 These cottonwood data confirms that, as should be expected, some individual tree species are  
4 substantially more sensitive than the median of NHEERL/WED (Figure 9-15). As shown in  
5 Section 9.8.2, the median models available for trembling aspen and soybean have verifiable  
6 predictive ability for those particular species. This suggests that the corresponding NCLAN- and  
7 NHEERL/WED-based models for multiple crop and tree species can provide reliable estimates of  
8 losses for similar assortments of species. However, their predictive ability would likely be poor for  
9 individual species not tested.

10 An alternative hypothesis for the difference between the response of cottonwood in this  
11 experiment and deciduous tree species in NHEERL/WED, or the difference between the response of  
12 cottonwood and aspen in NHEERL/WED and Aspen FACE, could be the presence of confounding  
13 factors in the environments where the experiment was conducted. However, variability in  
14 temperature, moisture, soil fertility, and atmospheric deposition of N were all ruled out by Gregg  
15 et al. (2003, [046996](#)) as contributing to the observed response to O<sub>3</sub>. In addition, this hypothesis  
16 would imply that the unrecognized confounder(s) were either absent from *both* OTC and FACE  
17 studies, or had the same value in both. This is not impossible, but the hypothesis that cottonwood is  
18 very sensitive to O<sub>3</sub> exposure is more parsimonious, and sufficient.

### 9.8.3.4. Meta-analyses of growth and yield studies

1 Since the 2006 O<sub>3</sub> AQCD, five studies have used meta-analytic methods to integrate results  
 2 from experimental studies of crops or tree species relevant to the U.S. It is possible to obtain  
 3 exposure-response data for growth and yield from those meta-analyses, but because all of them  
 4 provided summary measurements of O<sub>3</sub> exposure as hourly averages of various lengths of exposures,  
 5 comparisons with exposure-response results where exposure is expressed as W126 are problematic.  
 6 Table 9-15 summarizes the characteristics of the five meta-analyses. They all included studies  
 7 conducted in the U.S. and other locations worldwide, and all of them expressed responses as  
 8 comparative change between levels of exposure to O<sub>3</sub>, with carbon filtered air (CF) among those  
 9 levels. Using hourly average concentration to summarize exposure, CF rarely equates absence of O<sub>3</sub>,  
 10 although it almost always near zero when exposure is summarized as W126, SUM06, or AOT40.

**Table 9-15. 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 <sub>3</sub> levels	Duration of exposure
Ainsworth (2008, <a href="#">191646</a> )	12	1980-2007	rice	Yield	2	unreported
Feng et al. (2008, <a href="#">191453</a> )	53	1980-2007	wheat	Yield	5	> 10 days
Feng and Kobayashi (2009, <a href="#">199223</a> )	All crops together : 81	1980-2007	Potato, barley, wheat, rice, bean, soybean	Yield	3	> 10 days
Grantz et al. (2006, <a href="#">191545</a> )	16	1992-2004	34 herbaceous dicots 21 herbaceous monocots 5 tree species	Relative Growth Rate	2	2-24 weeks
Wittig et al. (2009, <a href="#">191631</a> )	All responses:263 Articles that included biomass:unreported	1970-2006	4 gymnosperm tree genera 11 angiosperm tree genera	Total biomass	4	> 7 days

11 The only effect of O<sub>3</sub> exposure on yield of rice reported in Ainsworth (2008, [191646](#)) was a  
 12 decrease of 14% with exposure increasing from CF to 62 ppb average concentration. Feng et al.  
 13 (2008, [191453](#)) were able to separate exposure of wheat into four classes with average  
 14 concentrations of 42, 69, 97, and 153 ppb, in data where O<sub>3</sub> was the only treatment. Mean responses  
 15 relative to CF were yield decreases of 17, 25, 49, and 61% respectively. Feng et al. (2008, [191453](#))  
 16 observed that wheat yield losses were smaller under conditions of drought, and that Spring wheat  
 17 and Winter wheat appeared similarly affected. However, mean exposure in studies of Winter wheat  
 18 was substantially higher than in studies of Spring wheat (86 versus 64 ppb), which suggests that the  
 19 yield of Spring wheat was in fact more severely affected, since yield was approximately the same,  
 20 even though Spring wheat was exposed to lower concentrations. Exposures of the six crops  
 21 considered in Feng and Kobayashi (2009, [199223](#)) were classified into two ranges, each compared to  
 22 CF air. In the lower range of exposure (41-49 ppb), potato studies had the highest average exposure  
 23 (45 ppb), and wheat and rice the lowest (41 ppb). In the higher range (51-75 ppb), wheat studies had  
 24 the highest average exposure (65 ppb), and potato, barley and rice the lowest (63 ppb). In other  
 25 words, across the studies included, all crops were exposed to very similar levels of O<sub>3</sub>. At

1 approximately 42 ppb, the yield of potato, barley, wheat, rice, bean, and soybean declined by 5.3,  
2 8.9, 9.7, 17.5, 19, and 7.7% respectively, relative to CF air. At approximately 64 ppb O<sub>3</sub>, declines  
3 were 11.9, 12.5, 21.1, 37.5, 41.4, and 21.6%. Grantz et al. (2006, [191545](#)) reported Relative Growth  
4 Rate (RGR) rather than growth, and did not report O<sub>3</sub> exposure values in a way that would allow  
5 calculation of mean exposure for each of the three categories of plants for which RGR changes are  
6 reported. All studies used only two levels of exposure, with CF air as the lower one, and most used  
7 elevated exposure in the range of 40 to 70 ppb. Decline in RGR was 8.2% for the 34 herbaceous  
8 dicots, 4.5% for the 21 herbaceous monocots, and 17.9 for the 5 tree species. Finally, Wittig et al.  
9 (2009, [191631](#)) divided the studies analyzed into three classes of comparisons: CF versus ambient,  
10 CF versus elevated, and ambient versus elevated, but reported comparisons between three average  
11 levels of exposure besides CF: 40 ppb, 64 ppb, and 97 ppb. Corresponding decreases in total biomass  
12 relative to CF were 7, 17, and 17%.

13 These meta-analyses provide very strong confirmation of EPA's conclusions from previous O<sub>3</sub>  
14 AQCDs: compared to lower levels of ambient O<sub>3</sub>, current levels in many locations are having a  
15 substantial detrimental effect on the growth and yield of a wide variety of crops and natural  
16 vegetation. They also confirm strongly that decreases in growth and yield continue at exposure levels  
17 higher than current ambient levels. However, direct comparisons with the predictions of exposure-  
18 response models that use concentration-weighted cumulative metrics are difficult.

### **9.8.3.5. Additional exposure-response data**

19 The studies summarized in Tables 9-16 and 9-17 contain growth or yield exposure-response  
20 data at too few levels of exposure for exposure-response models, and/or used metrics other than  
21 W126. These tables update Tables AX9-16 through AX9-19 of the 2006 O<sub>3</sub> AQCD.

**Table 9-16. Summary of studies of effects of ozone exposure on growth and yield of agricultural crops**

Species Facility Location	Exposure Duration	O <sub>3</sub> Exposure (Additional Treatment)	Response Measured	percent change from CF (percent change from ambient)	Reference
Alfalfa ( <i>Medicago sativa</i> ) OTC; 0.27m <sup>3</sup> 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, <a href="#">191645</a> )
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, <a href="#">191403</a> )
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, <a href="#">191542</a> )
<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)	Himanan et al. (2009, <a href="#">191338</a> )
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. (2007, <a href="#">191456</a> )
Cotton cv. Pima OTC; 9-L pots France	8 wk	12-h avg: 12.8 ± 0.6; 79.9 ± 6.3; 122.7 ± 9.7  (N/A)	Above-ground biomass	-76 (n.s.)	Grantz and Shrestha (2006, <a href="#">191702</a> )
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, <a href="#">191542</a> )
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, <a href="#">094397</a> )
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, <a href="#">191558</a> )
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, <a href="#">191276</a> )
Peanut ( <i>Arachis hypogaea</i> ) OTC Raleigh, NC	3 yr	12-h avg: CF (22 ppb), Ambient (46 ppb), Elevated (75ppb)  (CO <sub>2</sub> : 375 ppm; 548 ppm; 730 ppm)	Yield (seed weight, g/m)	-33 (-8)	Burkey et al. (2007, <a href="#">191371</a> )

Species Facility Location	Exposure Duration	O <sub>3</sub> Exposure (Additional Treatment)	Response Measured	percent change from CF (percent change from ambient)	Reference
<i>Poa pratensis</i> OTC Braunschweig, Germany	2000-2002: 4-5 wk 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, <a href="#">191437</a> )
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 <sub>3</sub> ] report sig. ± slope with increasing [O <sub>3</sub> ]	N/A (-27 % +27%, most comparisons n.s.) Linear regression slope = -0.0098)	Vandermeiren et al. (2005, <a href="#">179992</a> )
Rice ( <i>Oryza sativa</i> ) OTC Raleigh, NC	1997-1998, June- September	12-h mean ppb: CF (27.5), Elevated (74.8)  (CO <sub>2</sub> )	Total biomass; Seed yield	-25(N/A)  -13 to 20 (N/A)	Reid, et al. (2008, <a href="#">191561</a> )
Rice ( <i>Oryza sativa</i> ) 20 Asian cultivars OTC Gunma Prefecture, Japan	2008 growing season	Daily avg (ppb): CF (2), 0.8xambient (23); 1 xambient (28); 1.5xambient (42); 2xambient (57)  (Cultivar comparisons)	Yield	From n.s. to -30 across all cultivars	Sawada and Kohno (2009, <a href="#">199426</a> )
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 (2xfaster decrease in yield/yr)	Volk et al. (2006, <a href="#">191434</a> )
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)	Jaoude et al. (2008, <a href="#">191223</a> )
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, <a href="#">079186</a> )
Soybean ( <i>Glycine max</i> cv. Essex) Chambers; 21 L Raleigh, NC	2x3 months	12-h avg: CF (28), Elevated (79), Elevated flux (112)  (CO <sub>2</sub> : 365 & 700)	Seed mass per plant	-30 (N/A)	Booker and Fiscus (2005, <a href="#">191652</a> )
Soybean ( <i>Glycine max</i> cv. Essex) OTCs; 21-L pots Raleigh, NC	2x3 months	12-h avg: CF (18); Elevated (72)  (CO <sub>2</sub> : 367 & 718)	Seed mass per plant	-34 (N/A)	Booker et al. (2004, <a href="#">079138</a> )
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, <a href="#">199411</a> )
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)	Betzelberger et al. (2010, <a href="#">644183</a> )

Species Facility Location	Exposure Duration	O <sub>3</sub> Exposure (Additional Treatment)	Response Measured	percent change from CF (percent change from ambient)	Reference
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. (2008, <a href="#">199812</a> )
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, <a href="#">191295</a> )
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, <a href="#">191361</a> )
Sugarcane ( <i>Saccharum spp</i> ) CSTR San Joaquin Valley, CA	2007; 11-13 wk.	12-h avg: CF (4 ppb); Ambient (58); Elevated (147) (N/A)	Total biomass (g/plant)	-40 (-30)	Grantz and Vu (2009, <a href="#">195237</a> )
Sweet Potato Growth chambers Bonn, Germany	4 wk	8-h avg: CF (0 ppb), Ambient (<40 ppb) Elevated (255 ppb) (N/A)	Tuber weight	-14 (-11.5)	Keutgen et al. (2008, <a href="#">191690</a> )
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.)	Calvo et al. (2005, <a href="#">191570</a> )
Trifolium Subterraneum 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, <a href="#">196963</a> )
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, <a href="#">191482</a> )
Yellow Nutsedge OTC; 9-L pots	8 wk	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, <a href="#">191702</a> )

In studies where variables other than O<sub>3</sub> were included in the experimental design, response to O<sub>3</sub> is only provided for the control level of those variables.

**Table 9-17. Summary of studies of effects of ozone exposure on growth of natural vegetation**

Species Facility Location	Exposure Duration	O <sub>3</sub> Exposure (Additional Treatment)	Response Measured	Response	Reference
Yellow nutsedge ( <i>Cyperus esculentus</i> ) CSTR Parlier, 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. (2010, <a href="#">102161</a> )
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 <sup>2</sup> ), CF+ (457 g/m <sup>2</sup> ), CF2+ (398 g/m <sup>2</sup> )	Pfleeger et al. (2010, <a href="#">644281</a> )
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, <a href="#">192230</a> )
Horseweed ( <i>Conyza canadensis</i> ) CSTR San Joaquin Valley, CA	2005, 2 runs, 28 days each (July-Aug, Sept)	W126 ppm-hr: 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, <a href="#">191312</a> )
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )

Species Facility Location	Exposure Duration	O <sub>3</sub> Exposure (Additional Treatment)	Response Measured	Response	Reference
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )
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. (2007, <a href="#">090348</a> )
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 <sup>3</sup> , Elevated: 4.73 dm <sup>3</sup>	Kubiske et al. (2006, <a href="#">093284</a> )
Hybrid Poplar ( <i>Populus trichocarpa x 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 Hinkley (2005, <a href="#">191359</a> )

In studies where variables other than O<sub>3</sub> were included in the experimental design, response to O<sub>3</sub> is only provided for the control level of those variables.

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A list of all references considered for inclusion in this chapter can be found at

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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# Chapter 10. The Role of Tropospheric Ozone in Climate Change and UV-B Effects

## 10.1. Introduction

1 Atmospheric O<sub>3</sub> plays an important role in the Earth's energy budget by interacting with  
2 incoming solar radiation and outgoing infrared radiation. Tropospheric O<sub>3</sub> makes up only a small  
3 portion of the total column of O<sub>3</sub>, but it has important incremental effects on the overall radiation  
4 budget. This chapter assesses the specific role that tropospheric O<sub>3</sub> plays in the earth's radiation  
5 budget and how perturbations in tropospheric O<sub>3</sub> might affect climate through its role as a  
6 greenhouse gas (Section 10.2), and health, ecology and welfare through its role in shielding the  
7 earth's surface from solar ultraviolet radiation (Section 10.3).

## 10.2. Effects of Tropospheric Ozone on Climate

### 10.2.1. Background

8 Tropospheric O<sub>3</sub> is a major greenhouse gas, and increases in its abundance may contribute to  
9 climate change (IPCC, 2007, [092980](#)). Models calculate that the global burden of tropospheric O<sub>3</sub>  
10 has doubled since the preindustrial era (Gauss et al., 2006, [630275](#)), while observations indicate that  
11 in some regions O<sub>3</sub> may have increased by factors as great as 4 or 5 (Marenco et al., 1994, [047733](#);  
12 Staehelin et al., 1994, [055369](#)). These increases are tied to the rise in emissions of O<sub>3</sub> precursors  
13 from human activity, mainly fossil fuel consumption and agricultural processes. The impact on  
14 climate of the O<sub>3</sub> change since preindustrial times has been estimated to be about 25-40% of  
15 anthropogenic CO<sub>2</sub> impact and about 75% of anthropogenic CH<sub>4</sub> impact (IPCC, 2007, [092980](#)),  
16 ranking it third in importance of the greenhouse gases. In the 21st century as the Earth's population  
17 continues to grow and energy technology spreads to developing countries, a further rise in the global  
18 burden of tropospheric O<sub>3</sub> is possible, with consequences for future climate.

19 To examine the science of a changing climate and to provide balanced and rigorous  
20 information to policy makers, the World Meteorological Organization (WMO) and the United  
21 Nations Environment Programme (UNEP) formed the Intergovernmental Panel on Climate Change  
22 (IPCC) in 1988. The IPCC supports the work of the Conference of Parties (COP) to the United  
23 Nations Framework Convention on Climate Change (UNFCCC). The IPCC periodically brings

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

1 together climate scientists from member countries of WMO and the United Nations to review  
2 knowledge of the physical climate system, past and future climate change, and evidence of human-  
3 induced climate change. IPCC climate assessment reports are issued every 5 to 7 years.

4 This chapter draws in part on the fourth IPCC Assessment Report (AR4) (IPCC, 2007,  
5 [092980](#)), as well as other peer-reviewed published research. Section 10.2.2 reviews the physics and  
6 chemistry of climate change and radiative forcing, together with evidence of climate change in the  
7 recent past and projections of future climate change. It also offers a brief description of tropospheric  
8 O<sub>3</sub> as compared to other greenhouse gases. Section 10.2.3 describes factors that influence the  
9 magnitude of O<sub>3</sub> effects of climate. Section 10.2.4 considers the competing effects of O<sub>3</sub> precursors  
10 on climate. Sections 10.2.5 and 10.2.6 describe the effects of changing tropospheric O<sub>3</sub> on present-  
11 day and future climate, respectively. Finally, Section 10.2.7 presents a summary of the effects of  
12 tropospheric O<sub>3</sub> on climate.

## 10.2.2. Physics and Chemistry of Climate Change and Radiative Forcing

### 10.2.2.1. Physics of Greenhouse Gases

13 The Earth's climate depends upon the flux of energy from the sun and its redistribution in the  
14 earth-atmosphere-ocean system. Radiant energy from the sun enters the atmosphere in a range of  
15 wavelengths, but peaks strongly in the shortwave (visible) part of the spectrum. Most solar energy at  
16 very short wavelengths (e.g., ultraviolet) is absorbed at high altitudes by gases such as stratospheric  
17 O<sub>3</sub>. About 30% of incoming solar radiation is reflected back to space, mainly by clouds or surfaces  
18 with high albedo (reflectivity), such as snow, ice, and desert sand. In the troposphere, gases and  
19 particles can interact with a fraction of the incoming solar radiation, but for the most part the  
20 troposphere is transparent to shortwave radiation. Thus about 70% of shortwave solar radiation  
21 penetrates to the Earth's surface and is absorbed. About one-third of the absorbed energy is then re-  
22 emitted in the longwave (infrared) portion of the spectrum. The rest goes into evaporating water or  
23 soil moisture or emerges as sensible heat.

24 The troposphere is opaque to the outgoing longwave radiation. Polyatomic gases such as CO<sub>2</sub>,  
25 CH<sub>4</sub>, and O<sub>3</sub> absorb and re-emit the radiation upwelling from the Earth's surface, reducing the  
26 efficiency with which that energy returns to space. In effect, these gases act as a blanket warming the  
27 Earth's surface. This phenomenon, known as the "Greenhouse Effect," was first quantified in the 19<sup>th</sup>  
28 century (Arrhenius, 1896, [043125](#)), and gives rise to the term "greenhouse gas".

### 10.2.2.2. Climate Change in the Recent Past

29 From the end of the Last Ice Age 12,000 years ago until the mid-1800s, observations from ice  
30 cores show that concentrations of the long-lived greenhouse gases CO<sub>2</sub>, CH<sub>4</sub>, and N<sub>2</sub>O have been  
31 relatively stable. Unlike these greenhouse gases, O<sub>3</sub> is not preserved in ice, and no record of it before  
32 the late 1800s exists. Models, however, suggest that it, too, has remained relatively constant during

1 this time period (Thompson, 1992, [043463](#); Thompson et al., 1993, [029510](#)). The stable mix of  
2 greenhouse gases in the atmosphere has kept the global mean temperature of the Earth close to 15°C.  
3 Without the presence of greenhouse gases in the atmosphere, the Earth’s temperature would be about  
4 30°C cooler, or -15°C. Since the start of the Industrial Revolution, human activity has led to  
5 significant increases of greenhouse gases in the atmosphere, mainly through fossil fuel combustion.  
6 According to the IPCC AR4 (IPCC, 2007, [092980](#)), we now have “very high confidence” that the net  
7 effect of anthropogenic greenhouse gas emissions since 1750 has led to warming, and it is “very  
8 likely” that human activity contributed to the 0.76°C rise in global mean temperature observed over  
9 the last century. The increase of tropospheric O<sub>3</sub> may have contributed 0.1-0.3°C warming to the  
10 global climate during this time period (Hansen et al., 2005, [190596](#); Mickley et al., 2004, [057416](#)).  
11 Global cooling due to anthropogenic aerosols (IPCC, 2007, [092980](#)) has likely masked the full  
12 warming effect of the anthropogenic greenhouse gases.

### 10.2.2.3. Projections of Future Climate Change

13 The IPCC AR4 projects a warming of ~0.2°C per decade for the remainder of the 21st century  
14 (IPCC, 2007, [092980](#)). Even at constant concentrations of greenhouse gases in the atmosphere,  
15 temperatures are expected to increase by about 0.1°C per decade, due to the slow response of oceans  
16 to the warming applied so far. It is likely that the Earth will experience longer and more frequent  
17 heat waves in the 21st century, together with more frequent droughts and/or heavy precipitation  
18 events in some regions, due to perturbations in the hydrological cycle that result from changing  
19 temperatures (IPCC, 2007, [092980](#)). Sea levels could increase by 0.3-0.8 m by 2300 due to thermal  
20 expansion of the oceans. The extent of Arctic sea ice is expected to decline, and contraction of the  
21 Greenland ice sheet could further contribute to the sea level rise (IPCC, 2007, [092980](#)).

22 Projections of future climate change are all associated with some degree of uncertainty. A  
23 major uncertainty involves future trends in the anthropogenic emissions of greenhouse gases or their  
24 precursors. For the IPCC AR4 climate projections, a set of distinct “storylines” or emission pathways  
25 was developed (IPCC, 2000, [080704](#)). Each storyline took into account factors such as population  
26 growth, mix of energy technologies, and the sharing of technology between developed and  
27 developing nations, and each resulted in a different scenario for anthropogenic emissions. When  
28 these trends in emissions are applied to models, these scenarios yield a broad range of possible  
29 climate trajectories for the 21st century.

30 A second factor bringing large uncertainty to model projections of future climate is the  
31 representation of climate and, especially, climate feedbacks. A rise in surface temperatures would  
32 perturb a suite of other processes in the earth-atmosphere-ocean system, which may in turn either  
33 amplify the temperature increase (positive feedback) or diminish it (negative feedback). One  
34 important feedback involves the increase of water vapor content of the atmosphere that would  
35 accompany higher temperatures (Bony et al., 2006, [630272](#)). Water vapor is a potent greenhouse gas;  
36 accounting for the water vapor feedback may increase the climate sensitivity to a doubling of CO<sub>2</sub> by  
37 nearly a factor of two (Held and Soden, 2000, [630279](#)). The ice-albedo feedback is also strongly

1 positive; a decline in snow cover and sea ice extent would diminish the Earth's albedo, allowing  
2 more solar energy to be deposited to the surface (Holland and Bitz, 2003, [630280](#); Rind et al., 1995,  
3 [630285](#)). A final example of a climate feedback involves the effects of changing cloud cover in a  
4 warming atmosphere. Models disagree on the magnitude and even the sign of this feedback on  
5 surface temperatures (Soden and Held, 2006, [631183](#)).

#### 10.2.2.4. Metrics of Potential Climate Change

6 Two different metrics are frequently used to estimate the potential climate impact of some  
7 perturbation such as a change in greenhouse gas concentration: (1) global warming potential (GWP);  
8 and (2) radiative forcing (RF).

9 GWP indicates the integrated radiative forcing over a specified period (usually 100 years)  
10 from a unit mass pulse emission of a greenhouse gas or its precursor, and are reported as the  
11 magnitude of this forcing relative to that of CO<sub>2</sub>. GWP is most useful for comparing the potential  
12 climate impacts of long-lived gases, such as N<sub>2</sub>O or CH<sub>4</sub>. Since tropospheric O<sub>3</sub> has a lifetime on the  
13 order of weeks to months, GWP is not seen as a valuable metric for quantifying the importance of O<sub>3</sub>  
14 on climate (Forster et al., 2007, [092936](#)).

15 Radiative forcing is a change in the radiative balance at a particular level of the atmosphere or  
16 at the surface when a perturbation is introduced in the earth-atmosphere-ocean system. In the global  
17 mean, radiative forcing of greenhouse gases at the tropopause (top of the troposphere) is roughly  
18 proportional to the surface temperature response  
19 (Committee on Radiative Forcing Effects on Climate; Climate Research Committee; National  
20 Research Council et al., 2005, [057409](#); Hansen et al., 2005, [190596](#)). It thus provides a useful metric  
21 for policymakers for assessing the response of the earth's surface temperature to a given change in  
22 the concentration of greenhouse gas. Positive values of radiative forcing indicate warming in a test  
23 case relative to the control; negative values indicate cooling. The units of radiative forcing are  
24 energy flux per area, or W/m<sup>2</sup>.

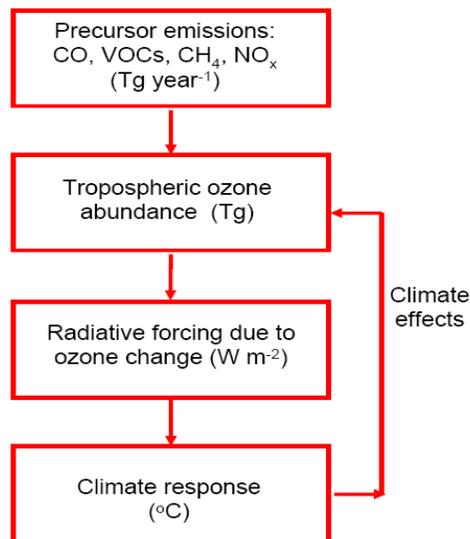
25 Radiative forcing requires just a few model years to calculate, and it shows consistency from  
26 model to model. However, radiative forcing does not take into account the climate feedbacks that  
27 could amplify or dampen the actual surface temperature response, depending on region (Section  
28 10.2.2.3). Quantifying the change in surface temperature requires a climate simulation in which all  
29 important feedbacks are accounted for. As these processes are not well understood, the surface  
30 temperature response to a given radiative forcing is highly uncertain and can vary greatly among  
31 models and even from region to region within the same model.

#### 10.2.2.5. Tropospheric Ozone as a Greenhouse Gas

32 Tropospheric O<sub>3</sub> differs in important ways from other greenhouse gases. It is not emitted  
33 directly, but is produced through photochemical oxidation of CO, CH<sub>4</sub>, and nonmethane volatile  
34 organic compounds (VOCs) in the presence of nitrogen oxide radicals (NO<sub>x</sub> = NO + NO<sub>2</sub>; see  
35 Section 3.2). It is also supplied by vertical transport from the stratosphere. The lifetime of O<sub>3</sub> in the

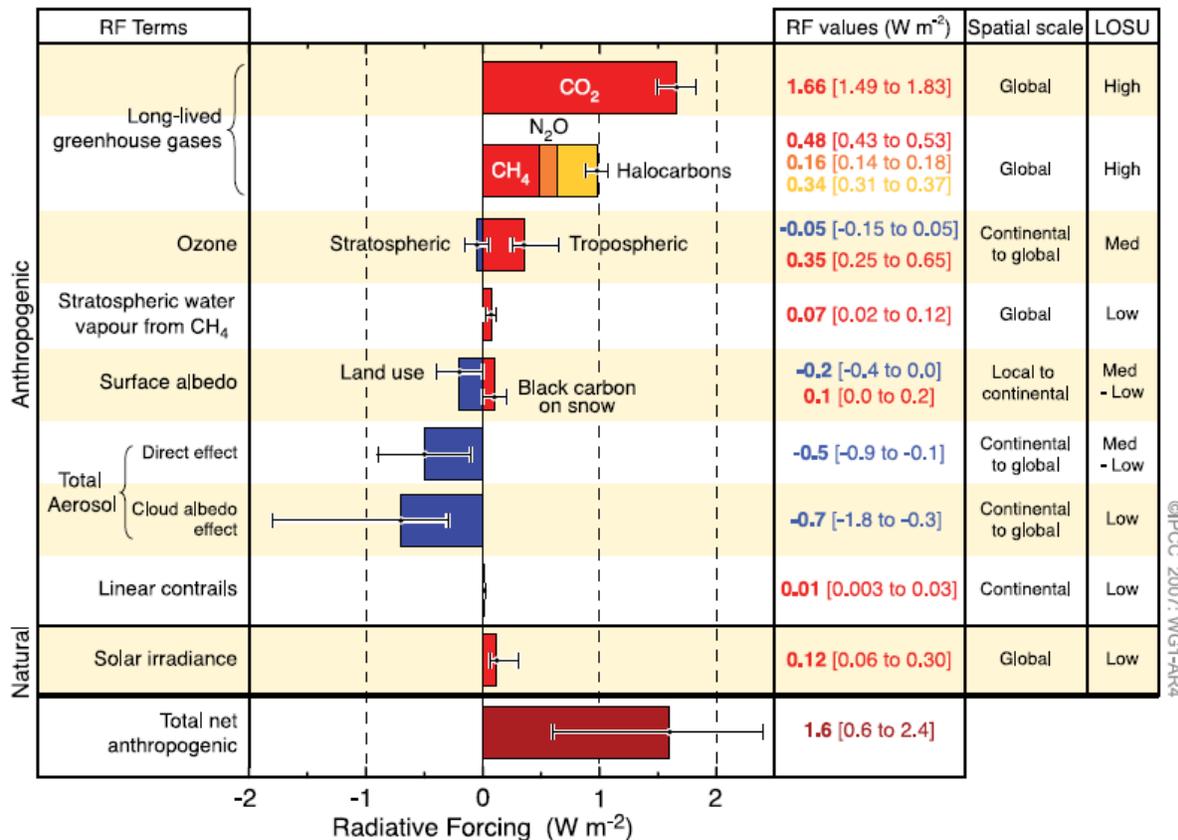
1 troposphere is typically a few weeks, resulting in an inhomogeneous distribution that varies  
2 seasonally; the distribution of the long-lived greenhouse gases like CO<sub>2</sub> and CH<sub>4</sub> are much more  
3 uniform. The longwave radiative forcing by O<sub>3</sub> is mainly due to absorption in the 9.6 μm window,  
4 where absorption by water vapor is weak. It is therefore less sensitive to local humidity than the  
5 radiative forcing by CO<sub>2</sub> or CH<sub>4</sub>, for which there is much more overlap with the water absorption  
6 bands (Lenoble, 1993, [630969](#)). And unlike other major greenhouse gases, O<sub>3</sub> absorbs in the  
7 shortwave as well as the longwave part of the spectrum.

8 Figure 10-1 shows the main steps involved in the influence of tropospheric O<sub>3</sub> on climate. An  
9 increase in the emissions of O<sub>3</sub> precursors leads to an increase in the burden of tropospheric O<sub>3</sub>. The  
10 added O<sub>3</sub> then perturbs the radiative balance of the atmosphere, an effect quantified by the radiative  
11 forcing metric. This forcing results in climate change, usually expressed as a change in surface  
12 temperature. Climate change can also perturb tropospheric O<sub>3</sub>, as will be discussed in Section  
13 10.2.6.3. As shown in Figure 10-2, the IPCC (IPCC, 2007, [092980](#)) reports a radiative forcing of  
14 0.35 W/m<sup>2</sup> for the change in tropospheric O<sub>3</sub> since the preindustrial era, ranking it third in  
15 importance after the greenhouse gases CO<sub>2</sub> (1.66 W/m<sup>2</sup>) and CH<sub>4</sub> (0.48 W/m<sup>2</sup>). The error bars  
16 encompassing the tropospheric O<sub>3</sub> radiative forcing estimate range from 0.25 to 0.65 W/m<sup>2</sup>, making  
17 it relatively more uncertain than the long-lived greenhouse gases.



**Figure 10-1. Flow chart for the effects of tropospheric ozone on climate. Emissions of the ozone precursors CO, VOCs, CH<sub>4</sub>, and NO<sub>x</sub> lead to production of tropospheric ozone. A change in the burden of tropospheric ozone perturbs the radiative balance of the atmosphere, leading to radiative forcing. The earth-atmosphere-ocean system responds to the forcing with a change in climate. Climate change, in turn, can affect the abundance of tropospheric ozone through multiple mechanisms. Units shown are those typical for each quantity, with the climate response expressed as a change in surface temperature.**

### RADIATIVE FORCING COMPONENTS



Source: Used with permission from Cambridge University Press, IPCC (IPCC, 2007, [092980](#))

**Figure 10-2. Global average radiative forcing (RF) estimates and ranges in 2005 for anthropogenic CO<sub>2</sub>, CH<sub>4</sub>, ozone and other important agents and mechanisms, together with the typical geographical extent (spatial scale) of the 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 forcing factors not included here are considered to have a very low LOSU.

### 10.2.3. Factors that Influence the Effect of Tropospheric Ozone on Climate

1 This section describes the main factors that influence the magnitude of the climate response to  
 2 changes in tropospheric O<sub>3</sub>. They include: (1) trends in the burden of tropospheric O<sub>3</sub>; (2) the effect  
 3 of surface albedo on O<sub>3</sub> forcing; (3) the effect of vertical distribution on O<sub>3</sub> forcing; (4) feedback  
 4 factors that can alter the climate response to O<sub>3</sub> forcing; and (5) the indirect effects of tropospheric  
 5 O<sub>3</sub> on the carbon cycle. Trends in stratospheric O<sub>3</sub> may also affect temperatures at the Earth's  
 6 surface, but that topic is beyond the scope of this assessment.

### 10.2.3.1. Trends in the Burden of Tropospheric Ozone

1 To first order, the effect of tropospheric O<sub>3</sub> on climate is proportional to the change in O<sub>3</sub>  
2 burden. The earth's surface temperatures are most sensitive to O<sub>3</sub> perturbations in the mid to upper  
3 troposphere. This section therefore focuses mainly on observed O<sub>3</sub> trends in the free troposphere or  
4 in regions far from O<sub>3</sub> sources, where a change in O<sub>3</sub> concentrations may indicate change throughout  
5 the troposphere. Data from ozonesondes, mountaintops, and remote surface sites are discussed, as  
6 well as satellite data.

#### Observed Trends in Ozone Since the Preindustrial Era

7 Measurements of O<sub>3</sub> at two European mountain sites dating from the late 1800s to early 1900s  
8 show values at about 10 ppb, about one-fifth the values observed today at similar sites (Marengo et  
9 al., 1994, [047733](#); Pavelin et al., 1999, [087296](#)). The accuracy of these early measurements is  
10 questionable however, in part because they exhibit O<sub>3</sub> concentrations equivalent to or only a couple  
11 of parts per billion greater than those observed at nearby low-altitude sites during the same time  
12 period (Mickley et al., 2001, [080134](#); Volz and Kley, 1988, [041650](#)). A larger vertical gradient in  
13 tropospheric O<sub>3</sub> would be expected because of its stratospheric source and its longer lifetime aloft. In  
14 another study, Staehelin et al. (1994, [055369](#)) revisited observations made in the Swiss mountains  
15 during the 1950s and found a doubling in O<sub>3</sub> concentrations from that era to 1989-1991.

16 Routine observations of O<sub>3</sub> in the troposphere began in the 1970s with the use of balloon-  
17 borne ozonesondes, but even this record is sparse. Trends from ozonesondes have been highly  
18 variable and dependent on region (Logan et al., 1999, [631175](#)). Over most sites in the U.S.,  
19 ozonesondes reveal little trend. Over Canada, observations show a decline in O<sub>3</sub> between 1980 and  
20 1990, then a rebound in the following decade (Tarasick et al., 2005, [631184](#)). Ozonesondes over  
21 Europe give a mixed picture, with Hohenpeissenberg in Germany showing declines through the  
22 troposphere in recent decades, while Zugspitze, also in Germany, exhibiting small increases  
23 (Oltmans et al., 2006, [180188](#)). Over Japan, O<sub>3</sub> in the lower troposphere increased about 0.2-  
24 0.4 ppb/y during the 1990s (Naja and Akimoto, 2004, [631178](#)).

25 Ground-based measurements in remote regions provide a record of background tropospheric  
26 O<sub>3</sub> extending as far back as the 1980s or, for ship measurements, the late 1970s. Springtime O<sub>3</sub>  
27 observations from several mountain sites in the western U.S. show a positive trend of about of 0.5-  
28 0.7 ppb/y since the 1980s (Cooper et al., 2010, [380093](#); Jaffe et al., 2003, [052229](#)). Ship-borne O<sub>3</sub>  
29 measurements for the time period 1977 to 2002 indicate increases of 0.1-0.7 ppb/y over the tropical  
30 and South Atlantic, but no significant change over the North Atlantic (Lelieveld et al., 2004,  
31 [630578](#)). The lack of trend for the North Atlantic would seem at odds with O<sub>3</sub> observations at Mace  
32 Head on the west coast of Ireland, which show a significant positive trend of about 0.5 ppb/y from  
33 1987 to 2003 (Simmonds et al., 2004, [631182](#)). Over Japan, O<sub>3</sub> at a remote mountain site has  
34 increased 1 ppb/y from 1998 to 2003 (Tanimoto, 2009, [620751](#)), a rate more than double that  
35 recorded by ozonesondes in the lower troposphere over Japan during the 1990s (Naja and Akimoto,  
36 2004, [631178](#)).

1 The satellite record is now approaching a length that can be useful for diagnosing trends in  
2 total column amounts of tropospheric O<sub>3</sub>. In contrast to the surface data from ships, tropospheric O<sub>3</sub>  
3 columns from the Total Ozone Mapping Spectrometer (TOMS) show no trend over the tropical  
4 Atlantic for the period 1980-1990 (Thompson and Hudson, 1999, [631185](#)). Over the Pacific, a  
5 longer, 25 year record of TOMS data again reveals no trend over the tropics, but shows increases in  
6 tropospheric column O<sub>3</sub> of about 2-3 Dobson Units (DU [1 DU = 2.69 × 10<sup>16</sup> molecules of O<sub>3</sub>/cm<sup>2</sup>])  
7 at midlatitudes in both hemispheres (Ziemke et al., 2005, [631193](#)); for comparison, the tropospheric  
8 O<sub>3</sub> burden averages about 34 DU.

9 Interpreting these recent trends in tropospheric O<sub>3</sub> is challenging. The first difficulty is  
10 reconciling apparently contradictory trends in the observations, e.g., over tropical oceans. A second  
11 difficulty is that the O<sub>3</sub> trends depend on several factors, not all of which can be well characterized.  
12 These factors include (1) trends in emissions of O<sub>3</sub> precursors, (2) variation in the stratospheric  
13 source of O<sub>3</sub>, (3) changes in solar radiation resulting from stratospheric O<sub>3</sub> depletion, and (4) trends  
14 in tropospheric temperatures (Fusco and Logan, 2003, [051229](#)). The positive trends in the western  
15 U.S. and over Japan are consistent with the rapid increase in emissions of O<sub>3</sub> precursors from  
16 mainland Asia and transport of pollution across the Pacific (Cooper et al., 2010, [380093](#); Tanimoto,  
17 2009, [620751](#)). The satellite trends over the northern mid-latitudes are consistent with this picture as  
18 well (Ziemke et al., 2005, [631193](#)). Increases in tropospheric O<sub>3</sub> in the Southern Hemisphere are also  
19 likely due to increased anthropogenic NO<sub>x</sub> emissions, especially from biomass burning. The declines  
20 in O<sub>3</sub> over Europe can be at least partly explained by decreases in O<sub>3</sub> precursor emissions there  
21 (Jonson et al., 2005, [630282](#)), though recent O<sub>3</sub> depletion in the lower stratosphere may also  
22 contribute to the decreases by reducing stratospheric input to the troposphere (Fusco and Logan,  
23 2003, [051229](#)).

### Calculation of Ozone Trends for the Recent Past

24 Attempts to simulate trends in tropospheric O<sub>3</sub> allow us to test current knowledge of O<sub>3</sub>  
25 processes and to predict with greater confidence trends in future O<sub>3</sub> concentrations. Time-dependent  
26 emission inventories of O<sub>3</sub> precursors have also been developed (e.g., Lamarque et al., 2010, [630289](#)  
27 for 1850-2000; Van Aardenne et al., 2001, [055564](#) for 1890-1990). These inventories allow for the  
28 calculation of changing O<sub>3</sub> burden over time.

29 One recent multi-model study calculated an increase in the O<sub>3</sub> burden since preindustrial times  
30 of 8-14 DU, or about 30-70% (Gauss et al., 2006, [630275](#)). The large spread in modeled estimates  
31 reveals our limited knowledge of processes in the pristine atmosphere. Models typically overestimate  
32 the late nineteenth and early twentieth century observations available in surface air and at mountain  
33 sites by 50-100% (Kiehl et al., 1999, [047917](#)) (Lamarque et al., 2005, [630287](#); Mickley et al., 2001,  
34 [080134](#); Shindell et al., 2003, [057417](#)). Reconciling the differences between models and  
35 measurements will require more accurate simulation of the natural sources of O<sub>3</sub> (Mickley et al.,  
36 2001, [080134](#)) and/or implementation of novel sinks such as bromine radicals, which may reduce  
37 background O<sub>3</sub> in the pristine atmosphere by as much as 30% (Parrella et al., In Press, [664506](#)).

1 For the more recent past (since 1970), application of time-dependent emissions reveals an  
2 equatorward shift in the distribution of tropospheric O<sub>3</sub> in the Northern Hemisphere due to the  
3 industrialization of societies at low-latitudes (Berntsen et al., 2000, [047916](#); Lamarque et al., 2005,  
4 [630287](#)). By constraining a model with historical (1950s-2000) observations, Shindell et al. (2002,  
5 [080130](#)) calculated a large increase of 8.2 DU in tropospheric O<sub>3</sub> over polluted continental regions  
6 since 1950. Their result appears consistent with the large change in tropospheric O<sub>3</sub> since  
7 preindustrial times implied by the observations from the late 1800s (Marengo et al., 1994, [047733](#);  
8 Pavelin et al., 1999, [087296](#)).

### 10.2.3.2. The Effect of Surface Albedo on Ozone Forcing

9 The Earth's surface albedo plays a role in O<sub>3</sub> forcing. Through most of the troposphere,  
10 absorption of incoming shortwave solar radiation by O<sub>3</sub> is small relative to its absorption of outgoing  
11 longwave terrestrial radiation. However, over surfaces characterized by high albedo (e.g., over snow,  
12 ice, or desert sand), incoming radiation is more likely to be reflected than over darker surfaces, and  
13 the probability that O<sub>3</sub> will absorb shortwave solar energy is therefore larger. In other words, energy  
14 that would otherwise return to space may instead be deposited in the atmosphere. Several studies  
15 have shown that transport of O<sub>3</sub> to the Arctic from mid-latitudes leads to radiative forcing estimates  
16 greater than 1.0 W/m<sup>2</sup> in the region, especially in summer (Liao et al., 2004, [057414](#); Mickley et al.,  
17 1999, [047918](#); Shindell et al., 2006, [631181](#)). Because the Arctic is especially sensitive to radiative  
18 forcing through the ice-albedo feedback, the large contribution in the shortwave to the total radiative  
19 forcing in the region may be important.

### 10.2.3.3. The Effect of Vertical Distribution on Ozone Forcing

20 In the absence of feedbacks, O<sub>3</sub> increments added near the tropopause produce the largest  
21 increases in surface temperature (Lacis et al., 1990, [037834](#); Wang et al., 1980, [674821](#)). This is a  
22 result of the colder temperature of the tropopause relative to the rest of the troposphere and  
23 stratosphere. Since radiation emitted by the atmosphere is approximately proportional to the fourth  
24 power of its temperature<sup>1</sup>, the colder the added O<sub>3</sub> is relative to the earth's surface, the weaker the  
25 radiation emitted and the greater the "trapping" of longwave radiation in the troposphere.

### 10.2.3.4. Feedback Factors that Alter the Climate Response to Changes in Ozone Forcing

26 Estimates of radiative forcing provide a first-order assessment of the effect of tropospheric O<sub>3</sub>  
27 on climate. In the real atmosphere, climate feedbacks and transport of heat alter the sensitivity of  
28 Earth's surface temperature to addition of tropospheric O<sub>3</sub>. Assessment of the full climate response to  
29 increases in tropospheric O<sub>3</sub> requires use of a climate model to simulate these interactions.

---

<sup>1</sup> 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 Due to its short lifetime, O<sub>3</sub> is heterogeneously distributed through the troposphere. Sharp  
2 horizontal gradients exist in the radiative forcing of O<sub>3</sub>, with the greatest radiative forcing since  
3 preindustrial times occurring over the northern mid-latitudes (more on this in Section 10.2.5). If  
4 climate feedbacks are particularly powerful, they may obscure or even erase the correlation between  
5 regional radiative forcing and climate response (Boer and Yu, 2003, [630271](#); Harvey, 2004, [190598](#)).  
6 For example, several model studies have reported that the horizontal pattern of surface temperature  
7 response from 2000-2100 trends in short-lived species (including O<sub>3</sub>) closely matches the pattern  
8 from the trends in the long-lived greenhouse gases over the same time period (Levy H et al., 2008,  
9 [631174](#); Shindell et al., 2007, [521350](#); Shindell et al., 2008, [190393](#)). This correspondence occurs  
10 even though the patterns of radiative forcing for the short-lived and long-lived species differ  
11 significantly. In a separate paper, Shindell (2007, [521350](#)) found that Arctic temperatures are  
12 especially sensitive to the mid-latitude radiative forcing from tropospheric O<sub>3</sub>.

13 Other studies have found that the signature of warming due to tropospheric O<sub>3</sub> does show  
14 some consistency with the O<sub>3</sub> forcing. For example, Mickley et al. (2004, [057416](#)) examined the  
15 change in O<sub>3</sub> since preindustrial times and found greater warming in the Northern Hemisphere than  
16 in the Southern Hemisphere (+0.4°C versus +0.2°C), as well as higher surface temperatures  
17 downwind of Europe and Asia and over the North American interior in summer. For an array of  
18 short-lived species including O<sub>3</sub>, Shindell and Faluvegi (2009, [631180](#)) found that radiative forcing  
19 applied over northern mid-latitudes yield more localized responses due to local cloud, water vapor,  
20 and albedo feedbacks than radiative forcing applied over the tropics.

21 Climate feedbacks can also alter the sensitivity of surface temperature to the vertical  
22 distribution of tropospheric O<sub>3</sub>. The previous section (Section 10.2.3.3) described the greater impact  
23 of O<sub>3</sub> added to the upper troposphere (near the tropopause) on radiative forcing, relative to additions  
24 in the mid- to lower troposphere. However, warming induced by increased O<sub>3</sub> in the upper  
25 troposphere could stabilize the atmosphere to some extent, limiting the transport of heat to the  
26 Earth's surface and mitigating the impact of the added O<sub>3</sub> on surface temperature (Christiansen,  
27 1999, [047920](#); Joshi et al., 2003, [193752](#)). Hansen et al. (1997, [043104](#)) determined that allowing  
28 cloud feedbacks in a climate model meant that O<sub>3</sub> enhancements in the mid-troposphere had the  
29 greatest effect on surface temperature.

30 Finally, climate feedbacks can amplify or diminish the climate response of one greenhouse gas  
31 relative to another. For example, Mickley et al. (2004, [057416](#)) found a greater temperature response  
32 to CO<sub>2</sub> forcing than to an O<sub>3</sub> forcing of similar global mean magnitude, due in part to the relatively  
33 weak ice-albedo feedback for O<sub>3</sub>. Since CO<sub>2</sub> absorbs in the same bands as water vapor, CO<sub>2</sub> forcing  
34 saturates in 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 CO<sub>2</sub>, and the greater mid-  
36 troposphere radiative forcing allows for greater surface temperature response, relative to that for O<sub>3</sub>.

### 10.2.3.5. Indirect Effects of Tropospheric Ozone on the Carbon Cycle

1 A proposed indirect effect of tropospheric O<sub>3</sub> on climate involves the carbon cycle. By directly  
2 damaging plant life in ways discussed in Chapter 9, increases in tropospheric O<sub>3</sub> may depress the  
3 land-carbon sink of CO<sub>2</sub>, leading to accumulation of CO<sub>2</sub> in the atmosphere and ultimately warming  
4 of the Earth's surface. Sitch et al. (2007, [093294](#)) calculated that this indirect warming effect of O<sub>3</sub>  
5 on climate has about the same magnitude as the O<sub>3</sub> direct effect. Their results suggest a doubled  
6 sensitivity of surface temperatures to O<sub>3</sub> forcing, compared to current model estimates.

### 10.2.4. Competing Effects of Ozone Precursors on Climate

7 Changes in O<sub>3</sub> precursors affect not just O<sub>3</sub> concentrations, but also other species that have  
8 importance to the radiative balance of the earth's climate system. For example, an increase in CO or  
9 VOCs would lead to a decrease in hydroxyl (OH) concentrations. Since OH is a major sink of the  
10 greenhouse gas CH<sub>4</sub>, a decline in OH would lengthen the CH<sub>4</sub> lifetime, enhance the CH<sub>4</sub> burden, and  
11 amplify surface warming. A rise in NO<sub>x</sub> emissions, on the other hand, could lead to an increase in  
12 OH in certain locations, shortening the CH<sub>4</sub> lifetime and leading to surface cooling (Fuglestvedt et  
13 al., 1999, [047431](#)).

14 Analyzing the net radiative forcing per unit emission for a suite of O<sub>3</sub> precursors, Shindell and  
15 Faluvegi (2009, [631180](#)) calculated positive (+0.25 W/m<sup>2</sup>) radiative forcing from the increase in  
16 anthropogenic emissions of CO and VOCs since preindustrial times, as well as for CH<sub>4</sub> (+1 W/m<sup>2</sup>).  
17 In contrast, they found negative (-0.29 W/m<sup>2</sup>) radiative forcing from anthropogenic emissions of  
18 NO<sub>x</sub> due mainly to the link between NO<sub>x</sub> and CH<sub>4</sub>. Other studies have found a near cancellation of  
19 the positive O<sub>3</sub> forcing and the negative CH<sub>4</sub> forcing that arise from an incremental change in  
20 anthropogenic NO<sub>x</sub> emissions (Fiore et al., 2002, [051221](#); Fuglestvedt et al., 1999, [047431](#); Naik et  
21 al., 2005, [193194](#)). In addition, Wild et al. (2001, [193196](#)) found that an increase in surface NO  
22 emissions would lead to net cooling, while an increase in aircraft NO emissions would lead to net  
23 warming.

24 These results point out the need for careful assessment of net radiative forcing involving  
25 multiple pollutants in developing climate change policy (Unger et al., 2008, [631186](#)). Naik et al.  
26 (2005, [193194](#)) has calculated that a carefully combined reduction of CO, VOCs, and NO<sub>x</sub> emissions  
27 could lead to net cooling. In addition, several studies point to CH<sub>4</sub> as an attractive target for  
28 emissions control since CH<sub>4</sub> is itself an important precursor of O<sub>3</sub> (Fiore et al., 2002, [051221](#); West  
29 et al., 2007, [622733](#)). Fiore et al. (2002, [051221](#)) found that reducing anthropogenic CH<sub>4</sub> emissions  
30 by 50% would lead to a global radiative cooling of -0.37 W/m<sup>2</sup>, mostly from CH<sub>4</sub>.

### 10.2.5. Calculating Radiative Forcing and Climate Response to Past Trends in Tropospheric Ozone

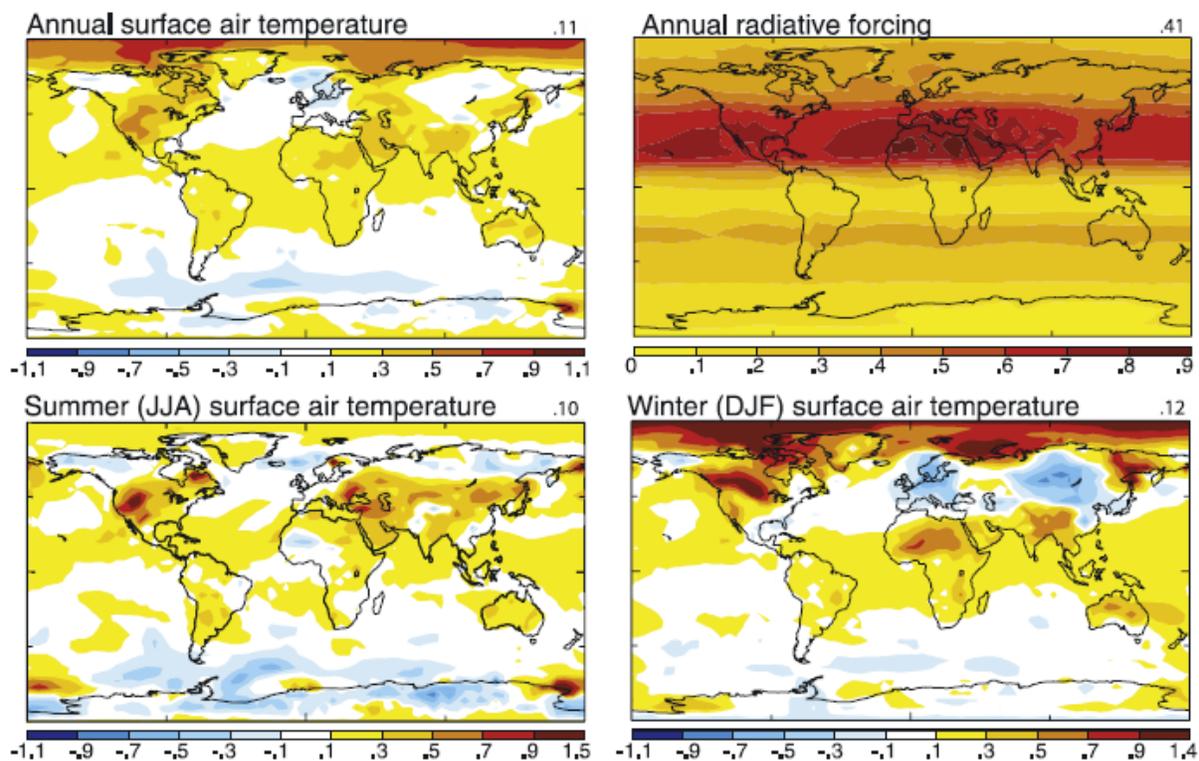
31 The magnitude of the radiative forcing from the change in tropospheric O<sub>3</sub> since the  
32 preindustrial era is uncertain. This uncertainty derives in part from the scarcity of early

1 measurements and in part from our limited knowledge regarding processes in the natural  
2 atmosphere. As noted previously, the IPCC AR4 reports a radiative forcing of  $0.35 \text{ W/m}^2$  from the  
3 change in tropospheric  $\text{O}_3$  since 1750 (Forster et al., 2007, [092936](#)), ranking it third in importance  
4 among greenhouse gases after  $\text{CO}_2$  and  $\text{CH}_4$ . The  $\text{O}_3$  forcing could, in fact, be as large as  $0.7 \text{ W/m}^2$ ,  
5 if reconstructions of preindustrial and mid-20th century  $\text{O}_3$  based on the measurement record are  
6 valid (Mickley et al., 2001, [080134](#); Shindell and Faluvegi, 2002, [080130](#)). In any event, Unger et al.  
7 (2010, [387104](#)) showed that present-day  $\text{O}_3$  forcing can be attributed to emissions from across many  
8 economic sectors, including on-road vehicles, household biofuel, power generation, and biomass  
9 burning. As much as one-third of the radiative forcing from the 1890 to 1990 change in tropospheric  
10  $\text{O}_3$  could be due to increased biomass burning (Ito et al., 2007, [608803](#)).

11 These calculated radiative forcing estimates can be compared to those obtained from satellite  
12 data. Using data from TOMS, Worden et al. (2008, [631188](#)) estimated a reduction in clear-sky  
13 outgoing longwave radiation of  $0.48 \text{ W/m}^2$  by  $\text{O}_3$  in the upper troposphere over oceans in 2006. This  
14 radiative forcing includes contributions from both anthropogenic and natural  $\text{O}_3$ . Assuming that the  
15 burden of  $\text{O}_3$  has roughly doubled since preindustrial times (Gauss et al., 2006, [630275](#)), the total  $\text{O}_3$   
16 forcing estimated with TOMS is consistent with that obtained from models estimating just the  
17 anthropogenic contribution.

18 Calculation of the climate response to the  $\text{O}_3$  radiative forcing is challenging due to  
19 complexity of feedbacks, as mentioned in Sections 10.2.2.3 and 10.2.3.4. In their model study,  
20 Mickley et al. (2004, [057416](#)) reported a global mean increase of  $0.28^\circ\text{C}$  since preindustrial times,  
21 with values as large as  $0.8^\circ\text{C}$  in continental interiors. For the time period since 1870, Hansen et al.  
22 (2005, [190596](#)) estimated a much smaller increase in global mean surface temperature ( $0.11^\circ\text{C}$ ), but  
23 they implemented 1880s anthropogenic emissions in their base simulation and also took into account  
24 trends in both stratospheric and tropospheric  $\text{O}_3$ ; the modeled decline of lower stratospheric  $\text{O}_3$ ,  
25 especially over polar regions, cooled surface temperatures in this study, counteracting the warming  
26 effect of increasing tropospheric  $\text{O}_3$ .

27 Figure 10-3 shows the Hansen et al. (2005, [190596](#)) results as reported in Shindell et al. (2006,  
28 [631181](#)). In that figure, summertime  $\text{O}_3$  has the largest radiative impact over the continental interiors  
29 of the Northern Hemisphere. In winter, the impact of tropospheric  $\text{O}_3$  is greatest over the snow and  
30 ice regions of the Arctic, where the probability of  $\text{O}_3$  absorption of shortwave radiation is high  
31 (Section 10.2.3.2). Shindell et al. (2006, [631181](#)) estimated that the change in tropospheric  $\text{O}_3$  over  
32 the 20<sup>th</sup> century could have contributed about  $0.3^\circ\text{C}$  to annual mean Arctic warming and as much as  
33  $0.4\text{-}0.5^\circ\text{C}$  during winter and spring. Over eastern China, Chang et al. (2009, [630273](#)) calculated a  
34 surface temperature increase of  $0.4^\circ\text{C}$  to the 1970-2000 change in tropospheric  $\text{O}_3$ . It is not clear,  
35 however, to what degree regional changes in  $\text{O}_3$  burden influenced this response, as opposed to more  
36 global changes.



Source: Used with permission from American Geophysical Union, Shindell et al. (2006, [631181](#))

**Figure 10-3. Ensemble average 1900-2000 surface temperature trends (°C per century) in response to tropospheric ozone changes and 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.

### 10.2.6. Calculating the 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  $O_3$  will also  
 3 depend on the changes in a suite of climate-sensitive factors, such as the water vapor content of the  
 4 atmosphere. This section describes the following issues: (1) projected trends in the anthropogenic  
 5 emissions of  $O_3$  precursors; (2) the effects of these emissions on the tropospheric  $O_3$  burden; (3) the

1 effects of changing climate on tropospheric O<sub>3</sub>; and (4) radiative forcing and climate response to 21st  
2 century trends in tropospheric O<sub>3</sub>.

### 10.2.6.1. Emissions of Anthropogenic Ozone Precursors across the 21st Century

3 The IPCC SRES effort devised scenarios for short-lived O<sub>3</sub> precursors as well as the well-  
4 mixed greenhouse gases including NO<sub>x</sub>, CO, and VOCs (IPCC, 2000, [080704](#)). Using the IMAGE  
5 socioeconomic model, Streets et al. (2004, [190423](#)) provided speciation for NO<sub>x</sub> and VOCs and  
6 allocated the trends in emissions over 17 regions and 8 economic sectors for the 2000-2050 time  
7 period. The worst-case IPCC scenario, A2, features continued dependence on fossil fuels, rapid  
8 population growth, and little sharing of technology between developed and developing nations. By  
9 2100 in this scenario, global NO<sub>x</sub> emissions increase by a factor of 3.4 and CO emissions and CH<sub>4</sub>  
10 by ~2.7, relative to 2000 (IPCC, 2000, [080704](#)). Most of these increases in emissions occur over  
11 developing countries. For example over Asia, NO<sub>x</sub> emissions in the A2 scenario increase by more  
12 than a factor of 4 by 2100. The more moderate A1B scenario has global NO<sub>x</sub> and CO emissions  
13 increasing by 25% and 90%, respectively by 2100, but global CH<sub>4</sub> emissions decreasing by 10%. In  
14 the B1 scenario, with its emphasis on clean and efficient technologies, global emissions of NO<sub>x</sub>, CO,  
15 and CH<sub>4</sub> all decrease by 2100 relative to the present day (-40%, -60%, and -30%, respectively).

16 Other emissions scenarios have been recently developed to describe trends in the short-term  
17 (up to 2030). The Current Legislation (CLE) scenario provides trends consistent with existing air  
18 quality regulations; the Maximum Feasible Reduction (MFR) scenario seeks to reduce emissions of  
19 O<sub>3</sub> precursors to the maximum extent possible. Emission source changes relative to the present day  
20 for CLE, MFR, and A2 are given in Stevenson et al. (2006, [089222](#)).

21 For the Fifth Assessment Report (IPCC AR5), a new set of scenarios has been developed: the  
22 Representative Concentration Pathways (RCPs) (Moss et al., 2010, [664501](#)). The RCPs will explore  
23 for the first time approaches to climate change mitigation. The scenarios are designed to achieve  
24 radiative forcing targets of 2.6, 4.5, 6.0 and 8.5 W/m<sup>2</sup> by 2100, and have been designated RCP 2.6,  
25 RCP 4.5, RCP 6.0, and RCP 8.5 (RCP 2.6 is also known as RCP3-PD.) In all scenarios, global  
26 anthropogenic NO<sub>x</sub> emissions decline 30-50% during the 21st century, though RCP 8.5 shows a peak  
27 during the 2020s at a value ~15% greater than that of 2000. Global anthropogenic VOC and CO  
28 emissions are relatively flat during the 2000-2050 time range, and then decline by 30-50% by the  
29 end of the century. For CH<sub>4</sub>, global mean emission trends for the four RCP scenarios differ  
30 significantly across the 21st century, with RCP 8.5 showing a tripling of emissions by 2100, and  
31 RCP 2.6 showing the emissions cut by half in this time range. All these global trends, however,  
32 contain some regional variation. For example, Asian emissions of both NO<sub>x</sub> and VOCs show  
33 significant increases in the near term (2030s to 2050s). Plots of the RCP trends can be found at  
34 <http://iiasa.ac.at/web-apps/tnt/RcpDb/dsd?Action=htmlpage&page=about> (RCP, 2009, [677552](#)).

## 10.2.6.2. Impact of 21st Century Trends in Emissions on Tropospheric Ozone

1 Due to its short lifetime, tropospheric O<sub>3</sub> will respond readily to changes in anthropogenic  
2 emissions of its precursors. As shown in Table 10-1, a recent multi-model study found increases in  
3 the tropospheric O<sub>3</sub> burden of 15% and 6% for the IPCC A2 and CLE scenarios respectively for the  
4 2000-2030 time period, and a decrease for the MFR scenario of 5% (Stevenson et al., 2006, [089222](#)).  
5 These results indicate that the growth in tropospheric O<sub>3</sub> between 2000 and 2030 could be reduced or  
6 even reversed, depending on emission controls. For the relatively moderate A1B emissions scenario  
7 over the 2000-2050 time period, Wu et al. (2008, [190039](#)) calculated a change in O<sub>3</sub> burden of about  
8 20%. Looking further into the 21st century, Gauss et al. (2003, [094204](#)) reported O<sub>3</sub> burden changes  
9 of 30-60% in response to application of the A2p anthropogenic emissions over the 2000-2100 time  
10 period (the A2p scenario was a preliminary version of the A2 scenario). Using the A2 scenario for  
11 the same 100 year time period, Pyle et al. (2007, [630284](#)) projected a 50% increase in the O<sub>3</sub> burden,  
12 consistent with Gauss et al. (2003, [094204](#)) and with Liao et al. (2006, [664500](#)) who calculated an O<sub>3</sub>  
13 change of 60% for the same conditions. Given the large (+40 ppb) monthly mean increases in  
14 surface O<sub>3</sub> that the A2 or A2p scenarios would yield over Asia and elsewhere by the end of the 21st  
15 century (Prather et al., 2003, [047879](#)), these 100-yr projections of the O<sub>3</sub> burden would lead to  
16 extremely unhealthy air quality.

17 As noted above, the RCP scenarios of AR5 show long-term declines in the global mean  
18 emissions of O<sub>3</sub> precursors, with some regional increases in the near-term. As of this writing, no  
19 model study has reported the response of the tropospheric O<sub>3</sub> burden to any of the IPCC AR5  
20 scenarios.

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**Table 10-1. 2000-2030 changes in anthropogenic emissions, and CH<sub>4</sub> and tropospheric ozone burdens, and the associated tropospheric ozone forcing for three scenarios; values are ensemble means**

Scenario	IPCC A2	Current Legislation (CLE)	Maximum Feasible Reduction (MFR)
Percent change in NO <sub>x</sub> emissions	+96%	+18%	-53%
Percent change in CO emissions	+62%	-16%	-53%
Percent change in CH <sub>4</sub> burden	+23%	+19%	0%
Percent change in tropospheric O <sub>3</sub> burden	+15%	+6%	-5%
Radiative forcing due to O <sub>3</sub> change <sup>a</sup> (W/m <sup>2</sup> )	0.3	0.18	-0.05

<sup>a</sup>Includes radiative forcing due to corresponding CH<sub>4</sub> change.

Source: Adapted from Stevenson et al. (2006, [089222](#)).

### 10.2.6.3. 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 burden of  
2 tropospheric O<sub>3</sub> can be traced to changing emissions. Model studies show that climate change so far  
3 has likely had little impact on the tropospheric O<sub>3</sub> (e.g., Grenfell et al., 2001, [664496](#)). In the future,  
4 however, climate change is expected to bring large changes in a suite of variables that could affect  
5 O<sub>3</sub> production, loss, and transport. For example, increased water vapor in a warming atmosphere is  
6 expected to enhance OH concentrations, which in remote, NO<sub>x</sub>-poor regions will accelerate O<sub>3</sub> loss  
7 rates (Johnson et al., 1999, [052390](#)).

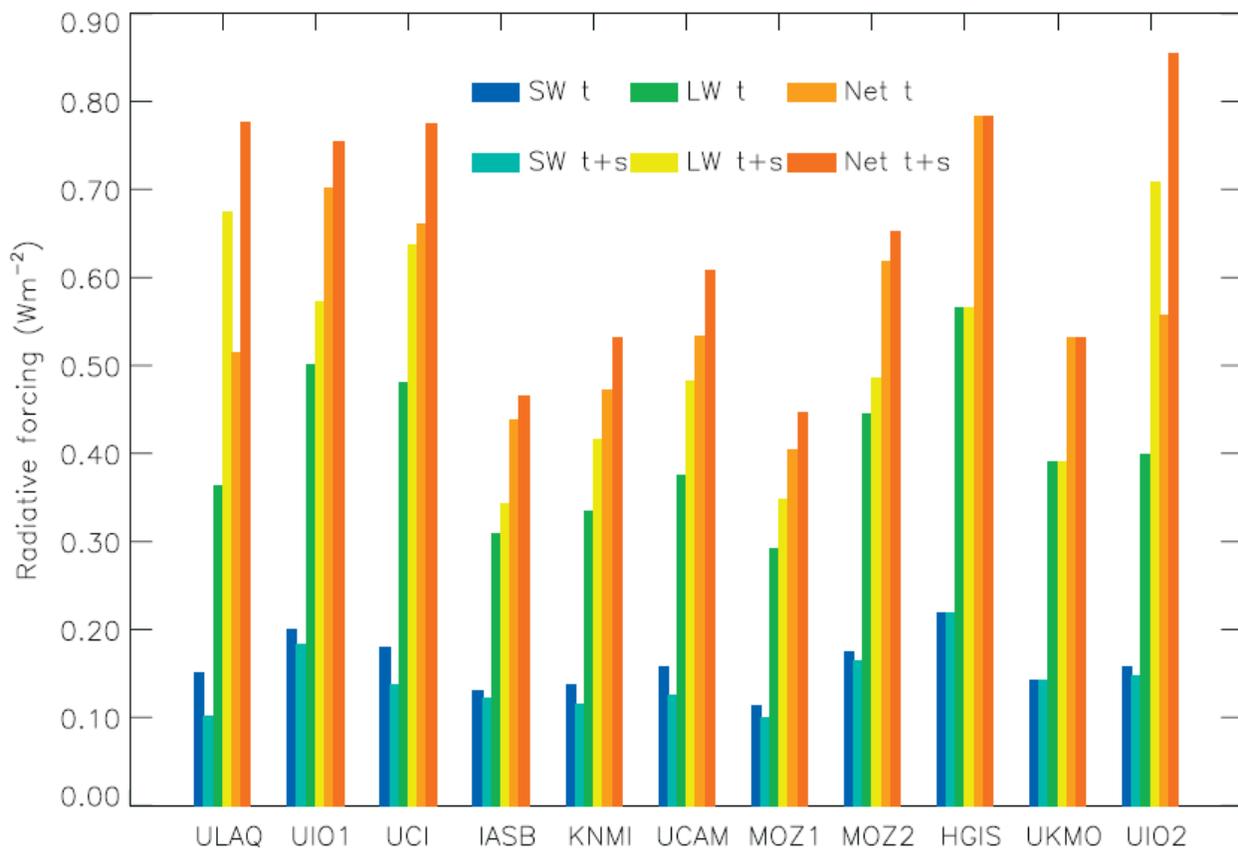
8 In the 2050s A1B climate, Wu et al. (2008, [629684](#)) calculated a 5 ppb decrease in surface O<sub>3</sub>  
9 over oceans. A rise in temperatures will also likely promote emissions of isoprene, an important  
10 biogenic precursor of O<sub>3</sub>. Model studies have calculated 21st-century increases in isoprene emissions  
11 ranging from 25-50%, depending on climate scenario and time horizon (Wu et al., 2008, [190039](#), and  
12 references therein). These studies however did not take into account the effects of changing climate  
13 and CO<sub>2</sub> burden on vegetation extent, which could have large consequences for biogenic emissions  
14 (Heald et al., 2008, [191617](#); Sanderson et al., 2003, [630286](#)). In any event, enhanced isoprene  
15 emissions will increase O<sub>3</sub> concentrations in VOC-limited regions, but decrease O<sub>3</sub> in NO<sub>x</sub>-limited  
16 regions (Pyle et al., 2007, [630284](#); Sanderson et al., 2003, [630286](#); Wu et al., 2008, [190039](#)).  
17 Convection frequencies and lightning flash rates will also likely change in a changing climate, with  
18 consequences for lightning NO<sub>x</sub> emissions and O<sub>3</sub> concentrations in the upper troposphere (Price and  
19 Rind, 1994, [630283](#); Sinha and Toumi, 1997, [047932](#)). While Wu et al. (2008, [190039](#)) calculated an  
20 increase in lightning NO<sub>x</sub> by 2050 due to enhanced deep convection, Jacobson and Streets (2009,  
21 [630281](#)) projected a decrease in lightning NO<sub>x</sub> due to a declining cloud ice in their future  
22 atmosphere. Finally, changes in transport processes will almost certainly accompany global climate  
23 change. For the 2050 A1B climate, Wu et al. (2008, [629684](#)) showed that flattening of the meridional  
24 temperature gradient in a warming world would lead to slower intercontinental transport of  
25 tropospheric O<sub>3</sub>. For the A2 climate in 2100, Zeng and Pyle (2003, [047492](#)) projected an 80%  
26 increase in the flux of stratospheric O<sub>3</sub> into the troposphere, relative to the present-day.

27 Taken together, these climate-driven processes could have significant effects on the burden  
28 and distribution of tropospheric O<sub>3</sub>. As shown in Wu et al. (2008, [629684](#)), model projections of the  
29 change in O<sub>3</sub> burden due solely to future climate change range from -12% to +3%, depending on the  
30 model, scenario, and time horizon.

### 10.2.6.4. Radiative Forcing and Climate Response from 21st Century Trends in Tropospheric Ozone

31 In the near term (2000-2030), Stevenson et al. (2006, [089222](#)) estimated an O<sub>3</sub> forcing of near  
32 zero for MFR, 0.18 W/m<sup>2</sup> for CLE, and +0.3 W/m<sup>2</sup> for the A2 scenario (Table 10-1). Menon et al.  
33 (2008, [613861](#)), following the moderate A1B scenario, calculated a radiative forcing of 0.12 W/m<sup>2</sup>  
34 from the 2000-2030 change in tropospheric O<sub>3</sub>, about the same as that derived by Stevenson et al.

1 (2006, [089222](#)) for the CLE scenario. Over the longer term (2000 to 2100) for the A1B scenario,  
 2 Gauss et al. (2003, [094204](#)) reported large positive radiative forcing (0.40 to 0.78 W/m<sup>2</sup>) due to the  
 3 change in tropospheric O<sub>3</sub>, as shown in Figure 10-4. Normalized radiative forcing for these model  
 4 calculations fell within a relatively narrow range, 0.032 to 0.040 W/m<sup>2</sup>/DU, indicating that the  
 5 largest uncertainty lies in the model-calculated changes in O<sub>3</sub> burden. Applying the A2 scenario,  
 6 Chen et al. (2007, [630274](#)) estimated a global mean radiative forcing of 0.65 W/m<sup>2</sup> from  
 7 tropospheric O<sub>3</sub> by 2100, consistent with the Gauss et al. (2003, [094204](#)) results. These studies took  
 8 into account only the impact of changing emissions on tropospheric O<sub>3</sub>. In their calculations of the  
 9 2000-2100 radiative forcing from O<sub>3</sub> in the A2 scenario, Liao et al. (2006, [664500](#)) found that  
 10 inclusion of climate effects on tropospheric O<sub>3</sub> reduced their radiative forcing estimate by 20%.



Source: Used with permission from American Geophysical Union, Gauss et al. (2003, [094204](#))

**Figure 10-4. Global mean radiative forcing estimates calculated by a set of models for the 2000-2100 change in tropospheric ozone. Shown are the components of radiative forcing in W/m<sup>2</sup>. SW = shortwave component; LW = longwave component; Net = total forcing; t = tropospheric ozone changes only; and t + s = both tropospheric and stratospheric changes.**

11 Several studies have included tropospheric O<sub>3</sub> in their investigations of the response in the  
 12 future atmosphere to a suite of short-lived species (e.g., Levy H et al., 2008, [631174](#); Shindell et al.,

1 2007, [521350](#); Shindell et al., 2008, [190393](#)). Few studies, however, have calculated the climate  
2 response to changes in tropospheric O<sub>3</sub> alone in the future atmosphere. For the A2 atmosphere, Chen  
3 et al. (2007, [630274](#)) estimated a global mean surface temperature increase of +0.34°C by 2100 in  
4 response to the change in O<sub>3</sub>. The largest temperature increases in this study, as much as 5°C,  
5 occurred over the populous regions of Asia and the Middle East and downwind of biomass burning  
6 regions in South Africa and South America.

### 10.2.7. Summary of the Effects of Tropospheric Ozone on Climate

7 Tropospheric O<sub>3</sub> is a major greenhouse gas, third in importance after CO<sub>2</sub> and CH<sub>4</sub>. While the  
8 developed world has successfully reduced emissions of O<sub>3</sub> precursors in recent decades, many  
9 developing countries have experienced large increases in precursor emissions and these trends are  
10 expected to continue, at least in the near term. Projections of radiative forcing due to changing O<sub>3</sub>  
11 over the 21st century show wide variation, due in large part to the uncertainty of future emissions of  
12 source gases. In the near-term (2000-2030), projections of O<sub>3</sub> radiative forcing range from near zero  
13 to +0.3 W/m<sup>2</sup>, depending on the emissions scenario (Stevenson et al., 2006, [089222](#)). Reduction of  
14 tropospheric O<sub>3</sub> concentrations could therefore provide an important means to slow climate change  
15 in addition to the added benefit improving surface air quality.

16 It is clear that increases in tropospheric O<sub>3</sub> lead to warming. However the precursors of O<sub>3</sub> also  
17 have competing effects on the greenhouse gas CH<sub>4</sub>, complicating emissions reduction strategies. A  
18 decrease in CO or VOC emissions would enhance OH concentrations, shortening the lifetime of  
19 CH<sub>4</sub>, while a decrease in NO<sub>x</sub> emissions could depress OH concentrations in certain regions and  
20 lengthen the CH<sub>4</sub> lifetime. Recent research, however, has shown that a carefully combined reduction  
21 of CO, VOCs, and NO<sub>x</sub> emissions could lead to net cooling (Naik et al., 2005, [193194](#)). In addition,  
22 abatement of CH<sub>4</sub> emissions would provide a straightforward means to address climate change since  
23 CH<sub>4</sub> is itself an important precursor of background O<sub>3</sub> (Fiore et al., 2002, [051221](#); West et al., 2006,  
24 [196558](#); West et al., 2007, [622733](#)).

25 Important uncertainties remain regarding the impact of O<sub>3</sub> on future climate change. To  
26 address these uncertainties, further research is needed to: (1) enhance our knowledge of the natural  
27 atmosphere; (2) interpret observed trends of O<sub>3</sub> in the free troposphere and remote regions; (3)  
28 understand the relationship between regional O<sub>3</sub> forcing and regional climate change; and (4)  
29 determine the optimal mix of emissions reductions that would act to limit future climate change.

## 10.3. UV-B Related Effects and Tropospheric Ozone

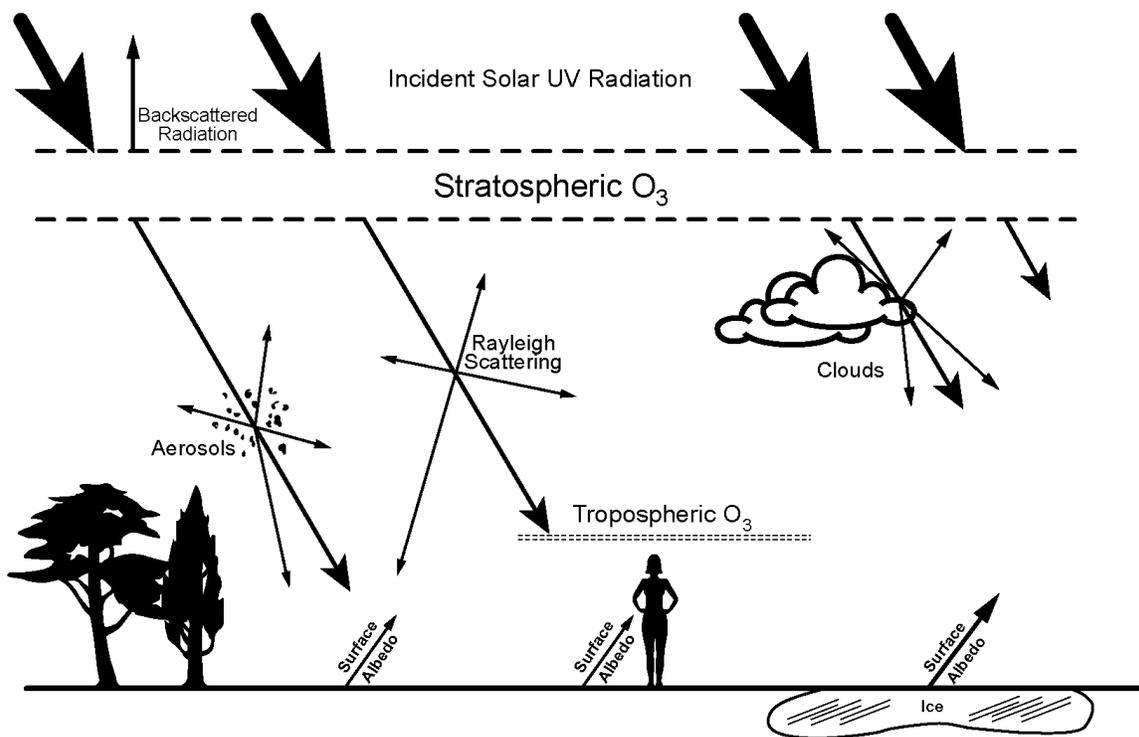
### 10.3.1. Background

30 Ultraviolet (UV) radiation emitted from the Sun contains sufficient energy when it reaches the  
31 Earth to break (photolyze) chemical bonds in molecules, thereby leading to damaging effects on  
32 living organisms and materials. Atmospheric O<sub>3</sub> plays a crucial role in reducing exposure to solar

1 UV radiation at the Earth's surface. Stratospheric O<sub>3</sub> is responsible for the majority of this shielding  
2 effect, as approximately 90% of total atmospheric O<sub>3</sub> is located there over mid-latitudes (Crist et al.,  
3 1994, [668881](#); Kar et al., 2010, [670423](#)). Investigation of the supplemental shielding of UV radiation  
4 provided by tropospheric O<sub>3</sub> is important for quantifying UV exposure and the incidence of related  
5 human health effects, ecosystem effects, and materials damage. The role of tropospheric O<sub>3</sub> in  
6 shielding of UV radiation is discussed in this section.

### 10.3.2. Physics of UV Radiation and Flux

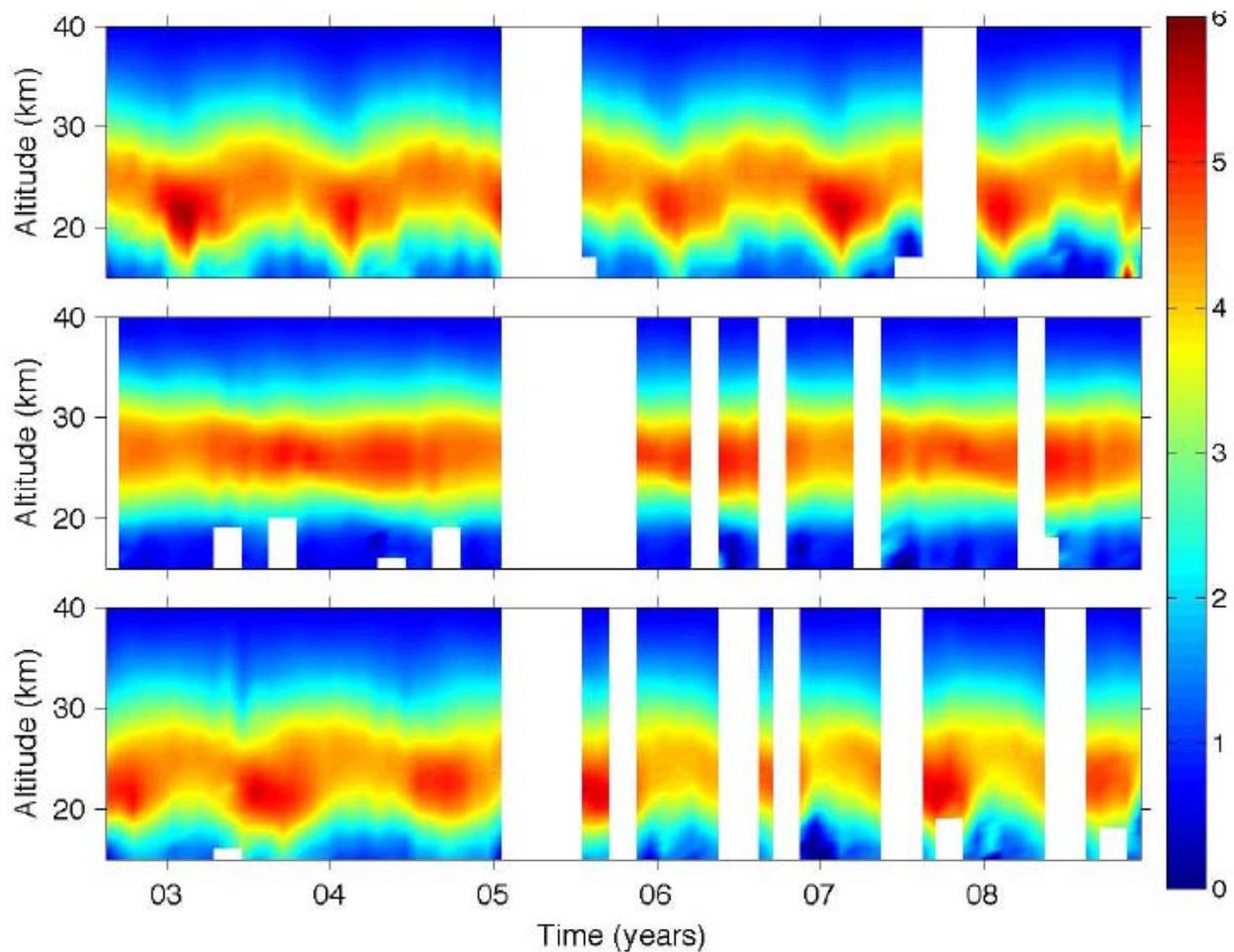
7 Solar UV radiation is subdivided into classes based on wavelength: UV-A refers to wavelengths from  
8 400-315 nm; UV-B from 315-280 nm; and UV-C from 280-100 nm. Since the energy possessed by a  
9 photon is inversely proportional to its wavelength, UV-A radiation is the least energetic and UV-C is  
10 the most energetic, with UV-B falling in-between. The wavelength determines how the photons  
11 interact with the complex mixture of gases, clouds and particles present in the atmosphere (see  
12 Figure 10-5). UV-A radiation can be scattered but is not absorbed to any meaningful degree by  
13 atmospheric gases including O<sub>3</sub>. UV-B radiation is absorbed and scattered in part within the  
14 atmosphere. UV-C is almost entirely blocked by the Earth's upper atmosphere, where it participates  
15 in photoionization and photodissociation processes. Since UV-A is less energetic and does not  
16 interact with O<sub>3</sub> and UV-C is almost entirely blocked by stratospheric O<sub>3</sub>, UV-B is the most  
17 important band of UV radiation to consider in relation to tropospheric O<sub>3</sub> shielding.



Source: 2006 O<sub>3</sub> AQCD (2006, [088089](#)).

**Figure 10-5. Diagram of the factors that determine human exposure to ultraviolet radiation.**

1 Solar flux has a temporal dependence, while radiative scattering and absorption have strong  
 2 wavelength, path length, and/or particle concentration dependencies. These combine to create  
 3 nonlinear effects on UV flux at the Earth's surface. Thus, careful quantification of atmospheric  
 4 absorbers and scatterers, along with a well-resolved description of the physics of these interactions,  
 5 is necessary for predicting the impact of ground-level O<sub>3</sub> on UV flux. Chapter 10 of the 2006 O<sub>3</sub>  
 6 AQCD (U.S. EPA, 2006, [088089](#)) describes in detail several key factors that influence the  
 7 spatiotemporal distribution of ground-level UV radiation flux, including: (1) long-term solar activity  
 8 including sunspot cycle; (2) solar rotation; (3) the position of the Earth in its orbit around the sun; (4)  
 9 atmospheric absorption and scattering of UV radiation by gas molecules and aerosol particles; (5)  
 10 absorption and scattering by stratospheric and tropospheric clouds; and (6) surface albedo. The  
 11 efficiencies of absorption and scattering are highly dependent on the concentration of the scattering  
 12 medium, particle size (for aerosols and clouds), and the altitude at which these processes are  
 13 occurring. These properties are sensitive to meteorology, which introduces additional elements of  
 14 temporal dependency in ground-level UV radiation flux. As seen in data collected by the Global  
 15 Ozone Monitoring by Occultation of Stars (GOMOS) instrument onboard the European Space  
 16 Agency's ENVISAT satellite (Figure 10-6), atmospheric O<sub>3</sub> density undergoes wide natural variation  
 17 on relatively short timescales, particularly at mid-latitudes (Kyrola et al., 2010, [667819](#)).



Source: Used with permission from Copernicus Publications, Kyrola et al., (2010, [667819](#)).

**Figure 10-6. Monthly stratospheric ozone number density (scaled by  $1 \times 10^{12}$  molecules/cm<sup>3</sup>), in 3 latitude belts as a function of time (August 2002 - December 2008) and altitude (15-40 km) from the Global Ozone Monitoring by Occultation of Stars (GOMOS) instrument onboard the European Space Agency’s ENVISAT satellite.**

**Latitude belts: 30°N-50°N (top), 10°S-10°N (middle), 30°S-50°S (bottom). White space in the panels means that there are not enough data available.**

1           The lower atmospheric pressure in the stratosphere means fewer gas molecules are present that  
 2 can absorb or scatter radiation. Stratospheric clouds and aerosols are also thinner and more dispersed  
 3 than those in the troposphere. In the language of the radiative transfer literature, these conditions  
 4 make the stratosphere a “single scattering” regime for UV radiation. The troposphere, due to its high  
 5 gas and particle concentrations is referred to as a “multiple scattering” regime. In practical terms,  
 6 UV radiation traverses the stratosphere with a substantially lower probability of encountering a gas  
 7 molecule, cloud, or aerosol particle than it would in the troposphere. The multiple scattering of UV  
 8 radiation in the troposphere accounts for the “disproportionate” role that tropospheric O<sub>3</sub> is said to  
 9 play in absorbing UV radiation versus stratospheric O<sub>3</sub> on a molecule per molecule basis (Balis et al.,

1 2002, [055023](#); Bruhl and Crutzen, 1989, [012518](#); Crist et al., 1994, [668881](#); Zerefos et al., 2002,  
2 [055169](#)).

3 Latitude and altitude are primary variables in defining UV-B flux at the Earth's surface,  
4 immediately followed in importance by clouds, surface albedo, PM concentration and composition,  
5 and then by gas phase pollution. Of all these variables, only latitude and altitude can be defined with  
6 small uncertainty in any effort to develop a UV climatology for use in a public health benefits  
7 analysis relevant to the areas not presently attaining the NAAQS for O<sub>3</sub>. Cloud cover, and its effect  
8 on surface UV flux, continues to be extremely difficult to define and predict. Particulate matter and  
9 gas-phase tropospheric pollutants are subject to similarly high degrees of uncertainty in predicting  
10 their relative concentration distributions, but recent advancements have been made (e.g., Bais et al.,  
11 2005, [669135](#); Bergstrom et al., 2004, [669158](#); Goering et al., 2005, [669164](#)). Land cover and,  
12 consequently, surface albedo is highly variable at the geographic scales relevant to NAAQS  
13 attainment.

14 The 2006 WMO assessment (WMO, 2006, [669178](#)) reported that global average total column  
15 O<sub>3</sub> had declined by 3.5% from pre-1980 concentrations due to the presence of anthropogenic O<sub>3</sub>-  
16 depleting substances in the atmosphere. In the period 2002-2005, no additional declines were found  
17 in the global average due to bans on and reduced emissions of O<sub>3</sub>-depleting substances. The report  
18 found that O<sub>3</sub> depletion has a strong latitude and seasonal dependence: total column O<sub>3</sub> declined by  
19 ~3% in the Northern Hemisphere, declined by ~6% in the Southern Hemisphere, and remained  
20 essentially unchanged over the tropics relative to pre-1980 total column O<sub>3</sub> abundances. Polar  
21 stratospheric O<sub>3</sub> depletion is more complex and exhibits large interannual variations driven by  
22 changes in meteorology.

### 10.3.3. Human Exposure and Susceptibility to Ultraviolet Radiation

23 The factors that potentially influence UV radiation exposure were discussed in detail in  
24 Chapter 10 of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) and are summarized here. These factors  
25 included outdoor activity, occupation, age, gender, geography, and protective behavior. Outdoor  
26 activity and occupation both influenced the amount of time people spend outdoors during daylight  
27 hours, the predominant factor for exposure to solar UV radiation. Participation in outdoor sports  
28 (e.g., basketball, soccer, golf, swimming, cycling) significantly increased UV radiation exposure  
29 (Moehrle, 2001, [057502](#); Moehrle et al., 2000, [057503](#); Thieden et al., 2004, [057558](#); Thieden et al.,  
30 2004, [057557](#)). Occupations that substantially increased exposure to UV radiation included farming  
31 (Airey et al., 1997, [057458](#); Schenker et al., 2002, [057522](#)), fishing (Rosenthal et al., 1988, [057513](#)),  
32 landscaping (Rosenthal et al., 1988, [057513](#)), construction (Gies and Wright, 2003, [057477](#)),  
33 physical education (Vishvakarman et al., 2001, [057614](#)), mail delivery (Vishvakarman et al., 2001,  
34 [057614](#)), and various other occupations that require workers to spend the majority of their day  
35 outdoors during peak UV radiation hours.

36 Age and gender were found to be factors that influence human exposure to UV radiation,  
37 particularly by influencing other factors of exposure such as outdoor activity and risk behavior.

1 Studies indicated that females generally spent less time outdoors and, consequently, had lower UV  
2 radiation exposure compared to males (Gies et al., 1998, [057478](#); Godar et al., 2001, [057165](#);  
3 Shoveller et al., 1998, [057524](#)). The lowest exposure to UV radiation among Americans in the Godar  
4 et al. (2001, [057165](#)) study was received in females during their child raising years (age  
5 22-40 years); the highest exposure was observed in males aged 41-59 years. A similar Canadian  
6 survey found that younger adult males had the greatest exposures to UV radiation (Shoveller et al.,  
7 1998, [057524](#)).

8 Geography influences the degree of solar UV flux to the surface, and hence exposure to UV  
9 radiation. In the U.S. study by Godar et al. (2001, [057165](#)), northerners and southerners were found  
10 to spend an equal amount of time outdoors; however, the higher solar flux at lower latitudes  
11 significantly increased the annual UV radiation dose for southerners. The annual UV radiation doses  
12 in southerners were 25 and 40% higher in females and males, respectively, compared to northerners.  
13 Other studies also have shown that altitude and latitude influence personal exposure to UV radiation  
14 (e.g., Kimlin et al., 1998, [057491](#); Rigel et al., 1999, [057511](#)).

15 Protective behaviors such as using sunscreen (e.g., Nole and Johnson, 2004, [057505](#)), wearing  
16 protective clothing (e.g., Rosenthal et al., 1988, [057513](#)), and spending time in shaded areas (e.g.,  
17 Moise et al., 1999, [057504](#)) were shown to reduce exposure to UV radiation. In one study, the use of  
18 sunscreen was associated with extended intentional UV radiation exposure (Autier et al., 1999,  
19 [057459](#)); however, a follow-up study indicated that sunscreen use increased duration of exposures to  
20 doses of UV radiation that were below the threshold level for erythema (Autier et al., 2000, [057069](#)).

21 Given these and other factors that potentially influence UV radiation exposure, the 2006 O<sub>3</sub>  
22 AQCD (U.S. EPA, 2006, [088089](#)) listed the following subpopulations potentially at risk for higher  
23 exposures to UV radiation:

- 24       ▪ Individuals who engage in high-risk behavior (e.g., sunbathing);
- 25       ▪ Individuals who participate in outdoor sports and activities;
- 26       ▪ Individuals who work outdoors with inadequate shade (e.g., farmers, construction  
27 workers, etc.); and
- 28       ▪ Individuals living in geographic areas with higher solar flux including lower latitudes  
29 (e.g., Honolulu, HI) and higher altitudes (e.g., Denver, CO).

30 The risks associated with all these factors are, of course, highly dependent on season and region  
31 (Sliney and Wengraitis, 2006, [651896](#)).

#### 10.3.4. Human Health Effects due to UV-B Radiation

1 Chapter 10 of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) covered in detail the human  
2 health effects associated with solar UV-B radiation exposure. These effects include erythema, skin  
3 cancer, ocular damage, and immune system suppression. These adverse effects, along with protective  
4 effects of UV radiation through increased production of vitamin D are summarized in this section.  
5 For additional details, the reader is referred to Chapter 10 of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006,  
6 [088089](#)) and references therein.

7 The most conspicuous and well-recognized acute response to UV radiation is erythema, or the  
8 reddening of the skin. Erythema is likely caused by direct damage to DNA by UV radiation  
9 (Matsumura and Ananthaswamy, 2004, [057184](#)). Many studies discussed in the 2006 O<sub>3</sub> AQCD  
10 (U.S. EPA, 2006, [088089](#)) found skin type to be a significant risk factor for erythema. Additional  
11 risk factors include atopic dermatitis (ten Berge et al., 2009, [651897](#)).

12 Skin cancer is another prevalent health effect associated with UV radiation. Exposure to UV  
13 radiation is considered to be a major risk factor for all forms of skin cancer (Diepgen and Mahler,  
14 2002, [093593](#); Gloster and Brodland, 1996, [057479](#)). Ultraviolet radiation is especially effective in  
15 inducing genetic mutations and acts as both a tumor initiator and promoter. Keratinocytes have  
16 evolved DNA repair mechanisms to correct the damage induced by UV; however, mutations can  
17 occur, leading to skin cancers that are appearing with increasing frequency (Hildesheim and Fornace,  
18 2004, [057168](#)). The relationship between skin cancer and chronic exposure to UV radiation is further  
19 explored in Chapter 10 of the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)).

20 Ocular damage from UV radiation exposure includes effects on the cornea, lens, iris, and  
21 associated epithelial and conjunctival tissues. The region of the eye effected by exposure to UV  
22 radiation depends on the wavelength of the incident UV radiation. Depending on wavelength,  
23 common health effects associated with UV radiation include photokeratitis (snow blindness; short  
24 wavelengths) and cataracts (opacity of the lens; long wavelengths).

25 Experimental studies have suggested that exposure to UV radiation may suppress local and  
26 systemic immune responses to a variety of antigens (Clydesdale et al., 2001, [057105](#); Garssen and  
27 Van Loveren, 2001, [057161](#); Selgrade et al., 1997, [036165](#)). In rodent models, these effects have  
28 been shown to worsen the course and outcome of some infectious diseases and cancers (Granstein  
29 and Matsui, 2004, [057747](#); Norval et al., 1999, [036089](#)). Results from human clinical studies suggest  
30 that immune suppression induced by UV radiation may be a risk factor contributing to skin cancer  
31 induction (Caforio et al., 2000, [080058](#); Lindelof et al., 2000, [080084](#); Ullrich, 2005, [095635](#)). There  
32 is also evidence that UV radiation has indirect involvement in viral oncogenesis through the human  
33 papillomavirus (Pfister, 2003, [057515](#)), dermatomyositis (Okada et al., 2003, [057769](#)), human  
34 immunodeficiency virus (Breuer-McHam et al., 2001, [057736](#)) and other forms of  
35 immunosuppression (Selgrade M-JK; Smith et al., 2001, [057454](#)).

36 A potential health benefit of increased UV-B exposure relates to the production of vitamin D  
37 in humans. Most humans depend on sun exposure to satisfy their requirements for vitamin D

1 (Holick, 2004, [057691](#)). Vitamin D deficiency can cause metabolic bone disease among children and  
2 adults, and also may increase the risk of many common chronic diseases, including type I diabetes  
3 mellitus and rheumatoid arthritis (Holick, 2004, [057691](#)). Substantial in vitro and toxicological  
4 evidence also support a role for vitamin D activity against the incidence or progression of various  
5 forms of cancer (Freedman et al., 2002, [035530](#); Garland et al., 1990, [025242](#); Giovannucci, 2005,  
6 [074099](#); Gorham et al., 1990, [000682](#); Grant, 2002, [034981](#); Grant, 2002, [025244](#); Grant and  
7 Garland, 2004, [075093](#); Hanchette and Schwartz, 1992, [025257](#); Hughes et al., 2004, [074101](#); John  
8 et al., 1999, [057489](#); John et al., 2005, [670422](#); Lefkowitz and Garland, 1994, [025253](#); Smedby et  
9 al., 2005, [669175](#); Studzinski and Moore, 1995, [057554](#)). In some studies, UV-B related production  
10 of vitamin D had potential beneficial immunomodulatory effects on multiple sclerosis, insulin-  
11 dependent diabetes mellitus, and rheumatoid arthritis (Ponsonby et al., (2002, [080061](#)); Cantorna,  
12 (2000, [080060](#))). More details on UV-B protective studies are provided in Chapter 10 of the 2006 O<sub>3</sub>  
13 AQCD (U.S. EPA, 2006, [088089](#)).

14 In establishing guidelines on limits of exposure to UV radiation, the International commission  
15 on Non-Ionizing Radiation Protection (ICNIRP) agreed that some low-level exposure to UV  
16 radiation has health benefits (ICNIRP, 2004, [057187](#)). However, the adverse health effects of higher  
17 UV exposures necessitated the development of exposure limits for UV radiation. The ICNIRP  
18 recognized the challenge in establishing exposure limits that would achieve a realistic balance  
19 between beneficial and adverse health effects. As concluded by ICNIRP (2004, [057187](#)), "[t]he  
20 present understanding of injury mechanisms and long-term effects of exposure to [UV radiation] is  
21 incomplete, and awaits further research".

### 10.3.5. Ecosystem and Materials Damage Effects Due to UV-B Radiation

22 A 2009 progress report on the environmental effects of O<sub>3</sub> depletion from the UNEP,  
23 Environmental Effects Assessment Panel (UNEP, 2009, [669084](#)) lists many ecosystem and materials  
24 damage effects from UV-B radiation. An in-depth assessment of the global ecosystem and materials  
25 damage effects from UV-B radiation per se is out of the scope of this assessment. However, a brief  
26 summary of some mid-latitude effects is provided in this section to provide context for UV-B related  
27 issues pertaining to tropospheric O<sub>3</sub>. The reader is referred to the UNEP report (UNEP, 2009,  
28 [669084](#)) and references therein for further details. All of these UV-B related ecosystem and materials  
29 effects can also be influenced by climate change through temperature and other meteorological  
30 alterations, making quantifiable predictions of UV-B effects difficult.

31 Terrestrial ecosystem effects from increased UV-B radiation include reduced plant productivity  
32 and plant cover, changes in biodiversity, susceptibility to infection, and increases in natural UV  
33 protective responses. In general, however, these effects are small for moderate UV-B increases at  
34 mid-latitudes. A field study on wheat in southern Chile found no substantial changes in crop yield  
35 with moderate increases in UV-B radiation (Calderini et al., 2008, [668893](#)). Similarly, field studies  
36 on silver birch (*Betula pendula*) in Finland found no significant effects in photosynthetic function  
37 with increases in UV-B radiation (Aphalo et al., 2009, [668923](#)). Subtle, but important, changes in

1 habitat and biodiversity have also been linked to increases in UV-B radiation (Mazza et al., 2010,  
2 [668911](#); Obara et al., 2008, [668913](#); Wahl, 2008, [668921](#)). Some plants have natural coping  
3 mechanisms for dealing with changes in UV-B radiation (Brown and Jenkins, 2008, [668892](#); Favory  
4 et al., 2009, [668897](#); Ioki et al., 2008, [668904](#); Jenkins, 2009, [668905](#)), but these defenses may have  
5 costs in terms of reduced growth (Clarke and Robinson, 2008, [668928](#); Phoenix et al., 2000, [668915](#);  
6 Semerdjieva et al., 2003, [668919](#); Snell et al., 2009, [668920](#)).

7 Aquatic ecosystem effects from increased UV-B radiation include sensitivity in growth,  
8 immune response, and behavioral patterns of aquatic organisms. One study looking at  
9 coccolithophores, an abundant phytoplankton group, found a 25% reduction in cellular growth with  
10 UV-B exposure (Gao et al., 2009, [668899](#)). Exposure to relevant levels of UV-B radiation has been  
11 shown to modify immune response, blood chemistry, and behavior in certain species of fish (Holtby  
12 and Bothwell, 2008, [668903](#); Jokinen et al., 2008, [668906](#); Markkula et al., 2009, [613291](#)). Adverse  
13 effects on growth and development from UV-B radiation have also been observed for amphibians,  
14 sea urchins, mollusks, corals, and zooplankton (Croteau et al., 2008, [668894](#); Croteau et al., 2008,  
15 [603785](#); Garcia et al., 2009, [668935](#); Marquis and Miaud, 2008, [668908](#); Marquis et al., 2008,  
16 [668909](#); Oromi et al., 2008, [668914](#); Romansic et al., 2009, [515730](#)).

17 Biogeochemical cycles, particularly the carbon cycle, can also be influenced by increased UV-  
18 B radiation. A study on high latitude wetlands found UV-induced increases in CO<sub>2</sub> uptake through  
19 soil respiration (Haapala et al., 2009, [607260](#)) while studies on arid terrestrial ecosystems found  
20 evidence for UV-induced release of CO<sub>2</sub> through photodegradation of above-ground plant litter  
21 (Brandt et al., 2009, [668891](#); Caldwell et al., 2007, [668927](#); Henry et al., 2008, [668902](#); Zepp et al.,  
22 2007, [668896](#)). Changes in solar UV radiation may also have effects on carbon cycling and CO<sub>2</sub>  
23 uptake in the oceans (Brewer and Peltzer, 2009, [669197](#); Fritz et al., 2008, [668898](#); Hader et al.,  
24 2007, [668901](#); Meador et al., 2009, [668912](#); Zepp et al., 2008, [668922](#)) as well as release of  
25 dissolved organic matter from sediment and algae (Mayer et al., 2009, [668910](#); Riggsbee et al., 2008,  
26 [668917](#)). Additional studies showing effects on these and additional biogeochemical cycles including  
27 the water cycle and halocarbon cycle can be found in the UNEP report (UNEP, 2009, [669084](#)) and  
28 references therein.

29 Materials damage from increased UV-B radiation include UV-induced photodegradation of  
30 wood (Kataoka et al., 2007, [670425](#)) and plastics (Pickett et al., 2008, [668916](#)). These studies and  
31 others summarizing photo-resistant coatings and materials designed to reduce photodegradation of  
32 materials are summarized in the UNEP report (UNEP, 2009, [669084](#)) and references therein.

### 10.3.6. UV-B Related Effects Associated with Changes in Tropospheric Ozone Concentrations

33 There are multiple complexities in attempting to quantify the relationship between changes in  
34 tropospheric O<sub>3</sub> concentrations and UV radiation exposure, as described above. Furthermore,  
35 quantifying the relationship between UV radiation and health or welfare effects is complicated by the  
36 uncertainties involved in the selection of an action spectrum and appropriate characterization of dose

1 (e.g., peak or cumulative levels of exposure, timing of exposures, etc.) The lack of published studies  
2 that critically examine these issues together--that is the incremental health or welfare effects  
3 attributable specifically to UV-B changes resulting from reductions in tropospheric O<sub>3</sub>  
4 concentrations--reflects the significant challenges in this field.

5 As reported in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)), one analysis by Lutter and Wolz  
6 (1997, [082672](#)) attempted to estimate the effects of a nationwide 10 ppb reduction in seasonal  
7 average tropospheric O<sub>3</sub> on the incidence of nonmelanoma and melanoma skin cancers and cataracts  
8 in humans. Their estimate, however, depended upon several simplifying assumptions, ranging from  
9 an assumed generalized 10-ppb reduction in O<sub>3</sub> column density, national annual average incidence  
10 rates for the two types of skin cancer, and simple, linear biological amplification factors.  
11 Specifically, the decrease of 10 ppbv in seasonally averaged O<sub>3</sub> concentrations is likely an  
12 overestimate since it doesn't account for the influence of background O<sub>3</sub> coming from the global  
13 accumulation or generation of regional chemistry (Adamowicz et al., 2004, [670421](#)). Further, the  
14 methodologies used in this analysis have ignored area-specific factors that are important in  
15 estimating the extent to which small, variable changes in ground-level O<sub>3</sub> mediate long-term  
16 exposures to UV-B radiation.

17 A handful of studies have addressed the relationship between changes in tropospheric pollutant  
18 concentrations and UV-B radiation exposure, providing some additional insight. A study by Palancar  
19 and Toselli (2002, [057207](#)) looked at changes in measured UV-B radiation in relation to ground-level  
20 air pollutants during several air pollution episodes in Cordoba, Argentina. They found that changes  
21 in aerosol concentrations explained the majority of UV-B radiation fluctuations, and that changes in  
22 tropospheric O<sub>3</sub> and SO<sub>2</sub> had little effect. Repapis et al. (1998, [038015](#)) performed a similar study on  
23 UV-B exposures during high and low air pollution days in Athens, Greece. They found cloud cover  
24 and aerosols to be the major factors in observed UV-B exposures reductions. Studies by Acosta and  
25 Evans (2000, [670420](#)) in Mexico City and Koronakis et al. (2002, [129938](#)) in Athens, Greece both  
26 found significant reductions in surface-level UV exposures during pollution episodes. Both these  
27 studies include tropospheric O<sub>3</sub> as a potential driver for the reductions, but neither study was able to  
28 quantify the influence of individual atmospheric components involved in the observed attenuation in  
29 UV-B radiation.

30 In the absence of studies specifically addressing UV-B related health effects from a reduction  
31 in tropospheric O<sub>3</sub>, inferences were made in the 2006 O<sub>3</sub> AQCD (U.S. EPA, 2006, [088089](#)) on the  
32 basis of studies focused on stratospheric O<sub>3</sub> depletion. Studies included in that review examined the  
33 potential effect of stratospheric O<sub>3</sub> depletion on the risk of erythema (Longstreth et al., 1998,  
34 [001200](#)), skin cancer (De Gruijl, 1995, [057471](#); Longstreth et al., 1995, [055174](#); Madronich and  
35 De Gruijl, 1993, [055183](#); Slaper et al., 1996, [055128](#); Urbach, 1997, [086255](#)), nonmelanoma skin  
36 cancer (Longstreth et al., 1995, [055174](#); Slaper et al., 1996, [055128](#)), and cataracts (Longstreth et al.,  
37 1995, [055174](#)). Note that several of the concerns expressed above in relation to the Lutter and Wolz  
38 (1997, [082672](#)) analysis are relevant to these analyses as well. Furthermore, these studies have a  
39 high degree of uncertainty due to inadequate information on the action spectrum and dose-response

1 relationships. As a result, caution is advised when assessing and interpreting the quantitative results  
2 of health risks due to stratospheric O<sub>3</sub> depletion in the context of tropospheric O<sub>3</sub> shielding.

3 Although the UV-B related health effects attributed to marginal reductions in tropospheric or  
4 ground-level O<sub>3</sub> that would result from attainment of the O<sub>3</sub> NAAQS have not been directly  
5 assessed, they would be expected to be small or nonexistent given the above findings and the fact  
6 that tropospheric O<sub>3</sub> makes up only ~10% of the total atmospheric O<sub>3</sub> column at mid-latitudes (Kar  
7 et al., 2010, [670423](#)). Furthermore, O<sub>3</sub> present in the planetary boundary layer makes up only ~10%  
8 of tropospheric O<sub>3</sub> (Thompson et al., 2007, [090796](#)) and the NAAQS has only a fractional influence  
9 on those ground-level O<sub>3</sub> concentrations (i.e., it is not the intent of the NAAQS to entirely eliminate  
10 ground-level O<sub>3</sub>). The net result is a very small influence on total column O<sub>3</sub> through attainment of  
11 the O<sub>3</sub> standard. In addition, the health benefits of UV-B in the production of vitamin D suggests that  
12 increased risks of human disease due to a slight excess in UV-B radiation exposure may be offset by  
13 the benefits of enhanced vitamin D production. However, as with other impacts of UV-B on human  
14 health, this beneficial effect of UV-B has not been studied in sufficient detail to allow for a credible  
15 health benefits assessment. Hence, the above mentioned health and welfare effects associated with  
16 UV-B exposures resulting from changes in ground-level O<sub>3</sub> concentrations would likely be small or  
17 nonexistent based on current information.

18 More reasonable estimates of the human health impacts of enhanced UV-B penetration  
19 following reduced ground-level O<sub>3</sub> concentrations require both (a) a solid understanding of the  
20 multiple factors that define the extent of human exposure to UV-B, and (b) well-defined and  
21 quantifiable links between human disease and UV-B exposure. Within the uncertain context of  
22 presently available information on UV-B surface fluxes, a risk assessment of UV-B-related health  
23 effects would need to factor in human habits (e.g., daily activities, recreation, dress, and skin care) in  
24 order to adequately estimate UV-B exposure levels. Little is known about the impact of variability in  
25 these human factors on individual exposure to UV radiation. Furthermore, detailed information does  
26 not exist regarding the relevant type (e.g., peak or cumulative) and time period (e.g., childhood,  
27 lifetime, or current) of exposure, wavelength dependency of biological responses, and inter-  
28 individual variability in UV resistance. In conclusion, the effect of changes in surface-level O<sub>3</sub>  
29 concentrations on UV-induced health outcomes cannot yet be critically assessed within reasonable  
30 uncertainty. The reader is referred to the U.S. EPA 2002 Final Response to Court Remand (2003,  
31 [015702](#)) for detailed discussions of the data and scientific issues associated with the determination of  
32 public health benefits resulting from the attenuation of UV-B by surface-level O<sub>3</sub>.

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A list of all references considered for inclusion in this chapter can be found at

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Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at <http://epa.gov/hero>. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISAs) and the Integrated Risk Information System (IRIS).

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